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Antiplatelet agents for chronic kidney disease (Review)

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[Intervention Review]

Antiplatelet agents for chronic kidney disease

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ABSTRACT

Background

Antiplatelet agents are widely used to prevent cardiovascular events. The risks and benefits of antiplatelet agents may be different in people with chronic kidney disease (CKD) for whom occlusive atherosclerotic events are less prevalent, and bleeding hazards might be increased. This is an update of a review first published in 2013.

Objectives

To evaluate the benefits and harms of antiplatelet agents in people with any form of CKD, including those with CKD not receiving renal replacement therapy, patients receiving any form of dialysis, and kidney transplant recipients.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 13 July 2021 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

We selected randomised controlled trials of any antiplatelet agents versus placebo or no treatment, or direct head-to-head antiplatelet agent studies in people with CKD. Studies were included if they enrolled participants with CKD, or included people in broader at-risk populations in which data for subgroups with CKD could be disaggregated.

Data collection and analysis

Four authors independently extracted data from primary study reports and any available supplementary information for study population, interventions, outcomes, and risks of bias. Risk ratios (RR) and 95% confidence intervals (CI) were calculated from numbers of events and numbers of participants at risk which were extracted from each included study. The reported RRs were extracted where crude event rates were not provided. Data were pooled using the random-effects model. Confidence in the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results

We included 113 studies, enrolling 51,959 participants; 90 studies (40,597 CKD participants) compared an antiplatelet agent with placebo or no treatment, and 29 studies (11,805 CKD participants) directly compared one antiplatelet agent with another. Fifty-six new studies were added to this 2021 update. Seven studies originally excluded from the 2013 review were included, although they had a follow-up lower than two months.

Random sequence generation and allocation concealment were at low risk of bias in 16 and 22 studies, respectively. Sixty-four studies reported low-risk methods for blinding of participants and investigators; outcome assessment was blinded in 41 studies. Forty-one studies were at low risk of attrition bias, 50 studies were at low risk of selective reporting bias, and 57 studies were at low risk of other potential sources of bias.

Compared to placebo or no treatment, antiplatelet agents probably reduces myocardial infarction (18 studies, 15,289 participants: RR 0.88, 95% CI 0.79 to 0.99, I^2 = 0%; moderate certainty). Antiplatelet agents has uncertain effects on fatal or nonfatal stroke (12 studies, 10.382 participants: RR 1.01, 95% CI 0.64 to 1.59, I^2 = 37%; very low certainty) and may have little or no effect on death from any cause (35 studies, 18,241 participants: RR 0.94, 95 % CI 0.84 to 1.06, I^2 = 14%; low certainty). Antiplatelet therapy probably increases major bleeding in people with CKD and those treated with haemodialysis (HD) (29 studies, 16,194 participants: RR 1.35, 95% CI 1.10 to 1.65, I^2 = 12%; moderate certainty). In addition, antiplatelet therapy may increase minor bleeding in people with CKD and those treated with HD (21 studies, 13,218 participants: RR 1.55, 95% CI 1.27 to 1.90, I^2 = 58%; low certainty). Antiplatelet treatment may reduce early dialysis vascular access thrombosis (8 studies, 1525 participants) RR 0.52, 95% CI 0.38 to 0.70; low certainty). Antiplatelet agents may reduce doubling of serum creatinine in CKD (3 studies, 217 participants: RR 0.39, 95% CI 0.17 to 0.86, I^2 = 8%; low certainty). The treatment effects of antiplatelet agents on stroke, cardiovascular death, kidney failure, kidney transplant graft loss, transplant rejection, creatinine clearance, proteinuria, dialysis access failure, loss of primary unassisted patency, failure to attain suitability for dialysis, need of intervention and cardiovascular hospitalisation were uncertain. Limited data were available for direct head-to-head comparisons of antiplatelet drugs, including prasugrel, ticagrelor, different doses of clopidogrel, abciximab, defibrotide, sarpogrelate and beraprost.

Authors' conclusions

Antiplatelet agents probably reduced myocardial infarction and increased major bleeding, but do not appear to reduce all-cause and cardiovascular death among people with CKD and those treated with dialysis. The treatment effects of antiplatelet agents compared with each other are uncertain.

PLAIN LANGUAGE SUMMARY

Are anti-blood clotting drugs beneficial for people with chronic kidney disease?

What is the issue?

People with chronic kidney disease (CKD) have an increased risk of heart disease that can block the blood supply to the heart or brain causing a heart attack or stroke. Drugs that prevent blood clots from forming (antiplatelet agents) can prevent deaths caused by clots in arteries in the general adult population. However, there may be fewer benefits for people who have CKD, because blood clots in arteries is a less common cause of death or reason to be admitted to hospital compared with heart failure or sudden death in these people. People with CKD also have an increased tendency for bleeding due to changes in how the blood clots. Antiplatelet agents may therefore be more hazardous when CKD is present.

What did we do?

This updated review evaluated the benefits and harms of antiplatelet agents to prevent cardiovascular disease and death, and the impact on dialysis vascular access (fistula or graft) function in people who have CKD. We identified 90 studies comparing antiplatelet agents with placebo or no treatment and 29 studies directly comparing one antiplatelet agent with another.

What did we find?

Antiplatelet agents probably prevent heart attacks, but do not clearly reduce death or stroke. Treatment with these agents may increase the risk of major and minor bleeding. Clotting of dialysis access was prevented with antiplatelet agents.

Conclusions

The benefits of antiplatelet agents for people with CKD is probably limited to the prevention of a heart attack. The treatment does not appear to prevent stroke or death and probably incurs excess serious bleeding that may require hospital admission or transfusion.

SUMMARY OF FINDINGS

Summary of findings 1. Antiplatelet agents versus control for chronic kidney disease

Antiplatelet agents versus control for chronic kidney disease

Patient or population: people with chronic kidney disease (predialysis (GFR 15 to 60 mL/min/1.73 m^2), HD, PD, transplant recipients)

Settings: all settings involving people with any stage of CKD

Intervention: antiplatelet agents (abciximab, aspirin, beraprost sodium, cilostazol, clopidogrel, dypiridamole, eptidifibatide, pentoxifylline, picotamide, prasugrel, prostacyclin, sarpogrelate, sulphinpyrazone, ticlopidine, tirofiban, alone or in combination)

Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)
	Risk with control	Risk with antiplatelet agents			
Fatal or nonfatal myocardial infarction Follow-up: 3 to 61.2 months (median 12 months)	All patients (predialysis, dialysis, transplant recipients)		RR 0.88 (0.79 to 0.99)	15,289 (18)	**moderate** [1] ⊕⊕⊕⊖
	70 per 1,000	8 fewer per 1,000 (1 to 15 fewer)			
	CKD patients (GFR 15 to 60 mL/min/1.73 m^2)		RR 0.85 (0.74 to 0.99)	11,912 (11)	**moderate** [1] ⊕⊕⊕⊖
	85 per 1,000	13 fewer per 1,000 (1 to 22 fewer)			
	HD patients		RR 0.83 (0.49 to 1.41)	2929 (6)	**moderate** [1] ⊕⊕⊕⊖
	20 per 1,000	3 fewer per 1,000 (10 fewer to 8 more)			
Fatal or nonfatal stroke Follow-up: 3 to 61.2 months (median 12 months)	All patients (predialysis, dialysis, transplant recipients)		RR 1.01 (0.64 to 1.59)	10,382 (12)	**very low** [1,2,3] ⊕⊖⊖⊖
	20 per 1,000	0 per 1,000 (7 fewer to 12 more)			
	CKD patients (GFR 15 to 60 mL/min/1.73 m^2)		RR 1.06 (0.64 to 1.74)	7062 (5)	**very low** [1,2,3] ⊕⊖⊖⊖
	25 per 1,000	2 more per 1,000 (9 fewer to 19 more)			

	HD patients		RR 0.62 (0.15 to 2.60)	2872 (6)	**very low** [1,2,3] ⊕⊖⊖⊖
	10 per 1,000	4 fewer per 1,000 (8 fewer to 16 more)			
Death (any cause) Follow-up: 0.9 to 88.2 months (median 12 months)	All patients (predialysis, dialysis, transplant recipients)		RR 0.94 (0.84 to 1.06)	18,241 (35)	**low** [1,2] ⊕⊕⊖⊖
	74 per 1,000	4 fewer per 1,000 (12 fewer to 4 more)			
	CKD patients (GFR 15 to 60 mL/min/1.73 m^2)		RR 0.97 (0.81 to 1.16)	13,234 (19)	**low** [1,2] ⊕⊕⊖⊖
	72 per 1,000	2 fewer per 1,000 (14 fewer to 12 more)			
	HD patients		RR 0.86 (0.72 to 1.03)	4523 (14)	**low** [1,2] ⊕⊕⊖⊖
	87 per 1,000	12 fewer per 1,000 (24 fewer to 3 more)			
Cardiovascular death Follow-up: 0.9 to 88.2 months (median 12 months)	All patients (predialysis, dialysis, transplant recipients)		RR 0.87 (0.65 to 1.15)	9606 (21)	**very low** [1,2,3] ⊕⊖⊖⊖
	36 per 1,000	5 fewer per 1,000 (13 fewer to 5 more)			
	CKD patients (GFR 15 to 60 mL/min/1.73 m^2)		RR 0.98 (0.60 to 1.59)	6525 (10)	**very low** [1,2,3] ⊕⊖⊖⊖
	37 per 1,000	1 fewer per 1,000 (15 fewer to 22 more)			
	HD patients		RR 0.71 (0.47 to 1.09)	2597 (9)	**very low** [1,2,3] ⊕⊖⊖⊖
	38 per 1,000	11 fewer per 1,000 (20 fewer to 3 more)			
Major bleeding Follow-up: 0.7 to 61.2 months (median 6 months)	All patients (predialysis, dialysis, transplant recipients)		RR 1.35 (1.10 to 1.65)	16,194 (29)	**moderate** [1] ⊕⊕⊕⊖
	29 per 1,000	10 more per 1,000 (3 to 19 more)			
	CKD patients (GFR 15 to 60 mL/min/1.73 m^2)		RR 1.51 (1.15 to 1.98)	11591 (12)	**moderate** [1] ⊕⊕⊕⊖
	35 per 1,000	18 more per 1,000			

		(5 to 34 more)			
	HD patients		RR 0.90 (0.53 to 1.55)	4119 (15)	**moderate** [1] ⊕⊕⊕⊖
	13 per 1,000	1 fewer per 1,000 (6 fewer to 7 more)			
Minor bleeding Follow-up: 0.5 to 84 months (median 6 months)	All patients (predialysis, dialysis, transplant recipients)		RR 1.55 (1.27 to 1.90)	13,218 (21)	**low** [1,3] ⊕⊕⊖⊖
	92 per 1,000	51 more per 1,000 (25 to 83 more)			
	CKD patients (GFR 15 to 60 mL/min/1.73 m^2)		RR 1.48 (1.20 to 1.83)	11,530 (12)	**low** [1,3] ⊕⊕⊖⊖
	103 per 1,000	50 more per 1,000 (21 to 86 more)			
	HD patients		RR 1.87 (0.65 to 5.40)	1240 (8)	**low** [1,3] ⊕⊕⊖⊖
	8 per 1,000	7 per 1,000 (3 fewer to 35 more)			
Early access thrombosis (before 8 weeks) Follow-up: 0.9 to 12 months (median 1.4 months)	HD patients		RR 0.52 (0.38 to 0.70)	1525 (8)	**low** [1,4] ⊕⊕⊖⊖
	200 per 1,000	6 fewer per 1,000 (60 to 124 fewer)			

*__The risk in the intervention group__ (and its 95% CI is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **CKD:** chronic kidney disease; **GFR:** glomerular filtration rate; **HD:** haemodialysis; **OIS:** Optimal Information Size

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Evidence certainty was downgraded by one level due to study limitations. Some or all studies were not blinded (participants and/or investigators)
[2] Evidence certainty was downgraded by one level due to imprecision
[3] Evidence certainty was downgraded by one level due to moderate between-study heterogeneity

[4] Evidence certainty was downgraded by one level due to imprecision (OIS criteria)

BACKGROUND

Description of the condition

Cardiovascular disease is the leading cause of morbidity and death among people at all stages of chronic kidney disease (CKD) (Casas 2005; Keith 2004; Mann 2001; Norris 2006; Sarnak 2003; Weiner 2004a; Weiner 2004b) including kidney transplant recipients (Aakhus 1999; ANZDATA 2019; Kasiske 2000; Ojo 2000; USRDS 2010). Compared with the general population, the risk of cardiovascular disease is increased two-fold in people with the early stages of CKD (Go 2004) and 30- to 50-fold in people who need dialysis (de Jager 2009; Fort 2005) in whom it accounts for half of all deaths (Collins 2003). Population representative surveys in Australia (AusDiab 2003) and the USA (NHANES 2010) have shown that CKD (defined as proteinuria or reduction of glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2) affects approximately 16% of the adult population. With the increasing prevalence of some of the known risk factors for CKD, including hypertension, obesity and diabetes (Fields 2004; Koren-Morag 2006; Mokdad 2003), the burden of CKD and its complications are projected to increase and to contribute significantly to global healthcare expenditure.

Description of the intervention

Excessive platelet activation occurs in CKD, even in the early stages of the disease. Specifically, the expression of P-selectin, glycoprotein 53 and activated fibrinogen receptor-1 on the platelet surface membrane is significantly increased in CKD patients. In ESRD, these abnormalities are more pronounced and may lead to access site thrombosis. Platelet activation is heavily implicated in the prothrombotic state observed in CKD patients, and oral antiplatelet agents have been extensively used in these patients (Alexopoulos 2011).

Dipyridamole is a phosphodiesterase inhibitor that reversibly inhibits platelet activation and aggregation by increasing adenosine levels and inhibiting cAMP-phosphodiesterase (Hung 2014).

The antithrombotic action of aspirin is due to inhibition of platelet function by acetylation of the platelet cyclooxygenase (COX) at the functionally important amino acid $serine_{529}$. This prevents the access of the arachidonic acid to the catalytic site of the enzyme at $tyrosine_{385}$ and results in irreversible inhibition of platelet-dependent thromboxane formation (Schror 1997).

$P2Y_{12}$ is a G-protein–coupled receptor that elicits specific intracellular responses to ADP resulting in the activation of the glycoprotein IIb/IIIa receptor. Active metabolites of thienopyridines (ticlopidine and clopidogrel) irreversibly bind to the ADP binding site and thereby prevent intracellular signalling and ADP-induced platelet aggregation. $P2Y_{12}$ antagonists, such as ticagrelor and prasugrel, inhibit adenosine reuptake in erythrocytes and other cells. The latter effect has been attributed to improved platelet inhibition and coronary blood flow and reduced infarct size (Gurbel 2019). Cilostazol, a selective reversible phosphodiesterase type III inhibitor, has antiplatelet effects due to subsequent increases in cyclic adenosine monophosphate within platelets. The potential to achieve platelet inhibition with minimal risk of bleeding might be explained by an endothelium-targeted antithrombotic therapy, that is, reduction of partially activated platelets by improved endothelial function (Woo 2011).

Glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide and tirofiban) administered parenterally interfere with platelet activity at the final common pathway of platelet-induced thrombosis, showing a much greater antiplatelet activity than aspirin with or without clopidogrel at normal doses. In addition to preventing platelet aggregation, GP IIb/IIIa antagonism has the ability to induce the dissolution of platelet-rich clots by disrupting fibrinogen platelet interaction (Stangal 2010).

Sulfinpyrazone appears to interfere with the adhesion of platelets to subendothelial structures and atherosclerotic plaques (Oelz 1979).

How the intervention might work

Antiplatelet agents prevent arterial occlusion from thrombus via direct prevention of platelet aggregation. Currently available data suggest antiplatelet agents might be beneficial in patients with CKD for primary (ATT 2002; HOT 1993; Ruilope 2001) and secondary (Berger 2003; McCullough 2002) prevention of cardiovascular events. Antiplatelet agents may have beneficial effects on the kidney, possibly reducing proteinuria and protecting kidney function in people with glomerulonephritis (Taji 2006; Zäuner 1994), and improving graft function in kidney transplant recipients (Bonomini 1986; Frascà 1986). However, some have reported that the efficacy of antiplatelet agents in CKD might be lower than for other high cardiovascular risk populations (Best 2008). Despite this, the Kidney Disease Outcomes Quality Initiative guideline program (KDOQI) has supported the use of aspirin for the primary prevention of cardiovascular disease in CKD. Antiplatelet agents appear to have a modest effect on the preservation of arteriovenous fistula patency (Dember 2005). Their use for fistula preservation and as part of a multifactorial intervention strategy for patients with CKD is advocated by guideline groups (CARI 2000; UK Renal Association 2010).

Why it is important to do this review

The previous meta-analyses did not clearly assess the benefits and harms of antiplatelet agents in people with CKD, including those undergoing dialysis (haemodialysis (HD) and peritoneal dialysis (PD)) and transplant recipients, and recently new studies have been performed in this area in contrast to the general population, people with CKD have a different profile of causes for major cardiovascular events, including a greater preponderance for arrhythmia and congestive heart failure (Amann 2003; Curtis 2005; Dikow 2005; Foley 1995; Remppis 2008), altered pharmacokinetics (Mosenkis 2004; Scheen 2008) and impaired haemostasis (Kaw 2006; Remuzzi 1988; Wattanakit 2008; Zwaginga 1991). Compared with people who do not have CKD, these factors might expose the CKD population to a different spectrum of risk and benefit from antiplatelet agents.

OBJECTIVES

To evaluate the benefits and harms of antiplatelet agents in people with any form of CKD, including those with CKD not receiving kidney replacement therapy, patients receiving any form of dialysis, and kidney transplant recipients.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) of antiplatelet agents in people with CKD were included.

Types of participants

Participants with CKD, including those who needed kidney replacement therapy (dialysis), had a functioning kidney transplant, or whose kidney function was impaired (defined as a reduced GFR < 60 mL/min/1.73 m^2), the presence of other markers of kidney damage such as proteinuria (KDOQI stages 1 to 5), or an elevated serum creatinine (SCr) level (SCr >120 µmol/L). Data from subgroups of participants with CKD within studies with broader inclusion criteria (e.g. people from the general population, people with diabetes, people with cardiovascular disease) were also included.

Types of interventions

Interventions included any antiplatelet agent. Agents could be administered at any dose or route of administration and compared with placebo, no treatment, different dose of the same or different antiplatelet agents, different administration regimens of the same or a different antiplatelet agent, or different combinations of antiplatelet agents. Antiplatelet agents included, but were not limited to:

- Acetylsalicylic acid (aspirin)
- Adenosine reuptake inhibitors (dipyridamole)
- Adenosine diphosphate receptor inhibitors (ticlopidine and clopidogrel)
- Phosphodiesterase 3 inhibitors (cilostazol)
- $P2Y_{12}$ antagonists (prasugrel, ticagrelor, cangrelor, elinogrel)
- Glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban, defibrotide)
- Sulphinpyrazone.

We excluded studies comparing antiplatelet agents to anticoagulants.

Types of outcome measures

Primary outcomes

- Myocardial infarction (MI) (nonfatal or fatal)
- Stroke (nonfatal or fatal)
- Death (any cause)
- Cardiovascular death
- Bleeding-related death
- Major bleeding
- Minor bleeding
- Haemorrhagic stroke
- Kidney failure (previously referred to as end-stage kidney disease (ESKD))
- Kidney transplant graft loss
- Transplant rejection
- Dialysis vascular outcomes (failure, early thrombosis, loss of unassisted patency, failure to attain suitability for dialysis, and need for access intervention)
- Hospitalisation
- Treatment withdrawal.

Secondary outcomes

- SCr
- Proteinuria.

Search methods for identification of studies

A systematic and comprehensive literature search was carried out to identify eligible RCTs. There was no language restriction.

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 13 July 2021 through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Searches of kidney and transplant journals, and the proceedings and abstracts from major kidney and transplant conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available on the Cochrane Kidney and Transplant website.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Contacting relevant individuals/organisations seeking information about unpublished or incomplete studies.
3. Grey literature sources (e.g. abstracts, dissertations and theses), in addition to those already included in the Cochrane Kidney and Transplant Register of Studies, were searched.

Data collection and analysis

Selection of studies

All RCTs enrolling participants with CKD were considered as well as studies in broader populations in which outcome data for subgroups with CKD could be disaggregated. Based on the search strategy described, we identified titles and abstracts that were potentially relevant to this systematic review. Four independent authors screened the titles and abstracts and selected those that met the inclusion criteria. Discrepancies in selection were resolved

by discussion or by the review of an experienced arbitrator. Studies reported in non-English language journals were translated before assessment.

Data extraction and management

Four authors independently read the full text of extracted articles and included studies that met the inclusion criteria. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data was used in the analyses.

The same independent authors used standardised data forms to extract data on:

- Study design
- Participants: baseline characteristics including age, sex, race, diabetic status (proportion with diabetes), hypertension status (proportion with hypertension), smoking status (proportion of smokers), visceral obesity (proportion with visceral obesity as defined by authors), previous cardiovascular events (proportion with existing cardiovascular disease), and stage of CKD (dialysis, predialysis, transplant)
- Interventions and comparisons: antiplatelet agent, dose and route of administration, duration of treatment
- Outcomes: as listed in Types of outcome measures.

Assessment of risk of bias in included studies

The following items were assessed independently by two authors using the risk of bias assessment tool (Higgins 2020) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

Measures of treatment effect

For dichotomous outcomes (e.g. such as death, cardiovascular events), results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (e.g. creatinine clearance (CrCl), GFR, SCr, proteinuria), the mean difference (MD) and its 95% CI was used. The final results are presented in International System (SI) units. When crude event data were not reported by investigators, available reported risk estimates and their 95% CIs were included in meta-analyses.

Unit of analysis issues

The unit of analysis was each participant recruited into the studies.

For cross-over studies, we looked for reporting of paired data in order to estimate within-user differences. Where no such data were provided, we used data from the first period only in the absence of washout periods to avoid the carry-over effect.

For studies with more than two arms, we treated each pair of arms as a separate pairwise comparison.

Dealing with missing data

Where possible, data for each outcome of interest were evaluated, regardless of whether the analysis was based on intention-to-treat. In particular, dropout rates were investigated and reported in detail, including dropout due to discontinuation of study drug, treatment failure, death, withdrawal of consent, or loss to follow-up. Corresponding authors of all large studies with broader inclusion were contacted to obtain data for the subgroup of CKD (Higgins 2020).

Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot. We then quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values was as follows:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a confidence interval for I^2) (Higgins 2020).

Assessment of reporting biases

We evaluated asymmetries in the inverted funnel plots (i.e. for systematic differences in the effect sizes between more precise and less precise studies). There are many potential explanations for why an inverted funnel plot may be asymmetric, including chance, heterogeneity, publication and reporting bias (Higgins 2020). Insufficient data were available to evaluate the robustness of the results according to publication, namely, publication as a full manuscript in a peer-reviewed journal versus studies published as abstracts/text/letters/editorials and publication.

Data synthesis

Data were pooled using the random-effects model. The GRADE approach developed by Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE Working Group) was used for evaluating the quality of evidence for outcomes to be reported. Based on the GRADE approach, the quality of a body of evidence, in terms of the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest, was defined.

Subgroup analysis and investigation of heterogeneity

Heterogeneity was explored using subgroup analyses according to the following parameters (where sufficient numbers of studies were available):

- Population characteristics
  - Stage of CKD (pre-dialysis, dialysis, transplant)
  - Presence or absence of comorbidities (diabetes, hypertension, dyslipidaemia, smoking, obesity, family history of cardiovascular disease, baseline cardiovascular disease); percentage of patients with these comorbidities in each study
  - Age
  - Sex
  - Mean systolic blood pressure (SBP) (< 140 mm Hg versus ≥ 140 mm Hg)
  - Ethnicity (proportion white)
  - Presence or absence of previous cardiovascular events (e.g. primary versus secondary prevention)
  - Time on dialysis (< 3 years versus ≥ 3 years) and modalities of dialysis (HD versus PD)
  - Time with a functioning transplant (< 3 years versus ≥ 3 years)
- Intervention characteristics
  - Types, doses and route of administration of the antiplatelet agents
  - Duration of intervention (< 6 months, 6 to 12 months, > 12 months).

Sensitivity analysis

Sensitivity analyses were undertaken to explore the robustness of findings to key decisions in the review process. We assessed the risks of death (any cause and cardiovascular death), nonfatal and fatal MI, and major bleeding only including studies with adequate allocation concealment, or at low risk of bias due to completeness of follow-up. Insufficient data were available to perform indirect comparisons of antiplatelet agent versus antiplatelet agent (Song 2003).

Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2020a). The 'Summary of findings' tables also includes an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011a). The GRADE approach defines the quality of a body of evidence as to the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, the precision of effect estimates, and the risk of publication bias (Schunemann 2020b). We presented the following outcomes in the 'Summary of findings' tables:

- MI (fatal or nonfatal)
- Stroke (fatal or nonfatal)
- Death (any cause)
- Cardiovascular death
- Major bleeding
- Minor bleeding
- Early access thrombosis

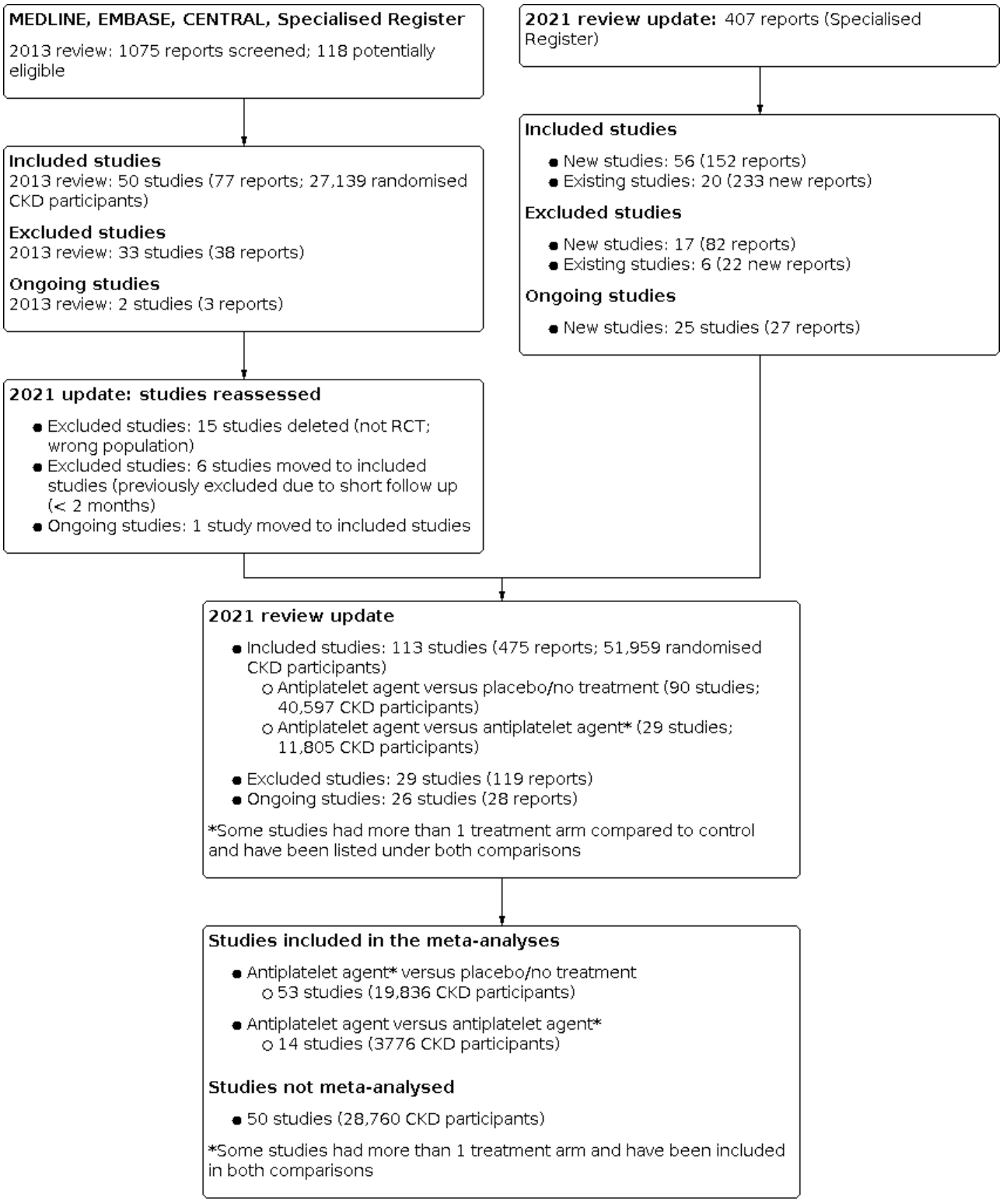
RESULTS

Description of studies

Results of the search

Search results are shown in Figure 1. For this 2021 review update, we screened 407 titles and abstracts identified by the updated search. After full-text assessment 98 new studies were identified. Fifty-six new studies (152 reports) were included, 17 (82 reports) were excluded, and 25 ongoing studies were identified. We also identified 233 new reports of 20 existing included studies and 22 new reports of six excluded studies.

Figure 1. Study flow diagram; study identification and selection process.



We reclassified six previously excluded studies as included studies (Dmoszynska-Giannopoulou 1990; Kamper 1997; Movchan 2001; RESIST 2008; Rubin 1982; Salter 1984), and one ongoing study has now been included (FAVOURED 2009).

For this 2011 update, 113 studies (475 reports, 51,959 CKD participants, Figure 1) were included, 29 studies were excluded, and there are 26 ongoing studies.

Included studies

The overall characteristics of the included studies are provided in the Characteristics of included studies. Information for three studies (1238 participants: Creek 1990; Ell 1982; Middleton 1992) including two internal study reports (Creek 1990; Middleton 1992) were only available in a previously published meta-analysis of antiplatelet agents (ATT 2002). For three studies (103 participants), the most complete data were provided in published conference proceedings (Dodd 1980; Gonzalez 1995; Taber 1992), and for one study (NCT01252056), information about study characteristics and endpoint data was extracted from www.clinicaltrials.gov.

Studies compared antiplatelet agents with placebo or no treatment, or another antiplatelet agent; several studies compared two or more antiplatelet agents.

- Ninety studies (40,597 CKD participants) compared an antiplatelet agent to placebo or no treatment (AASER 2017; Abacilar 2015; Abdul-Rahman 2007; Anderson 1974; Andrassy 1974; ATACAS 2008; CASSIOPEIR 2014; Chan 1987; CHANCE 2013; CHARISMA 2006; Cheng 1998a; Christopher 1987; CREDO 2005; Creek 1990; CURE 2000; Dember 2005; Dixon 2005; Dmoszynska-Giannopoulou 1990; Dodd 1980; Donadio 1984; EARLY ACS 2005; Ell 1982; EPIC 1994; EPILOG 1997; EPISTENT 1998; ETDRS 1992; FAVOURED 2009; Fiskerstrand 1985; Frascà 1997; Gaede 2003; Ghorbani 2009; Ghorbani 2013; Giustina 1998; GLOBAL LEADERS 2018; Goicoechea 2012; Gonzalez 1995; Gröntoft 1985; Gröntoft 1998; Guo 1998; Hansen 2000; Harter 1979; HOT 1993; IMPACT II 1997; Jiao 2013; JPAD 2008; Kaegi 1974; Kamper 1997; Kaufman 2003; Khajehdehi 2002; Kobayashi 1980; Kontessis 1993; Kooistra 1994; Koyama 1990; Michie 1977; Middleton 1992; Milutinovic 1993; Movchan 2001; Mozafar 2013; Mozafar 2018; Nakamura 2001d; Nakamura 2002b; NCT01252056; Nyberg 1984; PEGASUS-TIMI 54 2014; Pierucci 1989; PLATO 2009; PREDIAN 2011; PRISM-PLUS 1998; PURSUIT 1997; Quarto Di Palo 1991; RAPPORT 1998; Reams 1985; RESIST 2008; Rouzrokh 2010; Rubin 1982; Salter 1984; Schulze 1990; Sreedhara 1994; Steiness 2018; STOP 1995; Storck 1996; Taber 1992; Tang 2014; Tayebi 2018; TRA 2P-TIMI 50 2009; TRACER 2013; UK-HARP-I 2005; Watanabe 2011b; Weseley 1982; Yuto 2012; Zäuner 1994)
- Twenty-nine studies (11,805 CKD participants) compared an antiplatelet agent to a second antiplatelet agent (Alexopoulos 2011; CASSIOPEIR 2014; CILON-T 2010; Dash 2013; EUCLID 2017; Frascà 1986; Hidaka 2013; J-PADD 2014; Kauffmann 1980; Khajehdehi 2002; Liang 2015; Movchan 2001; Ogawa 2008; OPT-CKD 2018; Ota 1996; PIANO-2 CKD 2011; PIANO-3 2015; PIANO-6 2017; PLATO 2009; RESIST 2008; Schnepp 2000; Sreedhara 1994; Taber 1992; TARGET 2000; Teng 2018; TRITON-TIMI 38 2006; Waseda 2016; Xydakis 2004; Yang 2016b).

Antiplatelet versus placebo or no treatment studies

Ninety studies comparing an antiplatelet to placebo or no treatment were published between 1974 and 2018. The number of CKD participants ranged from 6 to 4983 participants (median 85 participants) and the mean age of the participants ranged from 29 to 73.4 years. The duration of study follow-up ranged from 48 hours to 88.2 months (median six months).

- Forty-nine studies were conducted in people with CKD not yet requiring dialysis (37,013 participants: AASER 2017; ATACAS 2008; CASSIOPEIR 2014; Chan 1987; CHANCE 2013; CHARISMA 2006; Cheng 1998a; Christopher 1987; CREDO 2005; CURE 2000; Donadio 1984; EARLY ACS 2005; EPIC 1994; EPILOG 1997; EPISTENT 1998; ETDRS 1992; Frascà 1997; Gaede 2003; Giustina 1998; GLOBAL LEADERS 2018; Goicoechea 2012; Gonzalez 1995; Guo 1998; Hansen 2000; HOT 1993; IMPACT II 1997; Jiao 2013; JPAD 2008; Khajehdehi 2002; Kontessis 1993; Koyama 1990; Movchan 2001; Nakamura 2001d; NCT01252056; Nyberg 1984; PEGASUS-TIMI 54 2014; Pierucci 1989; PREDIAN 2011; PRISM-PLUS 1998; PURSUIT 1997; RAPPORT 1998; RESIST 2008; Steiness 2018 Tang 2014; TRA 2P-TIMI 50 2009; TRACER 2013; Watanabe 2011b; Zäuner 1994).
- Thirty-two studies enrolled HD patients (5097 participants: Abacilar 2015; Abdul-Rahman 2007; Andrassy 1974; Creek 1990; Dember 2005; Dixon 2005; Dmoszynska-Giannopoulou 1990; Dodd 1980; Ell 1982; Fiskerstrand 1985; Ghorbani 2009; Ghorbani 2013; Gröntoft 1985; Harter 1979; Kaegi 1974; Kamper 1997; Kaufman 2003; Kobayashi 1980; Kooistra 1994; Michie 1977; Middleton 1992; Milutinovic 1993; Mozafar 2013; Mozafar 2018; Nakamura 2002b; Rouzrokh 2010; Salter 1984; Sreedhara 1994; STOP 1995; Taber 1992; Tayebi 2018; Yuto 2012).
- Three studies were in patients treated with PD (40 participants: Reams 1985; Rubin 1982; Weseley 1982).
- Four studies enrolled kidney transplant recipients (141 participants: Anderson 1974; Quarto Di Palo 1991; Schulze 1990; Storck 1996).
- Two studies enrolled participants with earlier stages of CKD and those treated with HD (673 participants: FAVOURED 2009; Gröntoft 1998)
- In one study (UK-HARP-I 2005; 448 participants), participants included those with earlier stages of CKD, transplant recipients and participants treated with dialysis (both HD and PD).

In the 90 studies that compared an antiplatelet agent with placebo or no treatment, the interventions included:

- Acetylsalicylic acid
  - Aspirin (16 studies, 6140 participants: AASER 2017; Abdul-Rahman 2007; Andrassy 1974; ATACAS 2008; ETDRS 1992; FAVOURED 2009; Gaede 2003; Guo 1998; Hansen 2000; Harter 1979; HOT 1993; JPAD 2008; Kooistra 1994; Mozafar 2013; Storck 1996; UK-HARP-I 2005)
  - Aspirin plus dextran (1 study, 45 participants; Taber 1992)
- Adenosine reuptake inhibitors
  - Dilazep dihydrochloride (2 studies, 62 participants: Nakamura 2001d; Nakamura 2002b)
  - Dipyridamole (7 studies, 615 participants: Anderson 1974; Koyama 1990; Movchan 2001; Reams 1985; Rubin 1982; Schulze 1990; Weseley 1982)
  - Dipyridamole plus aspirin (11 studies, 2004 participants: Chan 1987; Christopher 1987; Dixon 2005; Donadio 1984; Gonzalez 1995; Khajehdehi 2002; Middleton 1992; Salter 1984; Sreedhara 1994; Tayebi 2018; Zäuner 1994)
  - Dypiridamole or aspirin (1 study, 501 participants: Rouzrokh 2010)
- Adenosine diphosphate receptor inhibitors
  - Clopidogrel (7 studies, 7931 participants: CHANCE 2013; CHARISMA 2006; CREDO 2005; CURE 2000; Dember 2005; Ghorbani 2009; Mozafar 2018)

- Clopidogrel and aspirin (1 study, 200 participants: Kaufman 2003)
- Clopidogrel and prostacyclin (1 study, 96 participants: Abacilar 2015)
- Ticlopidine (12 studies, 986 participants: Cheng 1998a; Creek 1990; Dodd 1980; Ell 1982; Fiskerstrand 1985; Ghorbani 2013; Gröntoft 1985; Gröntoft 1998; Kamper 1997; Kobayashi 1980; Milutinovic 1993; Nyberg 1984)

- Haemorrhagic agents
  - Pentoxifylline (2 studies, 260 participants: Goicoechea 2012; PREDIAN 2011)
- PAR-1 antagonist
  - Vorapaxar (1 study, 4983 participants: TRA 2P-TIMI 50 2009)
- Phosphodiesterase 3 inhibitors
  - Cilostazol (3 studies, 483 participants: Jiao 2013; NCT01252056; Tang 2014)
  - Beraprost sodium (1 study, 892 participants: CASSIOPEIR 2014)
- $P2Y_{12}$ antagonists
  - Ticagrelor (1 study, 4849 participants: PEGASUS-TIMI 54 2014)
  - Ticagrelor plus aspirin then ticagrelor alone (1 study, 838 participants: GLOBAL LEADERS 2018)
- Glycoprotein IIb/IIIa inhibitors
  - Abciximab (5 studies, 1537 participants: EPIC 1994; EPILOG 1997; EPISTENT 1998; RAPPORT 1998; RESIST 2008)
  - Tirofiban (1 study, 611 participants: PRISM-PLUS 1998)
  - Eptifibatide (3 studies, 5065 participants: EARLY ACS 2005; IMPACT II 1997; PURSUIT 1997)
- Other
  - Defibrotide (1 study, 20 participants: Frascà 1997)
  - Picotamide (3 studies, 901 participants: Giustina 1998; Quarto Di Palo 1991; STOP 1995)
  - Sarpogrelate (2 studies, 132 participants: Watanabe 2011b; Yuto 2012)
  - Sulphinpyrazone (3 studies, 108 participants: Dmoszynska-Giannopoulou 1990; Kaegi 1974; Michie 1977)
  - Sulphonamide derivative (1 study, 6 participants: Pierucci 1989)
  - Thromboxane synthetase inhibitor (1 study, 15 participants: Kontessis 1993)
  - SER150 (novel anti-thromboxane) (1 study, 72 participants: Steiness 2018)
  - Vorapaxar (1 study, 1477 participants: TRACER 2013)

Vascular access studies

We identified 31 studies that reported dialysis vascular access endpoints in 6449 participants (Abacilar 2015; Abdul-Rahman 2007; Anderson 1974; Andrassy 1974; Creek 1990; Dember 2005; Dixon 2005; Dodd 1980; Ell 1982; FAVOURED 2009; Fiskerstrand 1985; Ghorbani 2009; Ghorbani 2013; Gröntoft 1985; Gröntoft 1998; Harter 1979; Kaegi 1974; Kaufman 2003; Kobayashi 1980; Kooistra 1994; Michie 1977; Middleton 1992; Milutinovic 1993; Mozafar 2013; Mozafar 2018; Rouzrokh 2010; Sreedhara 1994; STOP 1995; Taber 1992; Tayebi 2018; Yuto 2012). Generally, these studies were small; only five studies included more than 500 participants (Dember 2005; Dixon 2005; Middleton 1992; Rouzrokh 2010; STOP 1995), and sixteen studies enrolled fewer than 100 participants (Abacilar 2015; Abdul-Rahman 2007; Anderson 1974; Andrassy 1974; Ell 1982; Fiskerstrand 1985; Ghorbani 2009; Ghorbani 2013; Gröntoft 1985; Harter 1979; Kaegi 1974; Michie 1977; Milutinovic 1993; Taber 1992; Tayebi 2018 Yuto 2012).

Ticlopidine was most the commonly administered (9 studies, 884 participants: Creek 1990; Dodd 1980; Ell 1982; Fiskerstrand 1985; Ghorbani 2013; Gröntoft 1985; Gröntoft 1998; Kobayashi 1980; Milutinovic 1993), followed by aspirin (6 studies, 917 participants: Abdul-Rahman 2007; Andrassy 1974; FAVOURED 2009; Harter 1979; Kooistra 1994; Mozafar 2013). The combination of dipyridamole and aspirin was prescribed to 1720 participants in four studies (Dixon 2005; Middleton 1992; Sreedhara 1994; Tayebi 2018), three studies evaluated clopidogrel (1070 participants: Dember 2005; Ghorbani 2009; Mozafar 2018), two studies evaluated sulphinpyrazone (78 participants: Kaegi 1974; Michie 1977), and single studies assessed dipyridamole (27 participants: Anderson 1974), picotamide (832 participants: STOP 1995) and sarpogrelate (79 participants: Yuto 2012). One study each assessed the combination of clopidogrel and aspirin (200 participants: Kaufman 2003), the combination of dextran and aspirin (45 participants: Taber 1992), the combination of clopidogrel and prostacyclin (96 participants: Abacilar 2015), and the combination of aspirin or dipyridamole (501 participants: Rouzrokh 2010). The duration of the intervention varied from one month to 61,2 months, with a median of five months.

Studies evaluated whether treatment maintained patency of an arteriovenous fistula (10 studies, 1765 participants: Abacilar 2015; Andrassy 1974; Dember 2005; Fiskerstrand 1985; Ghorbani 2009; Ghorbani 2013; Gröntoft 1985; Gröntoft 1998; Kooistra 1994; Yuto 2012), shunt or graft (5 studies, 1063 participants: Dixon 2005; Harter 1979; Kaegi 1974; Kaufman 2003; Sreedhara 1994), fistula or graft (1 study, 16 participants: Michie 1977), or central venous catheter (1 study, 58 participants: Abdul-Rahman 2007).

Antiplatelet versus antiplatelet studies

Thirty-four studies comparing an antiplatelet drug with a second antiplatelet drug in people with CKD were published between 1980 and 2018. The number of CKD participants ranged from 6 to 4983 participants (median 85 participants) and the mean age of participants ranged from 33 to 74.4 years. The duration of follow-up ranged from 2 days to 48 months (median four months).

- Twelve studies were conducted in people with CKD not yet requiring dialysis (10,958 participants: CASSIOPEIR 2014; CILON-T 2010; Dash 2013; EUCLID 2017; Khajehdehi 2002; Liang 2015; Movchan 2001; Ogawa 2008; OPT-CKD 2018; PLATO 2009; TARGET 2000; TRITON-TIMI 38 2006).
- Thirteen studies evaluated treatment in people on HD (786 participants: Alexopoulos 2011; Hidaka 2013; J-PADD 2014; Ota 1996; PIANO-2 CKD 2011; PIANO-3 2015; PIANO-6 2017; Schnepp 2000; Sreedhara 1994; Teng 2018: Waseda 2016; Xydakis 2004; Yang 2016b).
- Two studies enrolled kidney transplant recipients (122 participants: Frascà 1986; Kauffmann 1980).

In the studies that compared an antiplatelet with another antiplatelet, interventions included:

- Acetylsalicylic acid

- Aspirin versus clopidogrel (3 studies, 202 participants: Dash 2013; Xydakis 2004; Yang 2016b)
- Aspirin versus clopidogrel versus ticlopidine (1 study, 30 participants: Schnepp 2000)
- Aspirin versus sarpogrelate (1 study, 40 participants: Ogawa 2008)

- Adenosine reuptake inhibitors
  - Dypiridamole versus aspirin (2 studies, 97 participants: Kauffmann 1980; Sreedhara 1994)
  - Dypiridamole versus defibrotide (1 study, 80 participants: Frascà 1986)
  - Dypiridamole versus aspirin versus dypiridamole plus aspirin versus placebo (1 study, 76 participants: Khajehdehi 2002)
  - Dypiridamole versus pentoxifylline (1 study, 40 participants: Movchan 2001)
- Adenosine diphosphate receptor inhibitors
  - Clopidogrel versus cilostazol (1 study, 74 participants: PIANO-2 CKD 2011)
  - Clopidogrel plus cilostazol versus clopidogrel (1 study, 184 participants: CILON-T 2010)
  - Clopidogrel versus ticagrelor (2 studies, 3701 participants: EUCLID 2017; PIANO-6 2017)
  - Low-dose clopidogrel versus high-dose clopidogrel (1 study, 370 participants: Liang 2015)
  - Ticlopidine versus satigrel (1 study, 224 participants: Ota 1996)
- Phosphodiesterase 3 inhibitors
  - Cilostazol versus beraprost sodium (1 study, 72 participants: J-PADD 2014)
  - Cilostazol versus sarpogrelate (1 study, 35 participants: Hidaka 2013)
- $P2Y_{12}$ antagonists
  - Ticagrelor versus clopidogrel (3 studies, 3322 participants: OPT-CKD 2018; PIANO-3 2015; PLATO 2009)
  - Ticagrerol pre-dialysis versus ticagrelor post-dialysis (1 study, 14 participants: Teng 2018)
  - Prasugrel versus clopidogrel (3 studies, 1544 participants: Alexopoulos 2011; TRITON-TIMI 38 2006; Waseda 2016)
- Glycoprotein IIb/IIIa inhibitor
  - Abciximab versus tirofiban (1 study, 790 participants: TARGET 2000)
- Other
  - Low versus high-dose beraprost sodium (1 study, 600 participants: CASSIOPEIR 2014)

Excluded studies

For this update, we reassessed all previously excluded studies. We deleted 15 studies (not randomised or wrong population) and reclassified six studies as included studies; these were previously excluded due to less than two months of follow-up. For the 2021 search, we excluded 17 new studies (82 reports) and identified 22 new reports of 6 already excluded studies. In total, we have excluded 29 studies (119 reports).

- Three studies were the wrong study design (Caravaca 1995a; Yang 2014a; Yeh 2017)
- Eleven studies enrolled the wrong population (Bang 1994; EXCITE 2000; POISE-2 2013; PRODIGY 2010; RAS-CAD 2009; REPLACE-2 2003; SPS3 2018; TRILOGY ACS 2010; Woo 1987; Wu 2018a; Zimmerman 1983).
- Nine studies used the wrong intervention (Coli 2006; Foroughinia 2017; Lee 1997; NITER 2005; Perkovic 2004; STENO-2 1999; Swan 1995a; Yoshikawa 1999; Zhang 2009a)
- Six studies used the wrong comparator (AVERROES 2010; Changjiang 2015; Gorter 1998; Lindsay 1972; Sakai 1991; Zibari 1995).

See Characteristics of excluded studies.

Ongoing studies

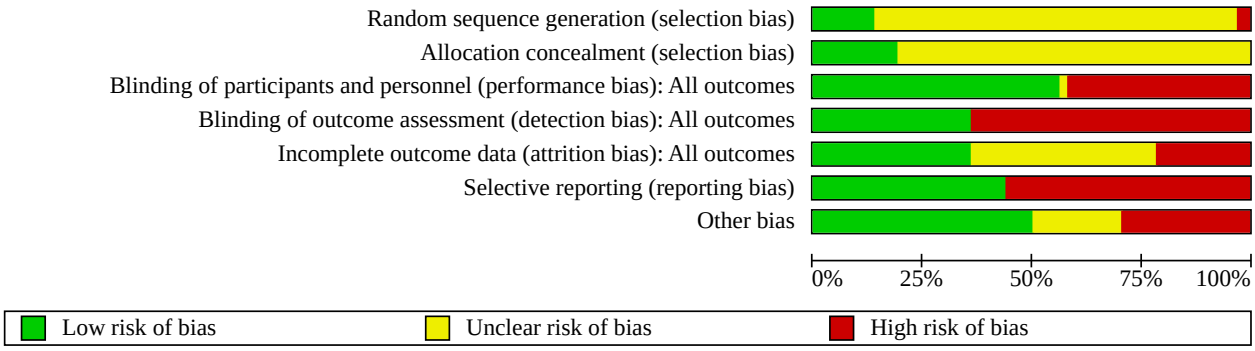
Twenty-six studies (27 reports) have yet to be completed (A-CLOSE 2019; ALTIC 2016; ALTIC-2 2018; ATTACK 2018; ChiCTR1900021393; IRCT2013012412256N1; IRCT2013100114333N8; IRCT20171023036953N1; LEDA 2017; Lemos Cerqueira 2018; NCT00272831; NCT01198379; NCT01743014; NCT02394145; NCT02459288; NCT03039205; NCT03150667; NCT03649711; Park 2010; PRASTO-III 2018; SERENADE 2015; SONATA 2013; TROUPER 2020; TWILIGHT 2016; UMIN000003891; VA PTXRx 2018).

See Characteristics of ongoing studies.

Risk of bias in included studies

The risk of bias in the included studies is summarised in Figure 2.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Allocation

Random sequence generation

Methods for generating the random sequence were deemed to be at low risk of bias in 16 studies (AASER 2017; Alexopoulos 2011; ATACAS 2008CASSIOPEIR 2014; CHANCE 2013; CREDO 2005; Dash 2013; EUCLID 2017; FAVOURED 2009; Goicoechea 2012; JPAD 2008; Mozafar 2018; PIANO-2 CKD 2011; PIANO-3 2015; PIANO-6 2017; UK-HARP-I 2005), at high risk of bias in three studies (Guo 1998; Kauffmann 1980; Rubin 1982), and unclear in 94 studies.

Allocation concealment

Allocation concealment was judged to be a low risk of bias in 22 studies (Anderson 1974; ATACAS 2008; CASSIOPEIR 2014; CHARISMA 2006; CURE 2000; Dixon 2005; EARLY ACS 2005; EPIC 1994; EPILOG 1997; EPISTENT 1998; EUCLID 2017; FAVOURED 2009; Ghorbani 2009; Ghorbani 2013; Giustina 1998; HOT 1993; Kaufman 2003; PEGASUS-TIMI 54 2014; PURSUIT 1997; TARGET 2000; TRA 2P-TIMI 50 2009; TRACER 2013), and unclear in 91 studies.

Blinding

Performance bias

Sixty-four studies were blinded and considered to be at low risk of bias for performance bias (Abacilar 2015; Abdul-Rahman 2007; Anderson 1974; Andrassy 1974; ATACAS 2008; CASSIOPEIR 2014; CHANCE 2013; CHARISMA 2006; Christopher 1987; CREDO 2005; CURE 2000; Dember 2005; Dixon 2005; Dodd 1980; Donadio 1984; EARLY ACS 2005; EPIC 1994; EPILOG 1997; EPISTENT 1998; ETDRS 1992; FAVOURED 2009; Fiskerstrand 1985; Gaede 2003; Ghorbani 2009; Ghorbani 2013; Giustina 1998; Gröntoft 1985; Gröntoft 1998; Guo 1998; Hansen 2000; Harter 1979; HOT 1993; IMPACT II 1997; Kaegi 1974; Kauffmann 1980; Kaufman 2003; Kobayashi 1980; Kontessis 1993; Kooistra 1994; Koyama 1990; Michie 1977; Milutinovic 1993; Mozafar 2013; Nyberg 1984; Ota 1996; PEGASUS-TIMI 54 2014; Pierucci 1989; PLATO 2009; PRISM-PLUS 1998; PURSUIT 1997; Quarto Di Palo 1991; RAPPORT 1998; Reams 1985; RESIST 2008; Rubin 1982; Salter 1984; Sreedhara 1994; STOP 1995; TARGET 2000; Tayebi 2018; TRA 2P-TIMI 50 2009; TRACER 2013; TRITON-TIMI 38 2006; Weseley 1982). One study was judged to have unclear risk of bias (EUCLID 2017) and 48 studies were not blinded and were considered at high risk of performance bias.

Detection bias

Blinding of outcome assessment was judged to be at low risk of bias for 41 studies (AASER 2017; ATACAS 2008; CASSIOPEIR 2014; Chan 1987; CHANCE 2013; Cheng 1998a; Christopher 1987; CILON-T 2010; CURE 2000; Dash 2013; EPIC 1994; EPILOG 1997; EPISTENT 1998; ETDRS 1992; EUCLID 2017; HOT 1993; IMPACT II 1997; Jiao 2013; JPAD 2008; Kontessis 1993; Koyama 1990; Movchan 2001; Nakamura 2001d; Nakamura 2002b; Ogawa 2008; PEGASUS-TIMI 54 2014; PIANO-2 CKD 2011; PREDIAN 2011; PRISM-PLUS 1998; PURSUIT 1997; RAPPORT 1998; Rubin 1982; Schnepp 2000; Storck 1996; TRA 2P-TIMI 50 2009; TRACER 2013; TRITON-TIMI 38 2006; Waseda 2016; Weseley 1982; Xydakis 2004; Zäuner 1994). Seventy-two studies were considered at high risk of detection bias.

Incomplete outcome data

Follow-up data was complete and judged to be at low risk of bias for 41 studies (AASER 2017; Abacilar 2015; Abdul-Rahman 2007; Alexopoulos 2011; Andrassy 1974; CASSIOPEIR 2014; CHARISMA 2006; CREDO 2005; CURE 2000; Dember 2005; Dixon 2005; EPIC 1994; EPILOG 1997; EPISTENT 1998; ETDRS 1992; Gaede 2003; Ghorbani 2013; Goicoechea 2012; Gröntoft 1998; Hansen 2000; Hidaka 2013: HOT 1993; JPAD 2008; Kamper 1997; Kaufman 2003; Khajehdehi 2002; Kobayashi 1980; Liang 2015; Nyberg 1984; OPT-CKD 2018; Ota 1996; PEGASUS-TIMI 54 2014; PLATO 2009; Quarto Di Palo 1991; RAPPORT 1998; Reams 1985; Storck 1996; Tang 2014; TRACER 2013; TRITON-TIMI 38 2006; Zäuner 1994), incomplete, and judged to be at high risk of bias for 24 studies (Chan 1987; Cheng 1998a; Dash 2013; Donadio 1984; EUCLID 2017; Fiskerstrand 1985; Frascà 1986; Ghorbani 2009; Giustina 1998; Gonzalez 1995; Gröntoft 1985; Harter 1979; J-PADD 2014; Kaegi 1974; Kooistra 1994; Michie 1977; PIANO-3 2015; PIANO-6 2017; Rouzrokh 2010; Sreedhara 1994; Steiness 2018; TRA 2P-TIMI 50 2009; UK-HARP-I 2005; Yang 2016b) and unclear in 48 studies.

Selective reporting

Fifty studies reported expected and clinically-relevant outcomes and were deemed to be at low risk of bias (AASER 2017; Abacilar 2015; Alexopoulos 2011; ATACAS 2008; CASSIOPEIR 2014; CHANCE 2013; CHARISMA 2006; CREDO 2005; Creek 1990; CURE 2000; Dember 2005; Dixon 2005; EARLY ACS 2005; Ell 1982; EPIC 1994; EPILOG 1997; EPISTENT 1998; ETDRS 1992; FAVOURED 2009; Frascà 1986; Ghorbani 2009; Ghorbani 2013; Gröntoft 1998; Harter 1979; HOT 1993; IMPACT II 1997; JPAD 2008; J-PADD 2014; Kaegi 1974;

Kaufman 2003; Kooistra 1994; Liang 2015; Michie 1977; Middleton 1992; Nyberg 1984; OPT-CKD 2018; Ota 1996; PEGASUS-TIMI 54 2014; PLATO 2009; PRISM-PLUS 1998; PURSUIT 1997; RAPPORT 1998; Sreedhara 1994; STOP 1995; TARGET 2000; TRA 2P-TIMI 50 2009; TRACER 2013; TRITON-TIMI 38 2006; UK-HARP-I 2005; Yang 2016b), and 63 studies did not report patient-centred outcomes of bleeding, cardiovascular events, adverse events, or death and were judged to be at high risk of bias.

Other potential sources of bias

Fifty-seven studies appeared to be free from other sources of bias (AASER 2017; Abacilar 2015; Abdul-Rahman 2007, Alexopoulos 2011; Anderson 1974; CASSIOPEIR 2014; Chan 1987; CHANCE 2013; CURE 2000; Dash 2013; Dixon 2005; EARLY ACS 2005; EPISTENT 1998; ETDRS 1992; Frascà 1986; Frascà 1997; Ghorbani 2009; Ghorbani 2013; Giustina 1998; Goicoechea 2012; Gröntoft 1985; Hansen 2000; Hidaka 2013; Jiao 2013; JPAD 2008; J-PADD 2014; Kaegi 1974; Kauffmann 1980; Khajehdehi 2002; Kobayashi 1980; Kontessis 1993; Kooistra 1994; Liang 2015; Michie 1977; Milutinovic 1993; Mozafar 2013; Mozafar 2018; Nakamura 2001d; Nakamura 2002b; Nyberg 1984; Ogawa 2008; PIANO-2 CKD 2011; PIANO-3 2015; PIANO-6 2017; Quarto Di Palo 1991; RESIST 2008; Rouzrokh 2010; Rubin 1982; Salter 1984; Schulze 1990; Storck 1996; Tang 2014; TARGET 2000; Tayebi 2018; TRITON-TIMI 38 2006; Yang 2016b; Zäuner 1994), 33 studies reported other sources of bias and were judged to be at high risk (Andrassy 1974; CHARISMA 2006; Cheng 1998a; CREDO 2005; Creek 1990; Dember 2005; Ell 1982; EPIC 1994; EPILOG 1997; FAVOURED 2009; Fiskerstrand 1985; Gaede 2003; GLOBAL LEADERS 2018; Gröntoft 1998; Guo 1998; Harter 1979; HOT 1993; IMPACT II 1997; Kamper 1997; Kaufman 2003; Middleton 1992; OPT-CKD 2018; PEGASUS-TIMI 54 2014; PLATO 2009; PRISM-PLUS 1998; PURSUIT 1997; RAPPORT 1998; Sreedhara 1994; STOP 1995; Teng 2018; TRA 2P-TIMI 50 2009; TRACER 2013; UK-HARP-I 2005), and risk of bias was judged to be unclear in 23 studies.

Effects of interventions

See: **Summary of findings 1** Antiplatelet agents versus control for chronic kidney disease

Antiplatelet agents versus control

Fatal or nonfatal myocardial infarction

Antiplatelet agents probably reduced the risk of fatal or nonfatal MI in people with CKD (Analysis 1.1 (18 studies, 15,289 participants): RR 0.88, 95% CI 0.79 to 0.99; I^2 = 0%; moderate certainty evidence). The evidence was downgraded for risk of bias.

Fatal or nonfatal stroke

It is uncertain whether antiplatelet agents made any difference to fatal or nonfatal stroke in people with CKD (Analysis 1.2 (12 studies, 10,382 participants): RR 1.01, 95% CI 0.64 to 1.59; I^2 = 37%; very low certainty evidence). The evidence was downgraded for risk of bias, inconsistency and imprecision. There was moderate heterogeneity observed between studies. Antiplatelet agents were used both for primary and secondary prevention.

Death (any cause)

Antiplatelet agents may have little or no effect on death (any cause) in people with CKD (Analysis 1.3 (35 studies, 18,241 participants): RR 0.94, 95% CI 0.84 to 1.06; I^2 = 14%; low certainty evidence). The evidence was downgraded for risk of bias and imprecision.

Haemorrhagic stroke

Antiplatelet agents had uncertain effects on haemorrhagic stroke in people with CKD (Analysis 1.4 (9 studies, 6844 participants): RR 1.22, 95% CI 0.69 to 2.17; I^2 = 0%; low certainty evidence). The evidence was downgraded for risk of bias and imprecision.

Cardiovascular death

It is uncertain whether antiplatelet agents made any difference to cardiovascular death in people with CKD (Analysis 1.5 (21 studies, 9606 participants): RR 0.87, 95% CI 0.65 to 1.15; I^2 = 32%; very low certainty evidence). The evidence was downgraded for risk of bias, imprecision, and inconsistency. There was moderate heterogeneity observed between studies.

Fatal bleeding

It is uncertain whether antiplatelet agents made any difference to fatal bleeding in people with CKD (Analysis 1.6 (21 studies, 7629 participants): RR 1.39, 95% CI 0.10 to 19.48; I^2 = 30%; very low certainty evidence). The evidence was downgraded for Risk of Bias, imprecision, and inconsistency. There was moderate heterogeneity observed between studies.

Major bleeding

Major bleeding events included: retroperitoneal; intra-articular; intra-ocular, intracranial or intracerebral haemorrhage; gastrointestinal bleeding; bleeding that was fatal, life-threatening, disabling or required transfusion; corrective surgery or hospitalisation, with or without a fall in haemoglobin (Hb) level of at least 2 g/dL; or melena.

Antiplatelet agents probably increased major bleeding in people CKD (Analysis 1.7 (29 studies, 16,194 participants): RR 1.35, 95% CI 1.10 to 1.65; I^2 = 12%; moderate certainty evidence). The evidence was downgraded for risk of bias.

Minor bleeding

Minor bleeding events were described as follows: not serious or significant; epistaxis; ecchymoses or bruising; blood loss and a drop of more than 10% points in the HCT or of 3 g/dL or more in the Hb concentration; not requiring transfusion; hospitalisation; and event-related study visit; bleeding from cannulation sites, or haematuria.

Antiplatelet agents may increase the risk of minor bleeding in people with CKD (Analysis 1.8 (21 studies, 13218 participants): RR 1.55, 95% CI 1.27 to 1.90; I^2 = 58%; low certainty evidence). The was heterogeneity was moderate. The evidence was downgraded for risk of bias and inconsistency.

Kidney failure (end-stage kidney disease)

Antiplatelet agents may have little or no effect on kidney failure (Analysis 1.9 (11 studies, 1722 participants): RR 0.89, 95% CI 0.70 to 1.14; I^2 = 23%; low certainty evidence). The evidence was downgraded for risk of bias and imprecision. There was low heterogeneity observed between the studies.

Doubling of serum creatinine

Antiplatelet agents may reduce doubling of SCr in people with CKD (Analysis 1.10 (3 studies, 217 participants): RR 0.39, 95% CI

0.17 to 0.86; I^2 = 0%; low certainty evidence). The evidence was downgraded for risk of bias and imprecision.

Kidney transplant graft loss

Antiplatelet agents had uncertain effects on kidney transplant graft loss (Analysis 1.11 (2 studies, 91 participants): RR 1.08, 95% CI 0.58 to 2.01; I^2 = 0%; low certainty evidence). The evidence was downgraded for risk of bias and imprecision.

Transplant rejection

Antiplatelet agents may have little or no effect on kidney transplant rejection (Analysis 1.12 (2 studies, 97 participants): RR 0.95, 95% CI 0.77 to 1.19; low certainty evidence). The evidence was downgraded for risk of bias and imprecision.

Creatinine clearance

It is uncertain whether antiplatelet agents made any difference to CrCl in people with CKD (Analysis 1.13 (3 studies, 90 participants): MD -5.46 mL/min, 95% CI -12.33 to 1.41; I^2 = 38%; very low certainty evidence). The evidence was downgraded for risk of bias, inconsistency and imprecision. There was moderate heterogeneity observed between studies.

Proteinuria

It is uncertain whether antiplatelet agents made any difference to proteinuria in people with CKD (Analysis 1.14 (3 studies, 80 participants): MD -0.74 g/day, 95% CI -1.35 to -0.13; very low certainty evidence) with substantial heterogeneity in the analysis (I^2 = 94%) which was as a result of Zäuner 1994; however, there was no difference in the direction of the effect when this study was removed from the meta-analysis (MD -0.14 g/day, 95% CI -0.20 to -0.08). The evidence was downgraded for risk of bias, inconsistency, and optimal information size not met.

Dialysis access failure (thrombosis or loss of patency)

For all access types, it is uncertain whether antiplatelet agents made any difference in reducing the risk of HD access failure (Analysis 1.15 (17 studies, 2847 participants): RR 0.62, 95% CI 0.50 to 0.78; I^2 = 46%; very low certainty evidence). The evidence was downgraded for risk of bias, indirectness, and inconsistency. There was moderate heterogeneity in this analysis which we explored using subgroup analysis by access type. In these analyses, it is uncertain whether antiplatelet agents (aspirin, sarpogrelate, ticlopidine, or clopidogrel with or without prostacyclin) made any difference in reducing the risk of fistula thrombosis or patency failure by 50% (Analysis 1.15.1 (10 studies, 1741 participants): RR 0.50, 95% CI 0.36 to 0.69; I^2 = 17%; very low certainty evidence), or shunt or graft failure (Analysis 1.15.2 (5 studies, 1052 participants): RR 0.80, 95% CI 0.62 to 1.03; I^2 = 49%; very low certainty evidence). It is uncertain whether antiplatelet agents made any difference to fistula or graft, or central venous catheter thrombosis (Analysis 1.15.3 (1 study, 16 participants): RR 0.50, 95% 0.06 to 4.47; very low certainty evidence) (Analysis 1.15.4 (1 study, 38 participants); 0.44, 95% CI 0.16 to 1.20; very low certainty evidence) respectively. Overall, there was no evidence of subgroup interaction based on access type across all types, suggesting the specific vascular access (fistula, graft, shunt, or central venous catheter) (P = 0.13%) was not an effect modifier for the treatment effects observed and indicating the overall effect estimate was the most appropriate.

Early access failure (within eight weeks of access creation)

Antiplatelet agents may reduce early dialysis vascular access thrombosis (Analysis 1.16 (8 studies, 1525 participants): RR 0.52, 95% CI 0.38 to 0.70; I^2= 8%; low certainty evidence). The evidence was downgraded for risk of bias and optimal information size not met.

Loss of primary unassisted patency

Two studies (Dixon 2005; Michie 1977) reported a loss of unassisted patency with Dixon 2005 providing 99% of the events. Antiplatelet agents may have little or no effect on reduction of loss of unassisted patency (Analysis 1.17 (2 studies, 665 participants): RR 0.95, 95% 0.89 to 1.03; I^2 = 0%; low certainty evidence). The evidence was downgraded for risk of bias and imprecision.

Failure to attain access suitability of dialysis (maturation)

The definitions of access suitability included: the ability to use the fistula for dialysis with two needles and maintain a blood flow rate ≥ 300 mL/min during eight of 12 dialysis sessions occurring during a 30 day suitability ascertainment period (Dember 2005); failure to use graft by week 12 in patients with a catheter for access (Dixon 2005); fistula ceased to function (Gröntoft 1985); permanent shunt thrombosis (Harter 1979); and failure to develop adequate flow (Michie 1977). It is uncertain whether antiplatelet agents made any difference in the reduction of failure to attain access suitability (Analysis 1.18 (5 studies, 1503 participants): RR 0.63, 95% CI 0.34 to 1.15; I^2 = 59%, very low certainty evidence). The evidence was downgraded for risk of bias, inconsistency and imprecision. There was moderate heterogeneity potentially due to the differences in definitions of access suitability.

Need for intervention to attain patency or assist maturation

The need for the intervention to attain patency or assist maturation was described: as surgical revision (FAVOURED 2009: Kaegi 1974); thrombectomy (Abacilar 2015; Michie 1977); percutaneous intervention to restore patency or promote maturation (Dember 2005); or angioplasty (Dixon 2005).

Antiplatelet agents may have little or no effect on the reduction of the risk for the need for the intervention to attain patency or assist maturation in people treated with HD (Analysis 1.19 (6 studies, 2067 participants): RR 0.87, 95% CI 0.72 to 1.05; I^2 = 0%: low certainty evidence). The evidence was downgraded for risk of bias and imprecision.

All-cause hospitalisation

Antiplatelet agents may have little or no effect on all-cause hospitalisation in people treated with HD (Analysis 1.20 (3 studies, 3535 participants): RR 0.97, 95% CI 0.87 to 1.10; I^2 = 0%; low certainty evidence). The evidence was downgraded for risk of bias and imprecision.

Cardiovascular hospitalisation

It is uncertain whether antiplatelet agents made any difference in cardiovascular hospitalisation in CKD and HD (Analysis 1.21 (3 studies, 3535 participants): RR 0.93, 95% CI 0.76 to 1.14; I^2 = 46%; very low certainty evidence). The evidence was downgraded for Risk of Bias, inconsistency and imprecision. There was moderate heterogeneity potentially due to differences in the adjudication of the outcome.

Treatment withdrawal

Antiplatelet agents may have little or no effect on withdrawal from treatment compared with placebo or no treatment in CKD and HD (Analysis 1.22 (15 studies, 2669 participants): RR 0.97, 95% CI 0.83 to 1.14; I^2 = 0%; low certainty evidence). The evidence was downgraded for risk of bias and imprecision.

Prasugrel versus clopidogrel

TRITON-TIMI 38 2006 compared prasugrel plus aspirin with clopidogrel plus aspirin and provided data for 1490 people with CKD during a median follow-up of 14.5 months. Data were not available for fatal or nonfatal stroke, haemorrhagic stroke, fatal bleeding, kidney failure, doubling of SCr, kidney transplant graft loss, transplant rejection, CrCl, proteinuria, dialysis access failure, early access thrombosis, loss of primary unassisted patency, failure to attain suitability for dialysis, need for intervention to attain patency or assist maturation, all-cause hospitalisation, cardiovascular hospitalisation, and treatment withdrawal.

Fatal or nonfatal myocardial infarction

TRITON-TIMI 38 2006 reported no difference between prasugrel plus aspirin compared to clopidogrel plus aspirin on fatal or nonfatal MI (Analysis 2.1 (1 study, 1490 participants): RR 0.78, 95% CI 0.58 to 1.05). Since not all participants experienced MI before treatment allocation, antiplatelet agents were used both for primary and secondary prevention.

Death (any cause)

TRITON-TIMI 38 2006 reported no difference between prasugrel plus aspirin compared to clopidogrel plus aspirin death (any cause) (Analysis 2.2 (1 study, 1490 participants): RR 0.81, 95% CI 0.56 to 1.18).

Cardiovascular death

TRITON-TIMI 38 2006 reported no difference between prasugrel plus aspirin compared to clopidogrel plus aspirin on cardiovascular death (Analysis 2.3 (1 study, 1469 participants): RR 1.35, 95% CI 0.87 to 2.10).

Major bleeding

Major bleeding was defined according to the Thrombolysis In Myocardial Infarction (TIMI) criteria for major bleeding (intracranial haemorrhage, clinically evident bleeding including imaging and a drop in the Hb of ≥5 g/dL). TRITON-TIMI 38 2006 reported no difference between prasugrel plus aspirin compared to clopidogrel plus aspirin on major bleeding (Analysis 2.4 (1 study, 1475 participants): RR 1.49, 95% CI 0.83 to 2.66).

Minor bleeding

Minor bleeding was defined as clinically evident bleeding including imaging and a fall in the Hb of between 3 and 5 g/dL. TRITON-TIMI 38 2006 reported no difference between prasugrel plus aspirin compared to clopidogrel plus aspirin on minor bleeding (Analysis 2.5 (1 study, 1469 participants): RR 1.35, 95% CI 0.87 to 2.10).

Ticagrelor versus clopidogrel

Three studies (OPT-CKD 2018; PIANO-3 2015; PIANO-6 2017) compared ticagrelor with or without aspirin with clopidogrel alone or in combination with aspirin. Data were not available for haemorrhagic stroke, kidney failure, doubling of SCr, kidney transplant graft loss, transplant rejection, CrCl, proteinuria, dialysis access failure, early access thrombosis, loss of primary unassisted patency, failure to attain suitability for dialysis, need for intervention to attain patency or assist maturation, all-cause hospitalisation, and cardiovascular hospitalisation.

Fatal or nonfatal myocardial infarction

OPT-CKD 2018 reported no difference between ticagrelor compared to clopidogrel on fatal or nonfatal MI in CKD during 30 days follow-up (Analysis 3.1 (1 study, 60 participants): RR 3.00, 95% CI 0.13 to 70.83). Since not all participants experienced MI before treatment allocation, antiplatelet agents were used both for primary and secondary prevention.

Fatal or nonfatal stroke

OPT-CKD 2018 reported no difference between ticagrelor compared to clopidogrel on fatal or nonfatal MI in CKD during 30 days follow-up (Analysis 3.2 (1 study, 60 participants): RR 3.00, 95% CI 0.13 to 70.83). Since it was not reported if all participants experienced a stroke before treatment allocation, it was not clear if antiplatelet agents were used either for primary or secondary prevention.

Death (any cause)

OPT-CKD 2018 and PIANO-6 2017 reported the effect of ticagrelor with clopidogrel while PIANO-3 2015 reported the effect of ticagrelor plus aspirin with clopidogrel plus aspirin between 14 to 30 days follow-up. Antiplatelet agents had uncertain effects on death (any cause) in CKD and HD (Analysis 3.3 (3 studies, 137 participants): RR 2.00, 95% CI 0.19 to 20.90; very low certainty evidence). The evidence was downgraded for risk of bias and imprecision.

Cardiovascular death

OPT-CKD 2018 and PIANO-6 2017 reported the effect of ticagrelor with clopidogrel while PIANO-3 2015 reported the effect of ticagrelor plus aspirin with clopidogrel plus aspirin between 14 to 30 days follow-up. Antiplatelet agents had uncertain effects on cardiovascular death in CKD and HD (Analysis 3.4 (3 studies, 137 participants): RR 5.00, 95% CI 0.25 to 99.59; low certainty evidence). The evidence was downgraded for risk of bias and imprecision.

Fatal bleeding

PIANO-3 2015 reported the effect of ticagrelor plus aspirin with clopidogrel plus aspirin and PIANO-6 2017 reported the effect of ticagrelor with clopidogrel in HD during 14 days follow-up. No fatal bleeding events were reported in either study (Analysis 3.5; 2 studies, 77 participants).

Major bleeding

Major bleeding was assessed using the Bleeding Academic Research Consortium (BARC) (OPT-CKD 2018) or according to the PLATO criteria (PIANO-3 2015). OPT-CKD 2018 reported the effect of ticagrelor with clopidogrel during 30 days follow-up, while PIANO-3 2015 reported the effect of ticagrelor plus aspirin with clopidogrel plus aspirin during 14 days follow-up. Antiplatelet agents had uncertain effects on major bleeding in CKD and HD (Analysis 3.6 (2 studies, 85 participants): RR 0.33, 95% CI 0.01 to 7.87; low certainty evidence). The evidence was downgraded for risk of bias and imprecision.

Minor bleeding

Minor bleeding was assessed using the Bleeding Academic Research Consortium (BARC). PIANO-6 2017 reported no difference between ticagrelor compared to clopidogrel on minor bleeding in HD during 14 days follow-up (Analysis 3.7 (1 study, 52 participants): RR 1.06, 95% CI 0.10 to 10.90).

Treatment withdrawal

PIANO-6 2017 reported no difference between ticagrelor compared to clopidogrel on treatment withdrawal in HD during 14 days follow-up (Analysis 3.8 (1 study, 52 participants): RR 1.59, 95% CI 0.18 to 14.19).

Clopidogrel (low-dose) versus clopidogrel (high-dose)

Liang 2015, which compared a low- versus high-dose clopidogrel, provided data for 370 people with CKD during 30 days follow-up. Data were not available for fatal or nonfatal MI, fatal or nonfatal stroke, death (any cause), fatal bleeding, major bleeding, minor bleeding, kidney failure, doubling of SCr, kidney transplant graft loss, transplant rejection, CrCl, proteinuria, dialysis access failure, early access thrombosis, loss of primary unassisted patency, failure to attain suitability for dialysis, need for intervention to attain patency or assist maturation, all-cause hospitalisation, cardiovascular hospitalisation, and treatment withdrawal.

Haemorrhagic stroke

Liang 2015 reported no haemorrhagic stroke events with either low-dose or high-dose clopidogrel (Analysis 4.1 (1 study, 370 participants)).

Cardiovascular death

Liang 2015 reported no difference between low- versus high-dose clopidogrel on cardiovascular death (Analysis 4.2 (1 study, 370 participants): RR 4.04, 95% CI 0.46 to 35.83).

Abciximab versus tirofiban

TARGET 2000 compared abciximab plus aspirin with tirofiban plus aspirin and provided unpublished data for 790 people with CKD between 6 and 12 months follow-up. Data were not available for fatal or nonfatal stroke, haemorrhagic stroke, cardiovascular death, fatal bleeding, major bleeding, minor bleeding, kidney failure, doubling of SCr, kidney transplant graft loss, transplant rejection, CrCl, proteinuria, dialysis access failure, early access thrombosis, loss of primary unassisted patency, failure to attain suitability for dialysis, need for intervention to attain patency or assist maturation, all-cause hospitalisation, cardiovascular hospitalisation, and treatment withdrawal.

Fatal or nonfatal myocardial infarction

TARGET 2000 reported abciximab plus aspirin may decrease fatal or nonfatal MI compared to tirofiban plus aspirin during 6 months follow-up (Analysis 5.1 (1 study, 790 participants): RR 2.33, 95% CI 1.57 to 3.45). Since not all participants experienced MI before treatment allocation, antiplatelet agents were used both for primary and secondary prevention.

Death (any cause)

TARGET 2000 reported no difference between abciximab plus aspirin compared to tirofiban plus aspirin on death (any cause) during 12 months follow-up (Analysis 5.2 (1 study, 790 participants): RR 1.73, 95% CI 0.92 to 3.23).

Defibrotide versus dypiridamole

Frascà 1986 compared defibrotide with dypiridamole and provided data for 80 people that received a kidney transplant during 4 years of follow-up. Data were not available for fatal or nonfatal MI, fatal or nonfatal stroke, haemorrhagic stroke, major bleeding, minor bleeding, kidney failure, doubling of SCr, transplant rejection, CrCl, proteinuria, dialysis access failure, early access thrombosis, loss of primary unassisted patency, failure to attain suitability for dialysis, need for intervention to attain patency or assist maturation, all-cause hospitalisation, cardiovascular hospitalisation, and treatment withdrawal.

Death (any cause)

Frascà 1986 reported no difference between defibrotide compared to dypiridamole on death (any cause) (Analysis 6.1 (1 study, 76 participants): RR 0.30, 95% CI 0.01 to 7.16).

Cardiovascular death

Frascà 1986 reported no difference between defibrotide compared to dypiridamole on cardiovascular death (Analysis 6.2 (1 study, 76 participants): RR 0.30, 95% CI 0.01 to 7.16).

Fatal bleeding

Frascà 1986 reported no fatal bleeding events with either defibrotide or dypiridamole (Analysis 6.3 (1 study, 76 participants)).

Kidney transplant graft loss

Frascà 1986 reported no difference between defibrotide compared to dypiridamole on kidney transplant graft loss (Analysis 6.4 (1 study, 76 participants): RR 0.13, 95% CI 0.02 to 1.00).

Cilostazol versus sarpogrelate

Hidaka 2013 compared cilostazol with sarpogrelate and provided data for 35 people undergoing HD during 24 weeks follow-up. Data were not available for fatal or nonfatal MI, fatal or nonfatal stroke, death (any cause), haemorrhagic stroke, cardiovascular death, fatal bleeding, minor bleeding, kidney failure, doubling of SCr, kidney transplant graft loss, transplant rejection, CrCl, proteinuria, dialysis access failure, early access thrombosis, loss of primary unassisted patency, failure to attain suitability for dialysis, need for intervention to attain patency or assist maturation, all-cause hospitalisation, cardiovascular hospitalisation and treatment withdrawal.

Major bleeding

Hidaka 2013 reported no major bleeding events with either cilostazol or sarpogrelate (Analysis 7.1 (1 study, 35 participants)).

Beraprost versus cilostazol or sarpogrelate

J-PADD 2014, which compared beraprost with cilostazol or sarpogrelate, provided data for 72 people undergoing HD during 24 weeks follow-up. Data were not available for haemorrhagic stroke, major bleeding, minor bleeding, kidney failure, doubling of SCr, kidney transplant graft loss, transplant rejection, CrCl, proteinuria, dialysis access failure, early access thrombosis, loss of primary unassisted patency, failure to attain suitability for dialysis, need

for intervention to attain patency or assist maturation, all-cause hospitalisation, cardiovascular hospitalisation, and treatment withdrawal.

Fatal or nonfatal myocardial infarction

J-PADD 2014 reported no fatal or nonfatal MI events with beraprost, cilostazol or sarpogrelate (Analysis 8.1 (1 study, 68 participants)). The treatment was performed for secondary prevention of MI.

Fatal or nonfatal stroke

J-PADD 2014 reported no difference between beraprost compared to cilostazol or sarpogrelate on fatal or nonfatal stroke (Analysis 8.2 (1 study, 68 participants): RR 0.19, 95% CI 0.01 to 3.79). The treatment was performed for secondary prevention of stroke.

Death (any cause)

J-PADD 2014 reported no difference between beraprost compared to cilostazol or sarpogrelate on death (any cause) (Analysis 8.3 (1 study, 68 participants): RR 0.94, 95% CI 0.06 to 14.47).

Cardiovascular death

J-PADD 2014 reported no difference between beraprost compared to cilostazol or sarpogrelate on cardiovascular death (Analysis 8.4 (1 study, 68 participants): RR 0.94, 95% CI 0.06 to 14.47).

Fatal bleeding

J-PADD 2014 reported no fatal bleeding events with beraprost, cilostazol or sarpogrelate (Analysis 8.5 (1 study, 68 participants)).

Sensitivity and subgroups analyses

Antiplatelet agents versus placebo

Fatal or nonfatal myocardial infarction

Since not all participants experienced MI before treatment allocation, antiplatelet agents could be used for primary and secondary prevention. Five studies (Creek 1990; Ell 1982; Kaufman 2003; STOP 1995; UK-HARP-I 2005) reported insufficient information to assess if the intervention was performed either for primary or secondary prevention. These studies were not included in the subgroup analyses for primary/secondary prevention against MI. Four studies (Dember 2005; Dixon 2005; ETDRS 1992; HOT 1993) prescribed antiplatelet agents both for primary and secondary prevention. Since data were not reported separately for patients with or without previous MI, it was not possible to include these studies in the subgroup analyses for primary/secondary prevention against MI.

Subgroup analysis for primary prevention against myocardial infarction - stratified by stage of CKD

There were no studies that assessed the intervention for primary prevention against MI, and subgroup analyses were not performed.

Subgroup analysis for secondary prevention against myocardial infarction - stratified by stage of CKD

Antiplatelet agents may have little or no effect on MI for secondary prevention in CKD (Analysis 9.1 (8 studies, 7270 participants): RR 0.93, 95% CI 0.81 to 1.06: I^2 = 0%; low certainty evidence). The evidence was downgraded for risk of bias and imprecision. However, a small number of studies contributed data to predialysis and no data were available for dialysis and transplant, meaning that the analysis may not be able to detect subgroup differences within different stages of CKD.

Sensitivity analysis for fatal or nonfatal myocardial infarction - stratified by adequate allocation concealment

Considering only studies with adequate allocation concealment, antiplatelet agents may reduce the risk of fatal or nonfatal MI in CKD (Analysis 10.1.1 (8 studies, 10,459 participants): RR 0.80, 95% CI 0.65 to 0.98; I^2 = 31%; low certainty evidence). The evidence was downgraded for risk of bias and inconsistency. There was moderate heterogeneity.

Sensitivity analysis for fatal or nonfatal myocardial infarction - stratified by a low risk of attrition bias

Considering only studies with low risk of attrition, antiplatelet agents probably reduce the risk of fatal or nonfatal MI in CKD (Analysis 11.1.1 (11 studies, 9387 participants): RR 0.75, 95% CI 0.62 to 0.90; I^2 = 0%; moderate certainty evidence). The evidence was downgraded for risk of bias.

Fatal or nonfatal stroke

Five studies (Creek 1990; Ell 1982; Kaufman 2003; STOP 1995; UK-HARP-I 2005) reported insufficient information to assess if the intervention was performed either for primary or secondary prevention. These studies were not included in the subgroup analyses for primary/secondary prevention against stroke. Four studies (Dember 2005; Dixon 2005; ETDRS 1992; HOT 1993) prescribed antiplatelet agents both for primary and secondary prevention. Since data were not reported separately for patients with or without previous stroke, it was not possible to include these studies in the subgroup analyses for primary/secondary prevention against stroke.

Subgroup analysis for stroke - stratified by stage of CKD

It is uncertain whether antiplatelet agents made any difference in stroke for secondary prevention in CKD (Analysis 12.1 (11 studies, 9544 participants): RR 1.00, 95% CI 0.58 to 1.72: I^2 = 43%; very low certainty evidence). The evidence was downgraded for risk of bias, inconsistency, and imprecision. The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.63), suggesting that different stages of CKD do not modify the effect of antiplatelet agents on the risk of stroke.

Subgroup analysis for stroke - stratified by diabetes

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.59), suggesting that diabetes does not modify the effect of antiplatelet agents on the risk of stroke (Analysis 12.2 (6 studies, 4368 participants): RR 1.49, 95% CI 0.68 to 3.25; I^2 = 40%; very low certainty evidence). The evidence was downgraded for risk of bias, inconsistency and imprecision.

The pooled effect estimate for studies with < 50% of diabetic patients favoured antiplatelet agents (Analysis 12.2.1 (3 studies, 1525 participants): RR 0.96, 95% CI 0.15 to 6.03; I^2 = 22%), while the pooled effects for studies where at least 50% of participants had diabetes (Analysis 12.2.2 (3 studies, 2843 participants): RR 1.70, 95% CI 0.64 to 4.49; I^2 = 64%) and favoured control.

Subgroup analysis for stroke - stratified by males

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.34), suggesting that gender does not modify the effect of antiplatelet agents on the risk of stroke (Analysis 12.3 (7 studies, 7987 participants): RR 1.19, 95% CI 0.68 to 2.07; I^2 = 43%; very low certainty evidence). The evidence was downgraded for risk of bias, inconsistency and imprecision.
However, a different number of studies and participants contributed data to the studies with less than 50% of males subgroup compared to the studies with at least 50% of males subgroup, meaning that the analysis may not be able to detect subgroup differences.

Subgroup analysis for stroke - stratified by duration of intervention

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.15), suggesting that duration of intervention does not modify the effect of antiplatelet agents on the risk of stroke (Analysis 12.4 (11 studies, 9544 participants): RR 1.00, 95% CI 0.58 to 1.72; I^2 = 43%; very low certainty evidence). The evidence was downgraded for risk of bias, inconsistency and imprecision.
However, a smaller number of studies and/or participants contributed data to the duration of intervention lower than 6 months and between 6 and 12 months subgroups than to the duration of the treatment greater than 12 months subgroup, meaning that the analysis may not be able to detect subgroup differences.

Death from any cause

Sensitivity analysis for death (any cause) - stratified by adequate allocation concealment

Considering only studies with adequate allocation concealment, it is uncertain whether antiplatelet agents made any difference to death (any cause) in CKD (Analysis 10.2 (10 studies, 11,443 participants): RR 1.00, 95% CI 0.83 to 1.22; I^2 = 37%; very low certainty evidence). The evidence was downgraded for risk of bias, inconsistency and imprecision. The heterogeneity was moderate.

Sensitivity analysis for death (any cause) - stratified by a low risk of attrition bias

Considering only studies with low risk of attrition, it is uncertain whether antiplatelet agents made any difference to death (any cause) in CKD and HD (Analysis 11.2 (19 studies, 10,966 participants): RR 0.99, 95% CI 0.82 to 1.20; I^2 = 30%; very low certainty evidence). The evidence was downgraded for risk of bias, inconsistency and imprecision. The heterogeneity was moderate.

Cardiovascular death

Sensitivity analysis for cardiovascular death - stratified by adequate allocation concealment

Considering only studies with adequate allocation concealment, it is uncertain whether antiplatelet agents made any difference to cardiovascular death mortality in CKD (Analysis 10.3 (2 studies, 5628 participants): RR 1.08, 95% CI 0.48 to 2.44; I^2 = 85%; very low certainty evidence). The evidence was downgraded for risk of bias, inconsistency and imprecision. There was substantial heterogeneity.

Sensitivity analysis for cardiovascular death - stratified by a low risk of attrition bias

Considering only studies with low risk of attrition, it is uncertain whether antiplatelet agents made any difference to cardiovascular death mortality in CKD, HD and transplant recipients (Analysis 11.3 (11 studies, 6872 participants): RR 0.94, 95% CI 0.60 to 1.47; I^2 = 66%; very low certainty evidence). The evidence was downgraded for risk of bias, inconsistency and imprecision. There was moderate heterogeneity.

Major bleeding

Sensitivity analysis for major bleeding - stratified by adequate allocation concealment

Considering only studies with adequate allocation concealment, antiplatelet agents may increase major bleeding in CKD (Analysis 10.4 (9 studies, 10,360 participants): RR 1.53, 95% CI 1.07 to 2.20; I^2 = 52%; low certainty evidence). The evidence was downgraded for risk of bias and inconsistency. There was moderate heterogeneity.

Sensitivity analysis for major bleeding - stratified by a low risk of attrition bias

Considering only studies with low risk of attrition, antiplatelet agents probably increased major bleeding in CKD and HD (Analysis 11.4 (17 studies, 9549 participants): RR 1.62, 95% CI 1.19 to 2.20; I^2 = 15%; moderate certainty evidence). The evidence was downgraded for risk of bias. There was low heterogeneity.

Minor bleeding

Subgroup analysis for minor bleeding - stratified by stage of CKD

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.16), suggesting that different stages of CKD do not modify the effect of antiplatelet agents on the risk of minor bleeding (Analysis 13.1).
However, a smaller number of studies and participants contributed data to both predialysis, dialysis and transplant and HD subgroups than to the CKD subgroup, meaning that the analysis may not be able to detect subgroup differences.

Subgroup analysis for minor bleeding - stratified by diabetes

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.08), suggesting that diabetes does not modify the effect of antiplatelet agents on the risk of minor bleeding (Analysis 13.2).

Subgroup analysis for minor bleeding - stratified by sex

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.42), suggesting that gender does not modify the effect of antiplatelet agents on the risk of minor bleeding (Analysis 13.3).

Subgroup analysis for minor bleeding - stratified by duration of intervention

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.74), suggesting that duration of intervention does not modify the effect of antiplatelet agents on the risk of minor bleeding (Analysis 13.4).
However, a smaller number of studies and participants contributed data to the duration of intervention lower than 6 months and greater than 12 months subgroups than to the duration of the

treatment between 6 and 12 months subgroup, meaning that the analysis may not be able to detect subgroup differences.

Dialysis access failure

Subgroup analysis for dialysis access failure - stratified by stage of CKD

Subgroup analyses based on the stage of CKD were not possible due to insufficient numbers of studies.

Subgroup analysis for dialysis access failure - stratified by diabetes

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.77), suggesting that diabetes does not modify the effect of antiplatelet agents on dialysis access failure (Analysis 14.1).

Subgroup analysis for dialysis access failure - stratified by male

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.34), suggesting that gender does not modify the effect of antiplatelet agents on dialysis access failure (Analysis 14.2).

Subgroup analysis for dialysis access failure - stratified by duration of intervention

The test for subgroup differences suggests that there is a statistically significant subgroup effect (P = 0.001), meaning that duration of intervention significantly modifies the effect of antiplatelet agents on dialysis access failure (Analysis 14.3 (17 studies, 2847 participants): RR 0.62, 95% CI 0.50 to 0.78; I^2 = 46%; low certainty evidence). The evidence was downgraded for risk of bias and inconsistency. There was moderate heterogeneity.
A sufficient number of studies and participants were not included in each subgroup, so the covariate distribution could be a concern for this subgroup analysis. Both the pooled effect estimate for the duration of the intervention less than 6 months (Analysis 14.3.1 (11 studies, 1705 participants): RR 0.55, 95% CI 0.44 to 0.70; I^2 = 0%; low certainty evidence), between 6 and 12 months (Analysis 14.3.2 (4 studies, 386 participants): RR 0.59, 95% CI 0.37 to 0.96; I^2 = 58%; very low certainty evidence) and greater than 12 months (Analysis 14.3.3 (2 studies, 756 participants): RR 0.94, 95% CI 0.79 to 1.11; I^2 = 0%; very low certainty evidence) favoured antiplatelet agents. There was substantial unexplained heterogeneity between the studies and the validity of the treatment effect estimated for each subgroup was uncertain, as individual study results were inconsistent.

Failure to attain access suitability of dialysis

Subgroup analysis for failure to attain access suitability of dialysis - stratified by stage of CKD

Subgroup analyses based on the stage of CKD were not possible due to insufficient numbers of studies.

Subgroup analysis for failure to attain access suitability of dialysis - stratified by diabetes

Subgroup analyses based on diabetes were not possible due to insufficient numbers of studies.

Subgroup analysis for failure to attain access suitability of dialysis - stratified by male

Subgroup analyses based on the prevalence of males were not possible due to insufficient numbers of studies.

Subgroup analysis for failure to attain access suitability of dialysis - stratified by duration of intervention

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.75), suggesting that duration of intervention does not modify the effect of antiplatelet agents on the failure to attain access suitability of dialysis (Analysis 15.1).
However, a smaller number of studies and participants contributed data to the duration of intervention greater than 12 months subgroup than to the duration of the treatment less than 6 months subgroup, meaning that the analysis may not be able to detect subgroup differences.

Antiplatelet agents versus antiplatelet agents

Sensitivity and subgroup analyses were not possible when comparing one antiplatelet with another antiplatelet due to the insufficient number of available studies.

DISCUSSION

Summary of main results

This updated review indicated that antiplatelet agents (acetylsalicylic acid, adenosine diphosphate receptor inhibitors, adenosine reuptake inhibitors, glycoprotein IIb/IIIa inhibitors, picotamide, or sulphinpyrazone) probably prevents fatal or nonfatal MI in people with CKD. Antiplatelet treatment probably increases major bleeding (including bleeding events that result in hospital admission, transfusion, or disability) and may increase minor bleeding in people with CKD. There is insufficient available evidence to define clearly the role of antiplatelet treatment in primary prevention (preventing cardiovascular events in people without existing cardiovascular disease) in those with CKD. Few studies reported the efficacy of antiplatelet therapies for secondary prevention against MI or stroke in CKD, and sparse or no data were available for dialysis and transplant recipients.

Antiplatelet agents started around the time of vascular access surgery may reduce early vascular access thrombosis or patency failure, but there was insufficient evidence to show that antiplatelet therapy improves dialysis access maturation, access suitability for dialysis or reduces the need for intervention to attain patency. Overall, the effect of antiplatelet agents on the prevention of kidney failure in people with CKD, kidney transplant loss, or transplant rejection is uncertain.

Direct comparisons of antiplatelet agents are limited to a few studies in which data for the subgroup of participants with CKD, HD and kidney transplant have been recently reported or provided. Currently, there are scant data to recommend that one antiplatelet agent is more efficacious than another in any clinical setting (primary prevention or secondary prevention), particularly for people with acute coronary syndromes or those undergoing percutaneous coronary interventions who frequently have coexistent CKD.

Overall completeness and applicability of evidence

While the analyses included data obtained from a comprehensive search and unpublished data from numerous investigators, particularly for cardiovascular events, the data were incomplete in several areas. Firstly, data for transplant recipients were limited and provided by smaller and older studies, published between

1974 and 1996. A study of aspirin included transplant recipients in addition to individuals with CKD and those requiring dialysis (UK-HARP-I 2005) but data for the transplant subgroup (133 participants) were not available and would have provided very few events for relevant clinical outcomes. Outcome data for kidney transplant recipients were restricted generally to transplant function or rejection in two studies, and information about major cardiovascular events was scarce. Further, only Frascà 1986 showed a head-to-head comparison of antiplatelet agents (glycoprotein IIb/IIIa inhibitor versus adenosine reuptake inhibitor) in kidney transplant recipients and further research is needed in these populations. Secondly, very few or no data for cardiovascular death were available in studies of glycoprotein IIb/IIIa inhibitors administered in addition to standard therapy, low dose versus high dose clopidogrel and cilostazol versus sarpogrelate in patients with CKD or undergoing HD.

Quality of the evidence

Although this review found consistent effect estimates for important clinical outcomes (MI and bleeding) in analyses that include approximately 16,000 people with CKD and between 500 to 1000 events, our conclusions must be considered more cautiously due to several potential limitations in the available data. Studies with zero events in both arms could not be analysed because they did not yield information on both the magnitude and direction of the relative treatment effects.

Study limitations

In this updated review, selective reporting of outcomes may reduce the strength of our conclusions. Data for MI in smaller studies with smaller treatment benefits were absent because these (less precise) studies did not systematically report cardiovascular events. Accordingly, selective outcome reporting reduced the reliability of this treatment effect (13% reduction) in both magnitude and direction, although the effect of bias could not be determined in the absence of all data for this outcome. The small proportion of studies reporting vascular access outcomes including approximately 6500 participants reduced the strength of evidence for antiplatelet agents on vascular access function and maturation. Only 50% of such studies reported access failure or thrombosis, and only 15% reported on maturation and suitability for dialysis outcomes in these people. Overall, some studies did not report adequate blinding, allocation concealment or random sequence generation, although sensitivity analyses did not find differences in treatment effects when analyses were restricted to studies of higher methodological quality, because lower quality studies tended to be smaller and contributed fewer events to analyses. In addition, the number of major bleeding events in studies of dual antiplatelet agents was insufficient to determine in indirect evidence whether the bleeding risk was increased with dual antiplatelet agents compared with monotherapy. Data from studies that directly compared two antiplatelet agents against a single antiplatelet agent were rarely reported.

Consistency of results

Our major findings were that antiplatelet agents probably reduce MI, probably increase major bleeding, and may increase minor bleeding in CKD and HD. More than one-third of studies reported death (any cause) in over 17,000 participants and showed no treatment effect in the majority of studies. The null result of antiplatelet agents on death (any cause) was due both to the lack of effect on aspirin on non-cardiovascular causes of death and to the competing non-atherosclerotic cardiovascular causes. Only CHARISMA 2006, which compared clopidogrel and aspirin versus aspirin alone in people with diabetic kidney disease, showed that there were more deaths amongst participants allocated to clopidogrel, although the reasons for this finding remain unclear. Similarly, in analyses for cardiovascular death that included 21 studies and nearly 10,000 participants, only CHARISMA 2006 had a 95% CI that did not include '1' suggesting the null effect of antiplatelet agents on cause-specific death is robust. There was also very low heterogeneity in the summary estimate for MI, although only 18/90 potentially eligible studies reported this outcome. Approximately one-third of placebo/no treatment studies reported major bleeding events with a consistent risk across all contributing studies of over 16,000 participants and nearly 600 events. The highly variable definitions of major bleeding in the included studies, together with the relative lack of specific reporting on intracranial haemorrhage, reduced the ability to weigh the relative benefits of treatment (reducing MI) with the comprehensive potential risks of harm for people with CKD and HD. The risks of minor bleeding varied among studies beyond chance alone and subgroup analyses, which included analyses for age, gender, pre-existing comorbidities or time on dialysis, did not reduce the reliability of the effect estimate identified for this outcome.

Directness of evidence

There were 27 studies reporting direct comparisons, and 14 were meta-analysed. . The small number of studies that directly compared different agents (prasugrel versus clopidogrel in one study; ticagrelor versus clopidogrel in three studies; different doses of clopidogrel in one study; abciximab versus tirofiban in one study; defibrotide versus dypiridamole in one study; sarpogrelate versus cilostazol in one study and beraprost versus cilostazol or sarpogrelate in one study) precluded indirect comparisons of the magnitude of the effect of each drug class (although such evidence is of lower quality than head-to-head comparisons of antiplatelet agents). Although we planned to identify whether a specific antiplatelet agent was particularly beneficial (or harmful) and if treatment effects varied with stage of CKD (dialysis versus earlier stages of CKD) using prespecified subgroup analyses, these analyses were not performed due to the small number of studies.

Precision

Effect estimates for major treatment benefits and harms (MI and major bleeding) had narrow confidence intervals, increasing their certainty and strengthening the evidence within the review for these clinical events. Several outcomes, however, included few participants and events, indicating the available evidence for benefits (and toxicities) of antiplatelet agents for these outcomes is of lower quality. These outcomes included death (any cause) and cardiovascular death, bleeding-related death, fatal and nonfatal stroke, haemorrhagic stroke, kidney failure, transplant function and rejection, dialysis vascular access maturation, and hospitalisation. Effect estimates for direct antiplatelet versus antiplatelet comparisons were also very imprecise.

Potential biases in the review process

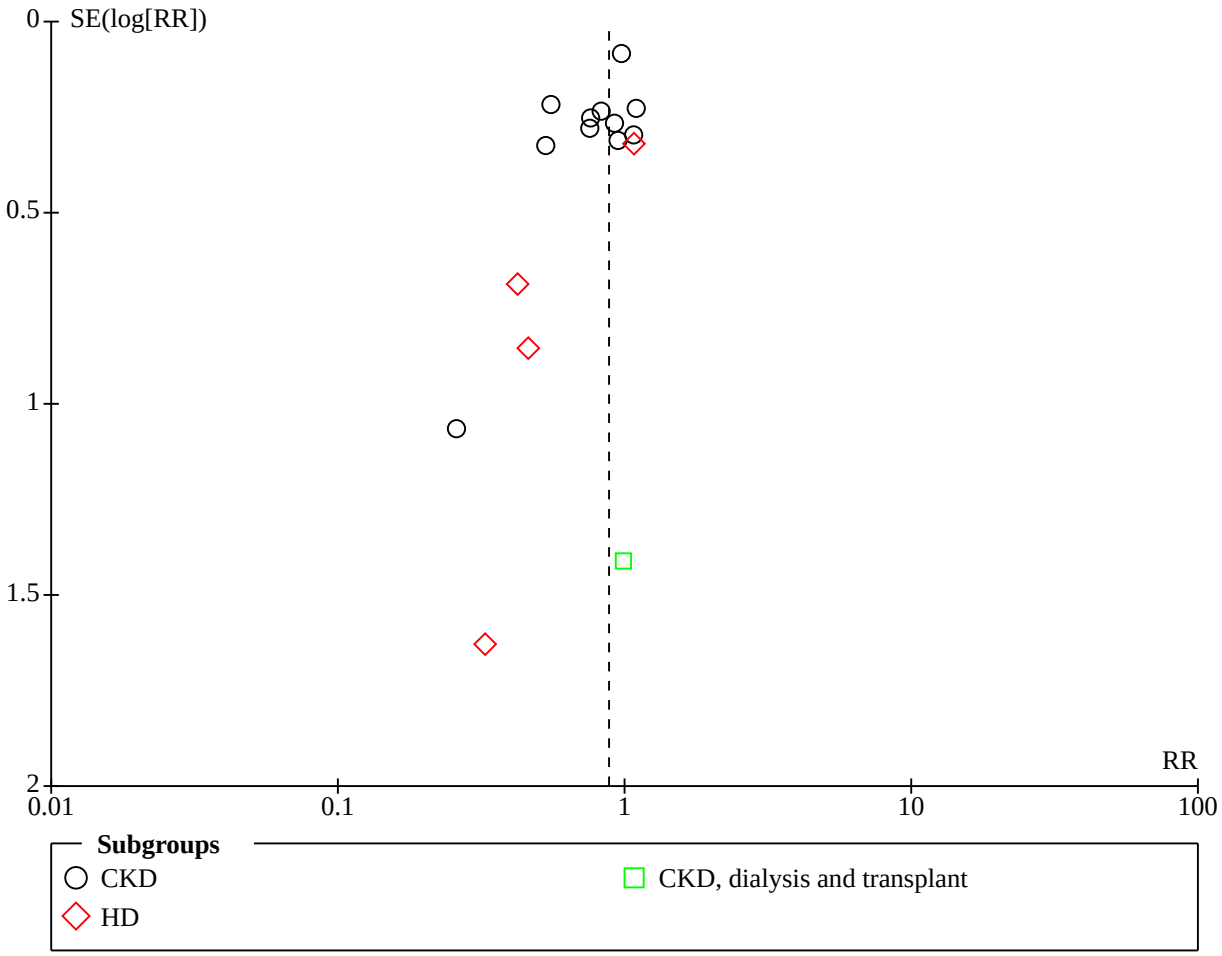
This review was carried out using standard Cochrane methods. Each step was completed independently by at least two authors including the selection of studies, data management, and risk

of bias assessment, thus reducing the risks of errors in the identification of eligible studies and adjudication of evidence certainty. A highly sensitive search of the Cochrane Kidney Transplant specialised register was completed without language restriction in July 2021. The registry contains hand-searched literature and conference proceedings, maximising the inclusion of grey literature in this review. We additionally requested data from authors. Some studies did not report key outcomes in a format available for meta-analysis.

Potential biases in this review were related to the data available in the individual studies. First, there was heterogeneity in treatment interventions and comparisons; due to the small number of data observations and the different number of participants in each subgroup category, robust statistical estimates of heterogeneity could not be estimated. Second, we could not assess for potential reporting bias because most studies did not report key outcomes in a format available for meta-analysis. Third, while most participants were on CKD (stage 1-5) not requiring dialysis, there was wide variation in the definition of kidney disease for inclusion in eligible studies. Fourth, adverse event reporting in the available studies was infrequent and inconsistent. Finally, selective outcome reporting was a limitation across the included studies.

Visual inspection of funnel plots did not suggest any evidence of small study effects indicating possible publication bias for MI (Figure 3).

Figure 3. Funnel plot of comparison of antiplatelet agents versus control for the outcome of fatal or nonfatal myocardial infarction



Agreements and disagreements with other studies or reviews

The updated results of this review expand the available evidence for people with CKD including data for 51,959 participants. An earlier collaborative systematic overview of 287 RCTs of an antiplatelet agent versus control (130,000 participants) or of one antiplatelet treatment versus another (77,000 participants) in people at high risk of cardiovascular disease (acute or previous vascular disease or other predisposing condition) included 2632 people requiring HD (ATT 2002). This review found that antiplatelet agents produced a 41% proportional reduction in serious vascular events in this population. However, only 99 vascular events and 46 major extracranial bleeds were available at the time of publication, limiting the reliability of the conclusions drawn (ATT 2002). Data for people with earlier stages of CKD were not available in this

earlier review and have only recently become more available. Another systematic review of individual patient data for aspirin in the primary and secondary prevention of vascular disease did not provide specific analyses for individuals based on the presence of CKD (ATT 2009).

Notably, our systematic review (that finds that antiplatelet agents probably lower by 12% the risk of MI, increase major bleeding, may reduce death (any cause), and may increase minor bleeding) differs from these two previous studies. We suggest that the benefits of antiplatelet agents on cardiovascular events may be smaller in people with CKD compared with other populations at risk of cardiovascular events. The relatively reduced efficacy for antiplatelet agents on total death in CKD is potentially explained by the competing mechanisms for cardiovascular death in this population. Progressive kidney dysfunction is characterised by vascular stiffening and calcification, cardiomyopathy, hyperkalaemia, and sudden cardiac death, in addition to occlusive vascular disease. About half of cardiovascular deaths in both dialysis and transplant patients are caused by cardiac arrest and heart failure (ANZDATA 2019) for which the predominant pathogenetic mechanisms include hypertension, volume expansion, vascular calcification, and arrhythmia, rather than platelet aggregation and thrombosis. Therefore, while we find that antiplatelet agents prevent occlusive vascular events (MI) in CKD as expected, they have a lower overall effect on non-thrombotic causes of death (both vascular and nonvascular). The results of the present review are consistent with the effects of antiplatelet agents in primary prevention of cardiovascular events, which reduce nonfatal MI by 20% but do not prevent stroke or vascular death with similar effects in men and women (ATT 2009). Notably, in that review, the authors concluded that aspirin may be of uncertain net value, because reducing occlusive events may not be outweighed by risks of major bleeding.

A previous meta-analysis of medical adjuvant treatment to increase the patency of arteriovenous fistulae and grafts included placebo-controlled studies of antiplatelet agents, low-dose warfarin, or fish oil was published in 2008 (Osborn 2008). In that systematic review, antiplatelet agents were considered separately in analyses that combined access types (graft or fistula) and analyses included a maximum of only three studies and 41 events. Analyses in that review may have been insufficient to provide reliable estimates of the benefits or toxicity of antiplatelet agents on vascular access outcomes. Our review also differs from the second review of antiplatelet agents for the prevention of arteriovenous fistula thrombosis of 10 studies (approximately 2000 participants), as we considered the outcomes of suitability for dialysis or access maturation, summarised study risks of bias, and explored sources of heterogeneity within treatment effects (Coleman 2010).

Our review showed similar results compared with a recent meta-analysis that provided data for approximately 28,000 CKD patients, where the risk of MI decreased, major and minor bleeding increased in the antiplatelet agent group compared with control (Su 2019). Moreover, the authors reported that the effects of antiplatelet agents on HD patients or kidney transplant patients were rarely or not reported.

AUTHORS' CONCLUSIONS

Implications for practice

Overall evidence ratings and recommendations for antiplatelet agents to prevent cardiovascular and dialysis access outcomes in people with CKD using the GRADE system for grading evidence are summarised (GRADE 2011b). This updated systematic review has shown that antiplatelet agents in people with CKD and HD probably reduces the risk of MI, while the impact on death from any cause, cardiovascular death and stroke is uncertain or there is little evidence of impact from treatment. Treatment incurs major and minor bleeding that may impact the decision-making process by patients and clinicians balancing the potential benefits and harms of therapy. Antiplatelet agents given at the time of access surgery may reduce thrombosis or failure of vascular access, but effects on dialysis vascular access suitability for dialysis and access maturation are uncertain. The relative benefits of treatment in kidney transplant recipients and with primary prevention strategies in CKD are insufficient to inform practice. Based on absolute risks of clinical outcomes, it might be expected that antiplatelet agents would prevent 13 people with CKD and 3 treated with HD for every 1000 people treated over 1 year (Summary of findings 1), while 18 people with CKD and 1 people treated with HD might experience a major bleeding event without strong evidence that treatment prevents death. This implies that the balance of benefits and harms for people with CKD and those treated with dialysis depends on treatment goals and the relative importance of reducing the risk of MI or avoiding a serious bleeding event.

Implications for research

This review shows that there are little data for antiplatelet agents to prevent cardiovascular events in kidney transplant recipients with chronic or acute coronary artery disease. Further, adequately powered placebo-controlled RCTs are required to determine whether antiplatelet agents provide primary prevention against cardiovascular disease in people with CKD, including kidney transplant recipients, compared with aspirin monotherapy. To inform decisions in clinical practice, powered RCTs on any antiplatelet therapy-based cardiovascular study should include at least 2000 participants for each stage of CKD to meet the optimal information size criterion and evaluate adequately the confidence in the estimate of effect, with a relative risk reduction of 25% (GRADE 2011c). Specific head-to-head studies of antiplatelet agent regimens in individuals with all stages CKD and established atherosclerotic disease, acute coronary syndrome or undergoing percutaneous coronary intervention are required, particularly comparing thienopyridines (prasugrel or ticagrelor) or P2Y antagonists versus clopidogrel, different doses of clopidogrel, glycoprotein IIb/IIIa inhibitors versus another glycoprotein IIb/IIIa inhibitor or adenosine reuptake inhibitors, cilostazol versus sarpogrelate and beraprost sodium versus cilostazol or sarpogrelate. Studies should be designed to use standardised criteria to capture systematically all cardiovascular outcomes and major bleeding events in studies in which severe CKD is not an exclusion criterion. More information is required on the relative benefits of antiplatelet agents compared with other antiplatelet agents in people with CKD and the effects of therapy on cardiovascular mortality and bleeding. The role of antiplatelet agents as a primary prevention strategy to reduce death (any cause) and cardiovascular death in individuals with CKD, dialysis (HD and

PD) and kidney transplant without existing cardiovascular disease appears to be a lower research priority.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

AASER 2017

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: mean follow-up 64.8 months
Participants	• Country: Spain • Setting: multicentre (7 sites) • Inclusion criteria: stage 3 or 4 CKD (eGFR 15 to 60 mL/min/1.73 m^2), according to the MDRD-4 equation; males 45 to 79 years or females 55 to 79 years • Number (randomised/reported): treatment group (54/54); control group (62/61) • Mean age ± SD (years): treatment group (68.0 ± 8.3); control group (66.1 ± 10.5) • Sex (M/F): treatment group (32/18); control group (43/18) • Exclusion criteria: previous cardiovascular event (cardiac arrhythmias, cardiac arrest, angina or acute MI, stroke, carotid stenosis of more than 50%, peripheral vascular arteriopathy documented); hospitalisation for any cause in the last 3 months prior to inclusion in the study allergy of acetylsalicylic acid; coagulopathy from any cause; thrombocytopenia < 150,000 platelets; liver disease from any cause; infection by hepatitis B virus, hepatitis C or HIV; Immunosuppressive treatment within 12 weeks before inclusion in the study
Interventions	Treatment group

AASER 2017 *(Continued)*

	• Aspirin: 100 mg/day for 12 months Control group • Standard care without antiplatelet agents Cointerventions • Not reported
Outcomes	• Composite of cardiovascular death, acute coronary syndrome (nonfatal MI, coronary revascularization, or unstable angina pectoris), cerebrovascular disease, heart failure, or nonfatal peripheral arterial disease • Fatal and nonfatal coronary events • Kidney events (defined as doubling of SCr, ≥ 50% decrease in eGFR, or KRT) • Bleeding episodes (including major bleeding) • Plasma 15-epi-LXA4 levels • Inflammatory markers (CRP, ESR, leukocytes, fibrinogen)
Notes	• Funding: Sociedad Española de Nefrologia (SEN) and Sociedad Madrileña de Nefrología (SOMANE). MG, GFJ, DA, AO, and JL are supported by ISCIII RETIC REDINREN RD016/ 009 and FEDER funds

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation list was generated by software that assigned the codes for all patients at each participating centre in order of enrolment."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The same independent researcher, blinded as to the therapeutic group, adjudicated renal and cardiovascular events in clinical documentation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	50/54 patients in aspirin group were included in analysis; 61/62 patients in control group were included in analysis
Selective reporting (reporting bias)	Low risk	Study endpoints included all critical outcomes that would be expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias. Funder was likely to influence data analysis and study reporting or interpretation

Abacilar 2015

Study characteristics

Methods	• Study design: parallel RCT

Abacilar 2015 *(Continued)*

	• Duration of study: April 2008 to December 2013 • Duration of follow-up: 1 year
Participants	• Country: Turkey • Setting: multicentre (number of sites not reported) • Inclusion criteria: ESKD undergoing HD and AVF creation • Number: treatment group (50); control group (46) • Mean age ± SE years): treatment group (54.23 ± 2.6); control group (55.8 ± 2.84) • Sex (M): treatment group (68%); control group (69.5%) • Exclusion criteria: active bleeding or bleeding events requiring RBC transfusion with the previous 12 weeks; platelets < 75,000/µL; coagulopathy; acute ulcer disease; DBP/SBP > 115/200 mm Hg; advanced liver disease; history of oesophagitis or gastritis; discontinued antiplatelet; pregnancy or lactating; history of MI; CVA within previous 12 months
Interventions	Treatment group • Clopidogrel: 75 mg/day • Oral prostacyclin analogue: 200 mg/day Control group • Placebo Cointerventions • All patients took study medication 7 to 10 days prior to surgery and continued postoperatively
Outcomes	• Death • Number of patients with AVF maturation failure • AVF survival • Number of patients with access re-intervention (re-operated participants) • Failure of the AVF to become suitable for dialysis • Vascular diameter • AVF blood flow • Bleeding event (including intracranial haemorrhage) • HCT • RHuEPO doses • Number of patients with early AVF thrombosis • Adverse events
Notes	• Funding: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The randomisation was stratified according to the medical centre with a permuted block scheme, with a block size of four and an equal allocation." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study

Abacilar 2015 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Venous and arterial line diameters were calculated using sonography." Comment: Some outcomes may have been influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "None of the patients died or were lost to follow-up." Comment: All participants were included in the analysis
Selective reporting (reporting bias)	Low risk	Study endpoints included all critical outcomes that would be expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias

Abdul-Rahman 2007

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: December 2004 to December 2005 • Duration of follow-up: 12 months
Participants	• Country: Saudi Arabia • Setting: single centre • Inclusion criteria: HD patients with tunnelled CVC • Number: treatment group 1 (19); treatment group 2 (20); control group (19) • Mean age ± SD (years): treatment group 1 (44.7 ± 7.4); treatment group 2 (48.3 ± 11.5); control group (45.4 ± 9.5) • Sex (M/F): treatment group 1 (9/10); treatment group 2 (8/12); control group (19) (7/12) • Exclusion criteria: blood loss requiring either hospitalisation or transfusion in previous 3 months; demonstrated advanced proliferative diabetic retinopathy; life expectancy < 12 months because of advanced organ-systemic disease or malignancy; uncontrolled hypertension (SBP > 200 mm Hg or DBP > 110 mm Hg on 3 different occasions in a period of 2 weeks); platelet count <100,000/cm^3, INR > 1.3, or partial thromboplastin time 5 sec longer than control; medical conditions that would make anticoagulant or antiplatelet therapy dangerous; receiving dipyridamole, sulphinpyrazone, ticlopidine, clopidogrel, or NSAIDs
Interventions	Treatment group 1 • Aspirin: 81 mg/day for 12 months Treatment group 2 • Warfarin: 2 to 5 mg/day for 12 months Control group • No treatment with antiplatelet agents Cointerventions • Bicarbonate dialysate was used in all patients

Abdul-Rahman 2007 *(Continued)*

Outcomes	• Number of patients with HD tunnelled catheter thrombosis (catheter malfunction (defined as failure to attain and maintain an extracorporeal blood flow sufficient to perform HD without significantly lengthening the HD treatment) because of CVC thrombosis • Time to the first episode of catheter thrombosis • Adeguate anticoagulation • Major bleeding event • Malfunction-free catheter survival • Hb • HCT • Serious adverse events
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The presence of haemodialysis tunnelled central venous catheter thrombosis was determined by a staff member, who was blinded to treatment allocation." Comment: Although the researcher was blinded, outcome adjudication (bleeding) may have been influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	High risk	Study endpoints did not include all critical outcomes (death, cardiovascular events) that would be expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias

Alexopoulos 2011

Study characteristics

Methods	• Study design: cross-over RCT • Duration of study: May to June 2010 • Duration of follow-up: 15 days (first phase)
Participants	• Country: Greece • Setting: single centre

Alexopoulos 2011 *(Continued)*

- Inclusion criteria: all patients on regular maintenance HD for > 6 months for approximately 4 hours, 3 times/week; receiving chronic treatment with clopidogrel; high on-treatment platelet reactivity
- Number: treatment group 1 (11); treatment group 2 (10)
- Mean age ± SD (years): treatment group 1 (64.0 ± 11.6); treatment group 2 (58.2 ± 12.2)
- Sex M/F: treatment group 1 (8/3); treatment group 2 (6/4)
- Exclusion criteria: history of stroke/TIA; bleeding diathesis; chronic oral anticoagulant treatment; contraindications to antiplatelet therapy; acute coronary syndrome; haemodynamic instability; PCI or CABG within the previous 3 months; platelet count < 100,000/μL; HCT < 28%

Interventions	Treatment group 1 • Prasugrel: 10 mg/day for 15 days Treatment group 2 • High-dose clopidogrel: 150 mg/day for 15 days Cointerventions • Not reported
Outcomes	• Platelet reactivity (measured in P2Y12 reaction units) • High on-treatment platelet reactivity • Number of patients with bleeding (major/minor or minimal bleeding) • Major adverse cardiovascular events (cardiovascular death, MI, and stroke)
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients with HTPR (as defined below) were randomised (day 0) in a 1:1 ratio, by the use of computerized random number generation by an independent investigator." Comment: Computer-generated random number is considered as low risk of bias
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Physicians and operators who performed platelet function testing were blinded as to the actual drug used, and an independent physician monitored bleeding and adverse event data." Comment: Independent physician monitored bleeding may have been influenced by knowledge of treatment assignment (not reported if the physician was blind)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed follow-up

Alexopoulos 2011 *(Continued)*

Selective reporting (reporting bias)	Low risk	Study endpoints included all critical outcomes that would be expected for a study of this type. Data reported for the first phase of the cross-over RCT
Other bias	Low risk	No evidence of other sources of bias

Anderson 1974

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 24 months
Participants	• Country: UK • Setting: single centre • Inclusion criteria: kidney transplant (living and cadaver donor) patients • Number: treatment group (15); control group (12) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Dipyridamole: initially given 1 mg/kg/day (IV), then 600 mg/day orally for 24 months Control group • Placebo Cointerventions • All patients received AZA and prednisone according to a standard regime
Outcomes	• Rejection episodes • Graft loss • Kidney function (SCr, CrCl) • Urinary proteinuria • Platelet factor 3 and factor 4 availability • Platelet adhesiveness • Platelet labelling with 51-chromium • Serum dipyridamole levels • Deep venous thrombosis
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Patients within each group were allocated at random by the hospital pharmacy."

Anderson 1974 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study endpoints did not include all critical outcomes that would be expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias

Andrassy 1974

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 1 month
Participants	• Country: Germany • Setting: multicentre (5 sites) • Inclusion criteria: ESKD (HD) • Number: treatment group (45); control group (47) • Mean age ± SD (years): not reported • Sex (M/F): treatment group (25/20); control group (25/22) • Exclusion criteria: not reported
Interventions	Treatment group • Aspirin: 1 g microencapsulated one day prior to access surgery then until the 28th day after surgery Control group • Placebo Cointerventions • No antihypertensive drugs were given except in critical clinical situations
Outcomes	• Number of patients with fistula clotting • Number of patients with fistula thrombosis
Notes	• Funding: not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Andrassy 1974 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for in analysis
Selective reporting (reporting bias)	High risk	Study endpoints did not include all critical outcomes that would be expected for this type of study
Other bias	High risk	Imbalance of baseline characteristics

ATACAS 2008

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: March 2006 to 2013 • Duration of follow-up: 30 days

Participants	• Country: international (5 countries)
	• Setting: multicentre (19 sites)
	• Inclusion criteria: > 18 years; elective coronary artery surgery; increased risk of major complications, defined by any of the following:
	  ○ Age > 70 years
	  ○ Left ventricular impairment
	  ○ Concomitant artery or valvular surgery
	  ○ Repeat cardiac surgery
	  ○ Chronic obstructive pulmonary disease
	  ○ Kidney impairment (SCr > 150 µmol/L or CrCl < 45 mL/min)
	  ○ Obesity
	  ○ Pulmonary hypertension
	  ○ Peripheral vascular disease
	• Number (total/CKD patients): treatment group (1047/69); control group (1053/81)
	• Mean age ± SD (years): not reported for CKD patients
	• Sex (M/F): not reported for CKD patients
	• Exclusion criteria: poor English language comprehension; pregnancy; clinical preference for antifibrinolytic drugs; urgent surgery; active peptic ulceration; allergy; thrombocytopenia; recent haematuria; thromboembolic disease; severe kidney impairment (SCr > 250 µmol/L or CrCl < 25 mL/min); aspirin within 4 days of surgery; warfarin or clopidogrel within 7 days of surgery

Interventions	Treatment group

ATACAS 2008 *(Continued)*

	• Aspirin: 100 mg Control group • Placebo Cointerventions • Not reported
Outcomes	• Death • Major ischaemic morbidity (including kidney and cardiovascular events) • Stroke and MI events • Pulmonary embolism • Bowel infarction • Major bleeding events • Transfusions • Cardiac tamponade • Intensive care unit stay • Duration of mechanical ventilation • Reintubation during hospital stay • Haemostasis, blood Loss, and adverse events • Hospitalisations • Creatine kinase–myocardial band (CK-MB) • Reoperations for haemorrhage
Notes	• Funding: National Health and Medical Research Council of Australia, The Australian and New Zealand Collage of Anaesthetists, and The UK National Institute of Health Research

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed with the use of a computer-generated code that was accessed by means of an automated telephone voice recognition or Web-based service. Treatment assignment was stratified according to study site with the use of permuted blocks."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed with the use of a computer-generated code that was accessed by means of an automated telephone voice recognition or Web-based service."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An adjudication committee whose members were unaware of the group assignments assessed all major study outcomes."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient data on CKD patients to permit judgement
Selective reporting (reporting bias)	Low risk	Study reported expected outcomes for this type of study

ATACAS 2008 *(Continued)*

Other bias	Unclear risk	Insufficient data on CKD patients to permit judgement. Funder was unlikely to influence data analysis and study reporting or interpretation

CASSIOPEIR 2014

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: 27 May 2010 to 29 August 2014 • Duration of follow-up: 4 years
Participants	• Country: multinational (China, Hong Kong, Japan, Malaysia, Republic of Korea, Taiwan, Thailand) • Setting: multicentre (160 sites) • Inclusion criteria: primary glomerular disease or nephrosclerosis • Number (randomised/analysed): treatment group 1 (299/296); treatment group 2 (301/298); control group (292/291) • Mean age ± SD (years): treatment group 1 (55.0 ± 12.9); treatment group 2 (54.5 ± 13.1); control group (54.0 ± 13.1) • Sex (M/F): treatment group 1 (166/130); treatment group 2 (179/119); control group (191/100) • Mean SCr ± SD (mg/dL): treatment group 1 (2.993 ± 0.632); treatment group 2 (2.985 ± 0.624); control group (2.955 ± 0.648) • Exclusion criteria: glomerular disease secondary to DKD; CKD caused by pyelonephritis, interstitial/tubular nephritis, gouty kidney, polycystic kidney disease, or nephroureterolithiasis; administered an oral/injectable steroid agent, newly or increase in dose for treatment of a kidney disease during the 1 year prior to the date of informed consent; taken NSAIDs during the 1 week prior to the date of informed consent (topical medications (other than suppositories), and aspirin medications (up to 324 mg/day) are acceptable); DM, nephrotic syndrome or renal-artery stenosis; kidney transplantation, HD or PD within a year prior to the date of informed consent; or planned kidney transplantation, HD, or PD within 24 weeks following the date of informed consent; malignant hypertension or uncontrolled hypertension; serious hepatic disease, blood dyscrasia, respiratory disease, GI disease, heart disorder, cerebellar or cerebral disorders; taken BPS during the 1 year prior to the date of informed consent; taken TRK-100STP during the phase II clinical trial patient's condition is complicated by malignant hypertension or uncontrolled hypertension
Interventions	Treatment group 1 • Beraprost sodium (TRK-100STP): 60 µg twice/day (120 µg in total) Treatment group 2 • Beraprost sodium (TRK-100STP): 120 µg twice/day (240 µg in total) Control group • Placebo Cointerventions • Not reported
Outcomes	• Doubling of SCr • ESKD (dialysis induction, kidney transplantation, or increase in SCr to ≥ 6.0 mg/dL) • Renal composite endpoint or death (from any causes) • Introduction of dialysis • Kidney transplantation • Increase in SCr to ≥ 6.0 mg/dL

CASSIOPEIR 2014 *(Continued)*

- Slope of 1/SCr versus time
- eGFR
- Adverse events
- Laboratory tests (including ACR)
- Vital signs (including BP)
- Bodyweight
- 12-lead ECG
- Cardiovascular events
- Bleeding events

Notes	• Funding: Akio Koyama

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After the run-in period, patients were randomly assigned in a 1:1:1 ratio via a computer generated randomisation sequence" Comment: Computer-generation is considered as low risk of bias
Allocation concealment (selection bias)	Low risk	Quote: "After the run-in period, patients were randomly assigned in a 1:1:1 ratio via a computer generated randomisation sequence, with either an interactive voice or web-response system" Comment: Interactive voice or web-response system are considered as low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Prior to the start of the study, an Endpoint Judgment Committee (EJC) and Data and Safety Monitoring Board (DSMB) were established. The EJC, comprised of three members not involved directly in the study, examined the validity of dialysis introduction, renal transplantation, and cardiovascular events among the efficacy endpoints in each institution. Both the EJC and DSMB provided oversight of the study without breaking the blinded randomisation of the patients." Comment: Since an external and blinded committee assessed the outcomes, it is considered at low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "After removing patients who did not provide the appropriate consent (n = 2), the safety population consisted of 890; patients 299 received TRK-100STP 120 µg, 300 received TRK-100STP 240 µg, and 291 received the placebo. After excluding patients who were missing data after receiving the study drug (n = 4) and who failed to meet the inclusion and exclusion criteria (n = 1), the full analysis set included 885 patients; 296 received TRK-100STP 120 µg, 298 received TRK-100STP 240 µg and 291 received the placebo." Comment: 296/299 in the treatment group 1, 298/301 in the treatment group 2 and 291/292 in the control group completed the intention to treat analysis, respectively (< 10% of lost to follow-up without differences between groups)
Selective reporting (reporting bias)	Low risk	Outcomes reported according to published protocol. Study endpoints included all critical outcomes that would be expected for this type of study

CASSIOPEIR 2014 *(Continued)*

Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

Chan 1987

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 33.2 months
Participants	• Country: Hong Kong • Setting: single centre • Inclusion criteria: biopsy-proven IgA glomerulonephritis • Number: treatment group (19); control group (19) • Mean age ± SEM (years): treatment group (29.0 ± 2.5); control group (27.5 ± 1.9) • Sex (M/F): treatment group (10/9); control group (14/5) • Mean SCr ± SEM (mmol/L): treatment group (0.125 ± 0.017); control group (0.130 ± 0.015) • Exclusion criteria: not reported
Interventions	Treatment group • Slow-release aspirin: 650 mg/day • Dipyridamole: 25 to 75 mg 3 times/day Control group • Vitamin B complex (placebo) Cointerventions • Not reported
Outcomes	• Slope of 1/Cr • BP • SCr (kidney function) • Serum albumin • Serum uric acid • Serum calcium • Serum phosphorous • Serum immunoglobulins (IgG, IgA, IgM) • 24-hour urine protein excretion • CrCl • Morphologic score
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement

Chan 1987 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported; outcomes were generally unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall, 14/52 did not complete follow-up. Uncertain reasons
Selective reporting (reporting bias)	High risk	Study endpoints did not include all critical outcomes that would be expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias

CHANCE 2013

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: October 2009 to July 2012 • Duration of follow-up: 90 days

Participants	• Country: China
	• Setting: multicentre (114 sites)
	• Inclusion criteria: ≥ 40 years (data reported for CKD patients); within 24 hours of the onset of minor ischaemic stroke or high-risk TIA; ability to start drug within 24 hours after symptom onset
	• Total number: 5170
	• Participants with eGFR < 60 mL/min/1.73 m^2
	  ○ Number: 354
	  ○ Median age (IQR): 73.35 years (65.59 to 77.15)
	  ○ M/F: 196/158
	• Exclusion criteria: severe kidney dysfunction, defined as SCr > 1.5 times ULN

Interventions	Treatment group • Clopidogrel: initial dose of 300 mg, followed by 75 mg for 90 days • Aspirin: 75 mg for the first 21 days Control group • Placebo • Asprin: 75 mg/day for 90 days Cointerventions • Not reported
Outcomes	• New stroke events

CHANCE 2013 *(Continued)*

	• Combined vascular event (ischaemic stroke, haemorrhagic stroke, MI, or vascular death) • Mild-to-severe bleeding episodes
Notes	• Funding: Grants from the Ministry of Science and Technology of the People's Republic of China (2006BAI01A11, 2011BAI08B01, 2011BAI08B02, 2012ZX09303-005-001, and 2013BAI09B03), a grant from the Beijing Biobank of Cerebral Vascular Disease (D131100005313003), a grant from Beijing Institute for Brain Disorders (BIBD-PXM2013_014226_07_000084), and a grant from Beijing high-level talents in healthcare system (2014-3-021)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The site investigator called into an automated system that randomly assigned a number corresponding to a medication kit stored at the study site, and the medication in the kit was administered to the patient." Comment: Automised system random number generator is considered as low risk of bias
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All reported efficacy and safety outcomes were confirmed by a central adjudication committee that was blinded to the study group assignments."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "A total of 5170 eligible patients were enrolled at 114 medical centres in China. Among them, 5150 (99.61%) subjects with renal parameters and 90-day outcome data were analysed in this study." Comment: Insufficient data on CKD patients to permit judgement
Selective reporting (reporting bias)	Low risk	Study endpoints included all critical outcomes that would be expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

CHARISMA 2006

Study characteristics

Methods	• Study design: parallel RCT (post hoc analysis) • Duration of study: not reported • Duration of follow-up: median of 28 months (18 to 42 months)
Participants	• Country: multinational (32 countries) • Setting: multicentre (768 sites) • Inclusion criteria: ≥ 45 years and one of the following conditions:

CHARISMA 2006 *(Continued)*

- Multiple atherothrombotic risk factors (type 1 or 2 diabetes with drug therapy, DKD, ABI < 0.9, asymptomatic carotid stenosis ≥ 70% of the luminal diameter, ≥ 1 carotid plaque as evidenced by intima-media thickness, SBP ≥ 150 mm Hg, despite the therapy for at least 3 months, primary hypercholesterolaemia, current smoking > 15 cigarettes/day, male sex and age ≥ 65 years or female sex and age ≥ 70 years
- Documented coronary disease (angina with documented multivessel coronary disease, history of multivessel PCI, history of multivessel coronary-artery bypass grafting, MI)
- Documented cerebrovascular disease (TIA during previous 5 years, ischaemic stroke during previous 5 years)
- Documented symptomatic peripheral arterial disease (current intermittent claudication and previous intervention; e.g. amputation, peripheral bypass, or angioplasty)
- Only patients with DKD were included in the post hoc analysis of the study

- Number: treatment group (1006); control group (1003)
- Mean age (years): treatment group (63.1); control group (63)
- Sex M/F: treatment group (661/345); control group (677/326)
- Exclusion criteria: oral antithrombotic medications or NSAIDs on a long term basis (although cyclooxygenase-2 inhibitors were permitted); established indications for clopidogrel therapy (such as a recent acute coronary syndrome); scheduled to undergo revascularization were not allowed to enrol until the procedure had been completed; such patients were excluded if they were considered to require clopidogrel after revascularization

Interventions	Treatment group • Clopidogrel: 300 mg loading dose followed by 75 mg, median of 28 months (18 to 42 months) • Aspirin: 75 to 162 mg/day, median of 28 months (18 to 42 months) Control group • Placebo • Aspirin: 75 to 162 mg/day, median of 28 months (18 to 42 months) Cointerventions • Not reported
Outcomes	• MI, stroke (of any cause) and MI and stroke events • Severe bleeding • Moderate bleeding • Minor bleeding • Fatal bleeding • Primary intracranial haemorrhage • Hospitalised for unstable angina, a TIA, or a revascularization procedure (coronary, cerebral, or peripheral) • Death from any cause and death from cardiovascular causes as well as MI, ischaemic stroke, any stroke, and hospitalisation for unstable angina, TIA, or revascularization, considered separately
Notes	• Funding: Sanofi Aventis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement

CHARISMA 2006 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "Study-drug assignment performed centrally by an interactive voice-response system, on the basis of a pre-established randomisation scheme, stratified according to site."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. However, outcomes assessment may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients were followed until a common study end date based on the prespecified target of 1040 primary efficacy end points was reached." Comment: Attrition was considered as a low risk of bias
Selective reporting (reporting bias)	Low risk	The study protocol was available. Study endpoints included all critical outcomes that would be expected for a study of this type
Other bias	High risk	No evidence of other sources of bias. The role of funding was not reported

Cheng 1998a

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 54 (26 to 56) (median and range) months
Participants	• Country: Hong Kong • Setting: single centre • Inclusion criteria: 21 to 65 years; biopsy-proven IgAN and at least 2 features suggestive of progressive disease, namely, proteinuria persistently above 1 g/day; MAP persistently > 107 mm Hg; kidney impairment (SCr > 0.12 but < 0.4 mmol/L) and the presence of tubulointerstitial scarring, tubular atrophy and global or segmental glomerulosclerosis on initial kidney biopsy • Number (randomised/analysed): treatment group (20/19); control group 1 (15/12); control group 2 (17/16) • Mean age ± SD (years): treatment group (38.5 ± 8.7); control group 1 (37.2 ± 7.0); control group 2 (35.8 ± 9.7) • Sex (M/F): treatment group (9/10); control group 1 (8/4); control group 2 (8/8) • Exclusion criteria: past history of MI or stroke; resting MAP < 80 mm Hg; previous history of allergy or intolerance to nadolol, captopril and ticlopidine; SLE, Henoch Scholein purpura and hepatic glomerulosclerosis
Interventions	Treatment group • Captopril: 6.25 mg twice/day • Ticlopidine: 250 mg twice/day for a median time of 54 months Control group 1 • Captopril: starting dose was 6.25 mg twice/day, without antiplatelet agent Control group 2

Cheng 1998a *(Continued)*

	• Nadolol: 40 mg/day, without antiplatelet agent Cointerventions • Not reported
Outcomes	• Urinary protein and albumin excretion • Kidney survival (defined as doubling of SCr levels) • Slope of 1/creatinine • ESKD • Slope of GFR • BP • Serum lipid • Calcium • Phosphate • Urate • Liver enzymes • Hb • WBC • Platelet counts
Notes	• Funding: Grant from the Renal Research Fund, The University of Hong Kong (Grant no. 360-0414599). "The authors wish to thank Bristol-Myer-Squibb (Hong Kong) Ltd and Sanofi Withrop Hong Kong Ltd for supporting the study"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and/or investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Outcome assessment was unlikely to be influenced by knowledge of treatment outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	1/17 (nadolol group), 3/15 (captopril group) and 1/20 (treatment group) participants in the three treatment groups withdrew prematurely (differences between groups)
Selective reporting (reporting bias)	High risk	Study endpoints did not include all critical outcomes that would be expected for a study of this type
Other bias	High risk	No evidence of other sources of bias. The role of Bristol-Myer-Squibb and Sanofi were not reported

Christopher 1987

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 2 years
Participants	• Country: USA • Setting: not reported • Inclusion criteria: diabetic glomerulosclerosis and proteinuria progress relentlessly to kidney failure • Number: treatment group (7); control group (6) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Aspirin: 325 mg once/day • Dipyridamole 75 mg 3 times/day Control group • Placebo Cointerventions • Not reported
Outcomes	• Kidney function (slope 1/SCr) • DBP • HbA1c • Urine protein excretion
Notes	• Abstract-only publication • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Outcomes were unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Christopher 1987 *(Continued)*

Selective reporting (reporting bias)	High risk	Study endpoints did not include all critical outcomes that would be expected for a study of this type
Other bias	Unclear risk	Insufficient information to permit judgement

CILON-T 2010

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: September 2006 to June 2009 • Duration of follow-up: 6 months
Participants	• Country: Korea • Setting: multicentre (5 sites) • Inclusion criteria: 18 to 80 years; had angina pectoris or a positive stress test, and had native coronary artery lesions for which DES implantation was feasible; consecutive patients undergoing DES implantation; eGFR 30 to 60 mL/min/1.73 m^2 (moderate kidney dysfunction) • Number (total population/CKD patients): (960/184); treatment group 1 (477/not reported); treatment group 2 (483/not reported) • Mean age ± SD (years) (total population/CKD patients): treatment group 1 (64.8 ± 13/not reported); treatment group 2 (64.0 ± 13/not reported) • Sex (M) (total population/CKD patients): treatment group 1 (68.6%/not reported); treatment group 2 (68.3%/not reported) • Exclusion criteria: hepatic dysfunction; kidney dysfunction (SCr ≥ 2.0 mg/dL or on dialysis); left ventricular ejection fraction 30% or NYHA class III or IV; uncorrected haematological disease; contraindication to or history of allergy to aspirin, clopidogrel, or cilostazol; or expected survival at 2 years because of other medical conditions; taking warfarin or antiplatelet agents except aspirin or clopidogrel
Interventions	Treatment group 1 • Triple antiplatelet therapy: loading doses aspirin (30 mg), clopidogrel (300 to 600 mg) and cilostazol (200 mg), then 100 mg/day, 75 mg/day, and 100 mg twice/day respectively Treatment group 2 • Dual antiplatelet therapy: loading doses aspirin (300 mg) and clopidogrel (300 to 600 mg), then 100 mg/day and 75 mg/day respectively Cointerventions • Not reported
Outcomes	• Platelet function • Change in GFR
Notes	• CKD patients reported in abstract • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement

CILON-T 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. However, outcomes were unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study endpoints did not include all critical outcomes that would be expected for a study of this type
Other bias	Unclear risk	Insufficient information to permit judgement

CREDO 2005

Study characteristics	
Methods	• Study design: parallel RCT (post hoc analysis) • Duration of study: June 1999 to April 2001 • Duration of follow-up: 1 year
Participants	• Country: USA and Canada • Setting: multicentre (99 sites) • Inclusion criteria: symptomatic CAD with objective evidence of ischaemia (e.g. symptoms of angina pectoris, positive stress test results, or dynamic ECG changes); referred for PCI, or thought to be at high likelihood for requiring PCI with either stent placement with or without conventional balloon angioplasty or another revascularization device; ≥ 21 years; informed consent before randomisation; agreed to comply with all protocol-specified procedures; mild or moderate CKD • Number (total population/GFR < 60 mL/min): treatment group (1053/203); control group (1063/208) • Mean age ± SD (years) (total population/GFR < 60 mL/min): treatment group (62 ± 11/not reported); control group (62 ± 11/not reported) • Sex (F) (total population/GFR < 60 mL/min): treatment group (29.3%/not reported); control group (27.9%/not reported) • Exclusion criteria: contraindications to antithrombotic/antiplatelet therapy; > 50% stenosis of the left main coronary artery; failed coronary intervention in the previous 2 weeks; coronary anatomy not amenable to stent placement; persistent ST elevation within 24 hours prior to randomisation; planned staged interventional procedure; administration of the following medications prior to randomisation: GpIIb-IIIa inhibitor within 7 days, clopidogrel within 10 days, or thrombolytics within 24 hours; SCr was not available at study entry
Interventions	Treatment group • Clopidogrel: loading dose of 300 mg followed by 75 mg/day • Aspirin: 325 mg/day for the first 28 days then 81 to 325 mg/day for 1 year Control group • Placebo

CREDO 2005 *(Continued)*

	• Aspirin: 325 mg/day for the first 28 days then 81 to 325 mg/day for 1 year Cointerventions • All patients received clopidogrel (75 mg/day) on days 0 to 28 and aspirin (325 mg daily until day 28, then at the discretion of the investigator) throughout the study period
Outcomes	• Composite of death, MI, and stroke • Individual components of the composite endpoints • Urgent target vessel revascularization or any other revascularization procedure • Major and minor bleeding • Early discontinuation of study drugs • Kidney function • CrCl • Transfusions
Notes	• Funding: This study was supported by a grant from the Bristol-Myers Squibb/Sanofi-Synthelabo partnership. Sanofi-Synthelabo provided the clopidogrel and matching placebo used in this study. Medical specialists employed by the sponsors provided scientific input into the study design and served as nonvoting members of the steering committee. The masked data were collected by an independent clinical research organization • "Drs. Steinhubl, Topol, Caro, and Weintraub received grant support from Sanofi-Synthelabo. Drs. Bouin and Gabriel are employees of Sanofi-Synthelabo. Drs. Jackson and Chen are employees of Bristol-Myers Squibb" • Data were reported in the previous version of this review (Razavian 2010). Authors were contacted on the 22nd December 2021 but they did not reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to groups using a prospective randomisation schedule. The randomisation was performed in blocks of two and stratified by centre." Comment: Random number is considered as low risk of bias
Allocation concealment (selection bias)	Unclear risk	Quote: "When a patient was ready to be randomised, the site dispensed a drug package that contained a unique 4-digit random number; this number was entered on the case report form and provided an identifier of the treatment assigned." Comment: Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. However, outcomes assessment may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients included in intention-to-treat and safety analysis

CREDO 2005 *(Continued)*

Selective reporting (reporting bias)	Low risk	Study endpoints included all critical outcomes that would be expected for a study of this type
Other bias	High risk	Four authors were employees of the Pharmaceutical companies providing the grants

Creek 1990

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 5 months
Participants	• Country: not reported • Setting: not reported • Inclusion criteria: HD patients • Number treatment group (144); control group (141) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Ticlopidine: 500 mg/day for 5 months Control group • Not reported Cointerventions • Not reported
Outcomes	• Death (any cause) • Cardiovascular death • MI • Stroke • Major bleeding
Notes	• Published in an earlier meta-analysis ATT 2002 • Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Creek 1990 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. However, outcomes assessment may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Study endpoints included all critical outcomes that would be expected for a study of this type
Other bias	High risk	Full study report not available

CURE 2000

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: December 1998 to September 2000 • Duration of follow-up: 12 months
Participants	• Country: multinational (28 countries) • Setting: multicentre (482 sites) • Inclusion criteria: hospitalised within 24 hours of the onset of symptoms; positive troponin or creatine kinase-MB levels, or ischaemic changes on ECG, other than ST-segment elevation ≥ 2 mm; eGFR < 64 mL/min were included in the systematic review • Number (total population/eGFR < 64 mL/min): 12,562/4087; treatment group (6259/not reported); control group (6303/not reported) • Mean age ± SD (years) (total population/eGFR < 64 mL/min): treatment group (64.2 ± 11.3/not reported); control group (64.2 ± 11.3/not reported) • Sex (F) (eGFR < 64 mL/min): treatment group (38.7%); control group (38.3%) • Exclusion criteria: contraindications to antithrombotic or antiplatelet therapy; high risk for bleeding; administration of oral anticoagulants; coronary revascularization in the previous 3 months; administration of IV glycoprotein IIb/IIIa inhibitors in the previous 3 days; planned long-term (> 3 months) administration of an NSAID medication
Interventions	Treatment group • Clopidogrel: loading dose 300 mg followed by 75 mg/day for 3 to 12 months (mean duration 9 months) • Aspirin: 75 to 325 mg Control group • Placebo • Aspirin: 75 to 325 mg Cointerventions • Not reported
Outcomes	• Composite of cardiovascular death, non-fatal MI, or stroke

CURE 2000 *(Continued)*

	• Life-threatening, major (requiring transfusion of ≥ 2 units of blood) or minor bleeds events • Need for revascularization
Notes	• Funding: "Sanofi-Synthelabo and Bristol-Meyers Squibb. The study was designed and coordinated and data were analysed independently by an international steering committee and the Canadian Cardiovascular Collaboration Project Office at Hamilton, Ontario, Canada. M.K. was supported by the Sze ´ chenyi Research Project of Hungary. M.T. was supported by the Alberta Heritage Foundation for Medical Research. S.Y. was supported by a Senior Scientist Award of the Canadian Institutes of Health Research and holds an endowed chair of the Heart and Stroke Foundation of Ontario. S.M. was supported by a Canadian Institutes of Health Research New Investigator Award"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients are randomised to either clopidogrel or placebo in CURE by a telephone call to a central, 24-h, computerized randomisation service. Permuted block randomisation, stratified by clinical centre is used." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Patients are randomised to either clopidogrel or placebo in CURE by a telephone call to a central, 24-h, computerized randomisation service located at the Canadian Cardiovascular Collaboration Project Office, McMaster University, Hamilton, Canada."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All primary outcomes and major bleeding complications were determined by adjudicators who were blinded to treatment status."
Incomplete outcome data (attrition bias) All outcomes	Low risk	0.1% were lost to follow-up
Selective reporting (reporting bias)	Low risk	Study endpoints included all critical outcomes that would be expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

Dash 2013

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 8 weeks
Participants	• Country: India • Setting: single centre • Inclusion criteria: CKD; SCr ≥ 1.8 mg/dL; type 2 diabetes; ≥ 50 years

Dash 2013 *(Continued)*

- Number: treatment group 1 (40); treatment group 2 (40)
- Mean age ± SD (years): treatment group 1 (63.2 ± 5.2); treatment group 2 (64.2 ± 5.9)
- Sex M/F: treatment group 1 (26/14); treatment group 2 (30/10)
- Exclusion criteria: underlying peptic ulcer disease, GI bleeding, bleeding disorders, gout, chronic liver disease, asthma, or underlying infection/sepsis; on therapy with anticoagulants, NSAIDs, anti-hypertensive or any antiplatelet agents within 2 months

Interventions	Treatment group 1 • Aspirin (oral): 150 mg once/day for 8 weeks Treatment group 2 • Clopidogrel (oral): 75 mg once/day for 8 weeks Cointerventions • Standard care
Outcomes	• BP • Glycaemia control (fasting and postprandial, HbA1c) • Lipid profile • Inflammatory markers (hypersensitive CRP, ESR, total leukocyte count) • Kidney function (CrCl, urea, SCr, albumin) • Serum electrolytes (sodium, potassium) • Platelet aggregation • United Kingdom Prospective Diabetes Study risk scoring
Notes	• Funding: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done by using computer-generated random list." Comment: Computer-generated random list is considered as low risk of bias
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Outcomes were unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	9/80 participants did not complete follow-up due to non-compliance (3/40 in clopidogrel group and 6/40 in aspirin group; differences between groups)
Selective reporting (reporting bias)	High risk	Study did not report all expected outcomes for this type of study
Other bias	Low risk	No evidence of other sources of bias

Dember 2005

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: 2003 to 2007 • Duration of follow-up: until 150 to 180 days (5 months)
Participants	• Country: USA • Setting: multicentre (9 sites) • Inclusion criteria: undergoing creation of a new upper extremity fistula were eligible for enrolment if they were receiving maintenance treatment with HD or were expected to begin maintenance HD within 6 months • Number: treatment group (441); control group (436) • Mean age ± SD (years): treatment group (52.7 ± 14.7); control group (54.5 ± 14.4) • Sex M/F: treatment group (273/168); control group (275/161) • Exclusion criteria: active bleeding or bleeding events requiring RBC transfusions within the previous 12 weeks; platelet count > 75,000/µL; known coagulopathy; acute ulcer disease; SBP > 200 mm Hg or DBP > 115 mm Hg; advanced liver disease; inability to discontinue antiplatelet or anticoagulant therapy including aspirin during the study drug administration period; pregnancy; current substance abuse
Interventions	Treatment group • Clopidogrel: loading dose of 300 mg on day 1 followed by 75 mg/day, orally for 6 weeks Control group • Placebo Cointerventions • Not reported
Outcomes	• Thrombosis (fistula patency) after fistula creation • Failure to attain suitability for dialysis • Death • Bleeding: fatal, life-threatening, intermediate, major and minor • QoL • Adverse events
Notes	• Funding: National Institutes of Health/national Institute of Diabetes and Digestive and Kidney Disease

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Computer-generated permuted block randomisation with stratification by location of the fistula (forearm vs upper arm) and by centre." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study

Dember 2005 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Independent determinations of the fistula patency were conducted by two independent observers in a random sub-set. Hovewer, outcomes (QoL, adverse events, bleeding) may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Thirty-seven participants (8.4%) in the clopidogrel group and 33 participants (7.6%) in the placebo group discontinued the study medication early. The reasons for early discontinuation of study medication did not differ between treatment groups." Comment: < 10% were lost to follow-up. Missing outcome data balanced in numbers across groups, with similar reasons across groups
Selective reporting (reporting bias)	Low risk	The study protocol was available. Study endpoints included all critical outcomes that would be expected for a study of this type
Other bias	High risk	The study was terminated early by the Data Safety Monitoring Board based in the prespecified stopping rule for efficacy of the intervention of the primary endpoint. Funder was unlikely to influence data analysis and study reporting or interpretation

Dixon 2005

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: January 2003 to 31 July 2007 • Duration of follow-up: 5.1 years (4.5 years for recruitment + 6 additional months of follow-up)
Participants	• Country: USA • Setting: multicentre (13 sites) • Inclusion criteria: ≥ 18 years scheduled to have a new AV graft placed for the purpose of HD and patients currently undergoing long-term HD or expected to undergo it within 6 months after randomisation • Number: treatment group (321); control group (328) • Mean age ± SD (years): (59.1 ± 13.5); control group (57.5 ± 14.9) • Sex (M/F): treatment group (132/189); control group (125/203) • Exclusion criteria: pregnancy or breast-feeding; increased risk of bleeding or a known bleeding disorder; active oesophagitis, gastritis, or peptic ulcer disease; platelet count < 75,000/mm^3; advanced liver disease; requiring an anticoagulant or antiplatelet agent other than aspirin; known allergy or adverse reaction to extended-release dipyridamole + aspirin or with uncontrolled hypertension
Interventions	Treatment group • Dipyridamole: 200 mg • Aspirin: 25 mg twice/day until the occurrence of the primary outcome (4.5 years + 6 additional months of follow-up) Control group • Placebo Cointerventions • Not reported

Dixon 2005 *(Continued)*

Outcomes	• Loss of primary unassisted graft patency, defined as the first occurrence of graft thrombosis • Cumulative graft failure (for patients undergoing regular HD with the use of a catheter, complete graft failure was defined by the failure to use the graft by 12 weeks after placement) • Bleeding (minor or intermediate, major, fatal, life-treating) and bleeding events • Transfusions • Hospitalisations • Adverse events • Serious adverse events • Death from any cause • Number of participants with cardiovascular events (MI and stroke)
Notes	• Funding: The National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, sponsored the study. Boehringer Ingelheim provided the extended-release dipyridamole plus aspirin (Aggrenox), matching placebo, and financial support but was not involved in the design, analysis, interpretation of the study data, or preparation of the manuscript

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was stratified according to clinical centre and access location (forearm or alternative site) with the use of a random permuted-block design." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Randomization is performed centrally via the Internet using a Web browser following verification of eligibility by the Data Coordinating Center (Cleveland Clinic)."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "A sample of angiograms from each clinical centre was reviewed in a blinded manner to confirm that the indication for intervention was uniform across study sites." Comment: Some outcomes may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed
Selective reporting (reporting bias)	Low risk	The study protocol was available. Study endpoints included all critical outcomes that would be expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias. Funder did not influence data analysis and study reporting or interpretation

Dmoszynska-Giannopoulou 1990

Study characteristics

Dmoszynska-Giannopoulou 1990 *(Continued)*

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 7 days
Participants	• Country: Poland • Setting: single centre • Inclusion criteria: undergoing chronic HD treatment for kidney diseases • Number: treatment group (10); control group 1 (10); control group 2 (10) • Mean age (years): treatment group (43.0); control group 1 (45.2); control group 3 (36.9) • Sex (M/F): treatment group (4/6); control group 1 (5/5); control group 2 (8/2) • Exclusion criteria: received drugs known to influence the platelet function for at least 10 days
Interventions	Treatment group • Sulphinpyrazone: 800 mg/day (4 x 200 mg) Control group 1 • Alpha-tocopherol: 600 mg/day (3 x 200 mg) Control group 2 • Standard care without antiplatelet agents. Patients received small doses of vitamin C as placebo (3 x 100 mg) Cointerventions • All patients received a 5000 IU loading dose of heparin with an hourly maintenance dose of 1000 IU
Outcomes	• Platelet count • Platelet aggregation • Platelet factor 3 • Spontaneous aggregation • Circulating platelet aggregates • Heparin neutralizing activity • Availability of PF 3 ratio • Bleeding time
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation

Dmoszynska-Giannopoulou 1990 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes were generally unlike to be influenced by knowledge of treatment allocation. However, bleeding time could be influenced by the knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study endpoints did not include all critical outcomes that would be expected for a study of this type
Other bias	Unclear risk	Insufficient information to permit judgement

Dodd 1980

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 1 month
Participants	• Country: UK • Setting: single centre • Inclusion criteria: individuals with AV shunts (HD patients) • Number: not reported • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Ticlopidine: 250 mg twice/day Control group • Placebo Cointerventions • Not reported
Outcomes	• Fistula function • Platelet aggregation
Notes	• Abstract-only publication • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement

Dodd 1980 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome assessment may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study did not report all outcomes expected in a study of this type
Other bias	Unclear risk	Insufficient information to permit judgement

Donadio 1984

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: April 1975 to August 1981 • Duration of follow-up: 12 months (long-term follow-up extended up to 7 years)
Participants	• Country: USA • Setting: single centre • Inclusion criteria: children and adults with biopsy-proven MPGN • Number (randomised/analysed): treatment group: number (25/21); control group (25/19) • Mean age, range (years): treatment group (32, 6 to 72); control group (29, 11 to 58) • Sex (M/F): treatment group (11/10); control group (12/7) • Exclusion criteria: SLE; essential mixed cryoglobulinaemia; post-streptococcal glomerulonephritis; requirement of dialysis
Interventions	Treatment group • Dipyridamole 75 mg, 3 times/day (225 mg in total) for 12 months • Aspirin: 325 mg, 3 times/day (975 mg in total) for 12 months Control group • Placebo Cointerventions • Not reported
Outcomes	• Kidney function: defined as a decline of 25% or more in iothalamate clearance from the pretreatment clearance • ESKD • Proteinuria and hematuria

Donadio 1984 *(Continued)*

	• SCr • Platelet survival • Whole blood samples • Number of participants with bleeding • Adverse events
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "Treatment was assigned randomly by our statistician in such a manner to achieve maximal balance between the two stratification factors." Comment: Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Some outcomes were likely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	10/50 participants (4/25 in the treatment group and 6/25 in the control group) not included in analyses
Selective reporting (reporting bias)	High risk	Study outcomes did not include critical outcomes expected for this type of study
Other bias	Unclear risk	Insufficient information to permit judgement

EARLY ACS 2005

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 30 days

Participants	• Country: multinational (29)
	• Setting: multicentre (440 sites)
	• Inclusion criteria: CrCl < 50 mL/min; ≥ 18 years; cardiac ischaemias at rest lasting for at least 10 minutes and occurring within 24 hours; presentation within 8 hours of randomisation; planned invasive treatment no sooner than the next calendar day; 2 or more of:
	  ○ Ischaemic changes on ECG
	  ○ Creatine kinase or troponin above ULN range
	  ○ Above 60 years
	• Number (total/CKD population): treatment group 1 (4722/816); treatment group 2 (3684/826)

EARLY ACS 2005 *(Continued)*

- Mean age ± SD (years): not reported
- Sex (M/F): not reported
- Exclusion criteria: increased risk of bleeding; allergy to heparin or eptifibatide; pregnancy; kidney dialysis within previous 30 days; intention of the investigator to use non-heparin anticoagulant; recent use of glycoprotein IIb/IIIa inhibitor; any other condition that imposed increases

Interventions	Treatment group 1 (early routine) • Eptifibatide: 180 µg/kg administered 10 minutes apart and standard infusion of 2.0 µg/kg/min administered concurrently with the first bolus then placebo before PCI • Aspirin: 162 to 325 mg orally or 150 to 500 mg IV followed by 75 mg/day Treatment group 2 (delayed provisional) • Placebo: 180 µg/kg administered 10 minutes apart and standard infusion of 2.0 µg/kg/min administered concurrently with the first bolus then eptifibatide before PCI • Aspirin: 162 to 325 mg orally or 150 to 500 mg IV followed by 75 mg/day Cointerventions • All randomised patients received a double-bolus 180 µg/kg and infusion regimen
Outcomes	• Death from any cause • MI • Recurrent ischaemias requiring revascularization • Thrombotic bailout • Haemorrhage • Transfusion • Surgical reexploration • Stroke • Thrombocytopaenia • Serious adverse events • Bleeding (major and minor) • Non–CABG related transfusion and major bleeding • Severe/moderate bleeding • CrCl
Notes	• Funding: Schering-Plough. These analyses were funded by research grant support from Merck. The authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the paper and its final contents • Data not available for CKD patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was managed through an interactive voice-response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study

EARLY ACS 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Stroke and all efficacy endpoints except death were adjudicated by an independent clinical events committee whose members were unaware of study group assignments. If classification of TIMI bleeding could not be determined by a programmed algorithm, blinded adjudication was performed." Comment: Outcome adjudication (adverse events and death) may have been influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall, 8/4722 in treatment group and 20/4684 in control group did not complete follow-up. Insufficient data on CKD patients
Selective reporting (reporting bias)	Low risk	Study endpoints included all critical outcomes that would be expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

Ell 1982

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 3 months
Participants	• Country: not reported • Setting: not reported • Inclusion criteria: HD patients • Number: treatment group (24); control group (26) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Ticlopidine: 500 mg/day for 3 months Control group • Not reported Cointerventions • Not reported
Outcomes	• Death (any cause) • Cardiovascular death • MI • Stroke • Major bleeding
Notes	• Published results from an earlier systematic review ATT 2002 • Funding: not reported

Ell 1982 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome assessment may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Study outcomes included critical outcomes expected for this type of study
Other bias	High risk	Full study report not available

EPIC 1994

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 1 year
Participants	• Country: USA • Setting: multicentre (56 sites) • Inclusion criteria: scheduled to undergo coronary angioplasty or directional atherectomy with high risk for abrupt vessel closure (data reported for CKD patients) • Number (total population/CKD): treatment group 1+2 (1393/334); control group (696/185) • Mean age (range): 60 years (52 to 68) (not reported for CKD patients) • Sex (M/F): not reported for CKD patients • Exclusion criteria: > 80 years; bleeding diathesis; major surgery within the preceding 6 weeks; stroke within the preceding 2 years
Interventions	Treatment group • c7E3 Fab: bolus dose of 0.25 mg/kg, followed by an infusion of 10 µg/min or infusion of placebo • Aspirin: 325 mg/day at least 2 hours before angioplasty or atherectomy and daily after Control group • Placebo • Aspirin: 325 mg/day at least 2 hours before angioplasty or atherectomy and daily after

EPIC 1994 *(Continued)*

	Cointerventions • Heparin: 10,000 to 12,000 U IV as a bolus, followed by an incremental bolus of up to 3000 U at 15 minutes intervals, but no more than 20,000 U during the procedure
Outcomes	• Composite of death from any cause, nonfatal MI, CABG or repeat percutaneous intervention for acute ischaemia, and insertion of a coronary endovascular stent because of procedural failure or placement of an intra-aortic counter-pulsation balloon pump to relieve refractory ischaemia • Unplanned repeat angioplasty to treat recurrent ischaemia, urgent coronary surgery to treat recurrent ischaemia or failure of an angioplasty, placement of an intracoronary stent to treat imminent or complete abrupt closure of the vessel undergoing angioplasty, and placement of an intra-aortic balloon pump for recurrent ischaemia when a repeat revascularization procedure was contraindicated • Major, minor or insignificant bleeding events • Transfusions • Blood count (HCT and platelet) • Adverse events
Notes	• Funding: grant from Centocor

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Central randomisation by telephone, and patients were stratified according to their study centre and where they having an acute evolving myocardial infarction."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded clinical endpoints committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data available for all baseline participants (and deaths included in intention-yo-treat analysis)
Selective reporting (reporting bias)	Low risk	The study protocol was available. Study outcomes included critical outcomes expected for this type of study
Other bias	High risk	No evidence of other sources of bias. The role of the funder was not reported

EPILOG 1997

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: 27 February 1995 to 14 December 1995 • Duration of follow-up: 1 year

EPILOG 1997 *(Continued)*

Participants	• Country: USA and Canada • Setting: multicentre (69 sites) • Inclusion criteria: undergoing elective or urgent percutaneous coronary revascularization with a device approved by the Food and Drug Administration; > 21 years; target lesion in which there was stenosis of at least 60% of the diameter of the vessel; data reported for CKD patients • Number (total population/CKD population): treatment group 1+2 (1853/325); control group (939/163) • Median, IQR (years): treatment group (60, 51 to 69); control group (60, 51 to 68); not reported for CKD patients • Sex (M/): treatment group (73%); control group (72%); not reported for CKD patients • Exclusion criteria: acute MI or unstable angina with associated ECG changes during the previous 24 hours; planned stent implantation or rotational atherectomy; PCI performed within the previous 3 months; left main coronary artery stenosis of more than 50% not protected by collateral vessels; concurrent warfarin therapy or a baseline prothrombin time > 1.2 times the control value; CVA within the previous 2 years or a residual neurologic deficit; intracranial neoplasm, aneurysm, or AV malformation; history of vasculitis, known haemorrhagic diathesis, or active internal bleeding; hypertension, with SBP > 180 mm Hg or DBP > 100 mm Hg; major surgery, GI bleeding, or genitourinary bleeding within the previous 6 weeks
Interventions	Treatment group • Abciximab: bolus of 0.25 mg/kg administered 10 to 60 minutes before inflation of the balloon or activation of the device, followed by an infusion of 0.125 µg/kg/min (maximum 10 µg/min) for 12 hours • Aspirin (oral): 325 mg 2 hours before the percutaneous revascularization procedure and daily thereafter Control group • Placebo • Aspirin (oral): 325 mg 2 hours before the percutaneous revascularization procedure and daily thereafter Cointerventions • Standard dose heparin (initial bolus of 100 U of heparin/kg (maximum 10,000 U) before the interventional procedure or low dose heparin (initial bolus of 70 U of heparin/kg (maximum 7000 U)
Outcomes	• Death from any cause, MI or reinfarction, or severe myocardial ischaemias requiring urgent coronary bypass surgery or repeated percutaneous coronary revascularization within 30 days after randomisation • Death, MI, or coronary bypass surgery or repeated percutaneous revascularization (urgent or non-urgent) within 6 months after randomisation • Bleeding: major or minor • Transfusion • Hospitalisation
Notes	• Funding: Centocor, Malvern, Pa., and Eli Lilly and Company, Indianapolis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly assigned in a double-blind fashion by means of a central telephone hot line to one of three treatment groups."

EPILOG 1997 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "End-point classifications of a clinical-events committee blinded to the study-group assignment were used for the final analysis."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up < 10%, without differences between groups
Selective reporting (reporting bias)	Low risk	The study protocol was available. Study outcomes included critical outcomes expected for this type of study
Other bias	High risk	Sample size was smaller than planned and the study was terminated earlier because a prespecified stopping rule was met after the first interim analysis. The role of funding was not reported

EPISTENT 1998

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: 22 July 1996 to 25 September 1997 • Duration of follow-up: 1 year
Participants	• Country: USA and Canada • Setting: multicentre (63 sites) • Inclusion criteria: scheduled to undergo elective or urgent percutaneous coronary revascularization were eligible for inclusion if target lesions had caused stenosis of at least 60% amenable to balloon angioplasty or stenting (data reported for CKD patients); target vessel was not an unprotected left mainstem stenosis • Number (total population/CKD patient): treatment groups 1+2 (1590/231); control group (809/137) • Mean age ± SD (years): treatment group 1 (59 ± 11); treatment group 2 (60 ± 11); control group (59 ± 11); not reported for CKD patients • Sex (M/F): treatment group 1 (599/195); treatment group 2 (598/198); control group (603/206); not reported for CKD patients • Exclusion criteria: bleeding diathesis, intracranial neoplasm, or history of stroke in the previous 2 years; uncontrolled hypertension (SBP >180 mm Hg, DBP >100 mm Hg); recent surgery or PCI within the previous 3 months; concurrent warfarin therapy or an INR > 1:5 at baseline
Interventions	Treatment group 1 • Stent • Abciximab: 0.25 mg/kg up to 60 min before intervention, followed by an infusion of 0.125 µg/kg every 1 minute (maximum 10 µg/min) for 12 hours • Aspirin: 325 mg orally at least 2 hours before the intervention, and daily thereafter • Ticlopidine: 250 mg twice/day (at the discretion of the investigator) Treatment group 2 • Balloon angioplasty

EPISTENT 1998 *(Continued)*

	• Abciximab: 0.25 mg/kg up to 60 min before intervention, followed by an infusion of 0.125 µg/kg every 1 minute (maximum 10 µg/min) for 12 hours • Aspirin: 325 mg orally at least 2 hours before the intervention, and daily thereafter Control group • Stent • Placebo • Aspirin: 325 mg orally at least 2 hours before the intervention, and daily thereafter • Ticlopidine: 250 mg twice/day (at the discretion of the investigator) Cointerventions • All patients received standard pharmacological therapy • Heparin: 70 U/kg (maximum 7000 U) with additional boluses as necessary to achieve and maintain an activated clotting time of at least 200 sec or initial bolus of 100 U/kg (maximum 10,000 U) with additional boluses to achieve and maintain an activated clotting time of at least 300 sec
Outcomes	• Combination of death from any cause, MI or reinfarction, or severe myocardial ischaemias requiring urgent coronary artery bypass surgery or revascularization within 30 days of intervention • Death or MI, and death or large, MI defined as new pathological Q waves or a value of creatine kinase or its MB isoenzyme at least 5 times the upper laboratory limit • Number of patients with major and minor bleeding • Transfusion
Notes	• Funding: Centocor. The sponsor were masked to study-drug assignment in the stent groups and results of the endpoints

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "We received the randomisation schedule by a telephone hotline."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All endpoint events were assessed by a clinical events committee that was unaware of study-group assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data provided for all patients
Selective reporting (reporting bias)	Low risk	The study protocol was available. Study outcomes included critical outcomes expected for this type of study
Other bias	Low risk	No evidence of other sources of bias. Funder did not influence data analysis and study reporting or interpretation

ETDRS 1992

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: April 1980 to July 1985 • Duration of follow-up: at least 5 years
Participants	• Country: USA • Setting: multicentre (22 sites) • Inclusion criteria: men and women 18 and 70 years at the first screening visit, who had a clinical diagnosis of diabetes and diabetic retinopathy (unpublished data for individuals with CKD (185 patients) defined as SCr > 133 µmol/L were available) • Number (total population/CKD patients): treatment group (1856/79); control group (1855/106) • Mean age ± SD (years): treatment group (55.2 ± 10.5); control group (52.1 ± 11.8) • Sex (M): treatment group (74.6%); control group (66.0%) • Exclusion criteria: SBP > 210 mm Hg and/or DBP > 110 mm Hg despite the use of antihypertensive medication; history of GI haemorrhage or diagnosis of active GI ulcer in the past 2 years; inability or unwillingness to stop taking anticoagulants or antiplatelet agents; allergy to aspirin; pregnancy or lactation; poor prognosis for 5 years follow-up because of a prior cardiovascular event, cancer or other chronic diseases
Interventions	Treatment group • Aspirin: 650 mg/day Control group • Placebo Cointerventions • Not reported
Outcomes	• Unpublished data for death (any cause), cardiovascular death, stroke, MI, ever on dialysis, ever kidney transplantation, dialysis or transplantation, serious CKD, cause-specific death, bleeding
Notes	• Unpublished data only used • Funding: National Eye Institute

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The randomisation was designed to provide balance in the number of patients assigned to aspirin or placebo within each clinical centre." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias)	Low risk	Outcomes assessment was performed without knowledge of treatment assignment

ETDRS 1992 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Unpublished data only used. All participants were analysed
Selective reporting (reporting bias)	Low risk	Unpublished data only used. Study outcomes included critical outcomes expected for this type of study
Other bias	Low risk	Unpublished data only used. No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

EUCLID 2017

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: December 2012 to March 2014 • Duration of follow-up: median 30 months
Participants	• Country: multinational (28 countries) • Setting: multicentre (811 sites) • Inclusion criteria: ≥ 50 years with lower extremity peripheral artery disease; required to have one of two inclusion criteria: 1) previous revascularization of the lower limbs for symptomatic disease more than 30 days before randomisation or 2) haemodynamic evidence of peripheral artery disease, as evidenced by an ABI of ≤ 0.80 at screening; subgroup analyses was performed in people with eGFR < 60 mL/min/1.73 m^2 and diabetes • Number (total population/CKD patients): 13,885/3949; treatment group 1 (6930/not reported for CKD patients); treatment group 2 (6955/not reported fro CKD patients) • Median age, IQR (years): treatment group 1 (66, 60 to 70); treatment group 2 (66, 60 to 73); not reported for CKD patients • Sex (F): treatment group1 (27/5%); treatment group 2n (28.5%); not reported for CKD patients • Exclusion criteria: planned use of dual antiplatelet therapy or the use of aspirin; high risk of bleeding; treatment with anticoagulation; poor metabolizers status for CYP2C19; planned revascularization (any territory); major amputation within 3 months
Interventions	Treatment group • Ticagrelor: 90 mg twice/day Control group • Clopidogrel: 75 mg/day Cointerventions • Not reported
Outcomes	• Composite of cardiovascular, death, MI, ischaemic stroke • Composite of CV death, MI, ischaemic stroke, and acute limb ischaemia • CV death • MI • Death (any cause) • Composite of CV death, MI, and all-cause stroke (ischaemic or haemorrhagic) • Acute limb ischaemia • Lower extremity revascularization

EUCLID 2017 *(Continued)*

- Any revascularization
- Net clinical benefit: composite of CV death/MI/ischaemic stroke/fatal bleeding/intracranial bleeding
- Net clinical benefit: composite of death (any cause)/MI/ischaemic stroke/fatal bleeding/intracranial bleeding
- Net clinical benefit: composite of death (any cause)/MI/ischaemic stroke/acute limb ischaemia/major amputation/fatal bleeding/intracranial bleeding
- Non-CV death
- Changes in Fontaine stage
- Changes in Rutherford classification
- Change in ABI/toe-brachial index
- Any amputation caused by peripheral artery disease
- Major amputation caused by peripheral artery disease
- CV-related hospitalisation
- Thrombolysis in MI major bleeding events
- Thrombolysis in MI major or minor bleeding events
- Platelet inhibition and patient outcomes major bleeding events
- Premature permanent discontinuation of study drug due to any bleeding event

Notes	• Funding: AstraZeneca • Note: Authors contacted on the 10/7/2021 but they did not reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from Hiatt 2017: "Randomization was performed with the use of an interactive voice-response or Web-response system."
Allocation concealment (selection bias)	Low risk	Quote from Hiatt 2017: "Randomization was performed with the use of an interactive voice-response or Web-response system."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double-blind." Comment: Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from Hiatt 2017: "All primary efficacy and safety end points were adjudicated by an independent clinical events committee in a blinded fashion."
Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Prespecified outcomes were reported. Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	Unclear risk	Quote from Hiatt 2017: "The Duke Clinical Research Institute held the clinical database and conducted all analyses for publication independent of the sponsor." Comment: Baseline characteristics were not reported for patients with CKD and diabetes. Funding did not influence analysis

FAVOURED 2009

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: 21 August 2008 and 28 February 2015 • Duration of follow-up: 12 months
Participants	• Country: multinational (Australia, Malaysia, New Zealand, UK) • Setting: multicentre (35 sites) • Inclusion criteria: adult patients with stage IV or V CKD; currently on HD or where HD is planned to start within 6 months in whom a planned upper or lower arm AVF is to be the primary HD access • Number: treatment group (203); control group (203) • Mean age ± SD (years): treatment group (52.3 ± 14.5); control group (53.8 ± 14.9) • Sex (M/F): treatment group (125/78); control group (131/72) • Exclusion criteria: increased bleeding risk; taking aspirin within 2 weeks or fish oil within 4 weeks; taking NSAIDs, anticoagulants, or antiplatelet agents or contraindications to study interventions
Interventions	Treatment group • Aspirin: 100 mg/day Control group • Placebo Cointerventions • Omega-3 fatty acids (fish oil)
Outcomes	• AVF access failure • AVF thrombosis • AVF abandonment • Cannulation failure • Adverse events, particularly bleeding events and GI adverse events • Death • Serious adverse events • Cardiovascular disease • AVF intervention
Notes	• Funding: Grant support from the National Health and Medical Research Council (NHMRC) project grant, grants from Mylan EPD (at the time of funding was Abbott Products Operations AG), grants from Amgen Australia Pty Ltd, grant support the Royal Australasian College of Physicians (Jacquot National Health and Medical Research Council Medical Award for Excellence)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by a central, web-based system (Flexetrials) using an adaptive minimization algorithm with study site and planned location of the AVF (upper vs lower arm) as minimization variables." Comment: Adaptive minimization algorithm is considered as low risk of bias
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by a central, web-based system (Flexetrials)."

FAVOURED 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome assessment may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Study outcomes included critical outcomes expected for this type of study
Other bias	High risk	Due to early cessation of recruitment, only the first interim analysis was performed after which the study continued as planned until terminated because of slower than anticipated accrual, funding issues, and lack of ongoing availability of trial medications. The role of the funder were not reported

Fiskerstrand 1985

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 1 month
Participants	• Country: Scotland • Setting: single centre • Inclusion criteria: requiring access surgery for chronic HD • Number: treatment group (8); control group (10) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: platelet-modifying agent or on anticoagulant therapy (apart from heparin while on HD); history of active peptic ulcer within the previous 3 years; any known haemorrhagic diathesis not due to uraemia; platelet count < 100,000/mm^3
Interventions	Treatment group • Ticlopidine: 250 mg twice/day started 2 days prior to access operation Control group • Placebo Cointerventions • Not reported
Outcomes	• Adverse events • Fistula thrombosis • Platelet aggregation

Fiskerstrand 1985 *(Continued)*

Notes	• Funding: Sanofi UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome adjudication may have been influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	3/18 patients did not complete the trial (1/10 in the placebo group and 2/8 in the treatment group)
Selective reporting (reporting bias)	High risk	Study outcomes did not include critical outcomes expected for this type of study
Other bias	High risk	Insufficient information to permit judgement. The role of the funder was not reported

Frascà 1986

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 4 years
Participants	• Country: Italy • Setting: single centre • Inclusion criteria: patients undergoing their first kidney transplant with immediate graft function restored • Number: treatment group (40); control group (40) • Mean age (years): treatment group (32); control group (34) • Sex (M/F): not reported • Exclusion criteria: DM
Interventions	Treatment group • Defibrotide: continuous IV infusion at 10 mg/kg/day for 3 to 5 days postoperatively, followed by the same dose orally thereafter for 12 to 34 months (mean 24 months) Control group

Frascà 1986 *(Continued)*

	• Dipyridamole: IV at 0.5 mg/kg/day for 2 to 4 days followed by 6 to 8 mg/kg/day orally thereafter for 14 to 36 months (mean 25 months) Cointerventions • All participants received the same immunosuppressive therapy, which consisted of methylprednisolone at the initial dose of 10 to 15 mg/kg/day (tapered to 1 mg/kg/day), AZA 2 to 3 mg/kg/day and antilymphocyte globulin at the dose of 10 mg/kg/day, administered for 8 to 12 days after surgery • All patients were transfused before transplantation
Outcomes	• Rejection • Second rejection • Functioning grafts at follow-up • Bleeding events • Death • Kidney damage (SCr) • Kidney function survival • Adverse events • MI
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome adjudication may have been influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	0/40 patients in group A and 4/40 patients in group were not included in analysis (differences between groups)
Selective reporting (reporting bias)	Low risk	Study outcomes included critical outcomes expected for this type of study
Other bias	Low risk	No evidence of other sources of bias

Frascà 1997

Study characteristics

Methods	• Study design: parallel RCT

Frascà 1997 *(Continued)*

	• Duration of study: not reported • Duration of follow-up: 24 months
Participants	• Country: Italy • Setting: single centre • Inclusion criteria: IgAN and reduced kidney function at diagnosis (SCr ≥ 1.4 mg/dL); 18 to 46 years • Number: treatment group (10); control group (10) • Mean age ± SD (years): treatment group (30 ± 6); control group (31 ± 9.8) • Sex (M/F): treatment group (8/2); control group (10/0) • Exclusion criteria: systemic or hepatic dysfunction; previous treatment for IgAN
Interventions	Treatment group • Defibrotide: 10 mg/kg/day • Prednisolone: 0.5 mg/kg/day on alternate days for 6 months Control group • Prednisolone: (standard care) without antiplatelet agents for 6 months Cointerventions • No patients underwent dietary protein restrictions • All patients underwent physical examination
Outcomes	• Change in SCr and daily protein excretion before and after treatment • Percentage change in CrCl • Adverse events
Notes	• Funding: 1996 MURST and University of Bologna

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome adjudication may have been influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study did not report all expected outcomes expected for a study of this type

Frascà 1997 *(Continued)*

Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

Gaede 2003

Study characteristics

Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 4 weeks
Participants	• Country: Denmark • Setting: single centre • Inclusion criteria: type 2 diabetes; UACR 30 to 300 mg/mg • Number: 31; treatment group (15); control group (16) • Mean age ± SD: 56.3 ± 7.1 years • Sex (M/F): 21/10 • Exclusion criteria: prior MI; prior cerebral thrombosis; NSAIDs; peptic ulcer disease
Interventions	Treatment group • Aspirin: 150 mg/day Control group • Placebo Cointerventions • Not reported
Outcomes	• GFR • UAE • BP • HbA1c • Bleeding gastric ulcer
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The randomisation was individual with concealed, computer-generated envelopes." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomisation was individual with concealed, computer-generated envelopes." Comment: Insufficient information to permit judgement (not reported if envelopes were opaque and numbered)

Gaede 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome adjudication (due to nature of outcomes) was generally unlikely to be influenced by knowledge of treatment allocation. However, bleeding may be influenced by the knowledge of the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "31 patients, who all gave informed consent, entered and completed the study." Comment: All participant completed the study
Selective reporting (reporting bias)	High risk	Study outcomes did not include all expected for this type of study. Data were not appropriately reported for a cross-over RCT
Other bias	High risk	Analyses were not reported appropriately for cross-over RCT design

Ghorbani 2009

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: December 2006 to March 2008 • Duration of follow-up: 6 months
Participants	• Country: Iran • Setting: single centre • Inclusion criteria: patients close to initiation of HD requiring AVF, chronic HD patients requiring a new AVF at a different site; > 18 years • Number: treatment group (46); control group (47) • Mean age ± SD (years): treatment group (44.23 ± 3.36); control group (45.8 ± 2.84) • Sex (M/F): treatment group (24/22); control group (24/23) • Exclusion criteria: history of GI bleeding or previous bleeding episodes within 6 months prior to initiation of the study; patients already on chronic antiplatelets or anticoagulation; patients with terminal or life-threatening disease; pregnancy; malignant hypertension; platelet count < 100,000/mm^3 and other medical conditions that would make antiplatelet therapy dangerous
Interventions	Treatment group • Clopidogrel: 75 mg/day starting 7 to 10 days prior to scheduled access surgery and continued up to 6 weeks postoperatively Control group • Placebo Cointerventions • Not reported
Outcomes	• Death • Severe life-threatening events • Severe bleeding (such as intracranial bleeding) • AVF failure 8 weeks after fistula creation

Ghorbani 2009 *(Continued)*

	• Adverse events • Platelet homeostatic function • Start dialysis during the study • Changes on HCT values or changes in rHuEPO doses
Notes	• Funding: Ahvaz Jondi Shapour University of Medical Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The randomisation was stratified according to medical centre with a permuted block scheme, with a block size of four and equal allocation." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed centrally, by the coordinating centre."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Fistula failure was determined by a member of the team who was blinded to treatment allocation. [...] Assessment of the severity of bleeding episodes was performed by a panel blinded to the treatment assignment." Comment: Although the panel was blinded, some outcomes adjudication may have been influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	75/93 patients completed study (38 participants in clopidogrel group and 37 participants in placebo group). Limited information provided
Selective reporting (reporting bias)	Low risk	Study outcomes included critical outcomes expected for this type of study
Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

Ghorbani 2013

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 9 weeks (the treatment was initiated 7 to 10 days prior to scheduled access surgery and continuing for 8 weeks postoperatively)
Participants	• Country: Iran • Setting: single centre • Inclusion criteria: ≥ 18 years; chronic HD requiring a new AVF or close to initiation of HD • Number: treatment group (32); control group (32) • Mean age ± SD (years): not reported

Ghorbani 2013 *(Continued)*

	• Sex (M/F): not reported • Exclusion criteria: history of GI bleeding or previous bleeding; receiving chronic anticoagulation therapy; terminal or life-threatening disease; pregnancy; malignant hypertension; platelet count < 100,000/µL or known anticoagulation abnormalities
Interventions	Treatment group • Ticlopidine: 250 mg twice/day initiated 7 to 10 days prior to scheduled access surgery Control group • Placebo Cointerventions • Not reported
Outcomes	• Unassisted fistula patency • Fistula suitability for dialysis • AVF failure • Adverse events • Death • Whole-blood bleeding time • Bleeding (mild and severe) and bleeding episodes • Start dialysis during the study • Changes on HCT values or changes in rHuEPO doses
Notes	• Funding: Ahvaz Jundishapur University of Medical Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The randomisation was stratified according to medical centre with a permuted block scheme, with a block size of four and equal allocation." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed centrally, by the coordinating centre."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessment of the severity of bleeding episodes was performed by a panel blinded to the treatment assignments. Hovewer, outcome adjudication may have been influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients were lost to follow-up
Selective reporting (reporting bias)	Low risk	Study outcomes included critical outcomes expected for this type of study

Ghorbani 2013 *(Continued)*

Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

Giustina 1998

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 12 months
Participants	• Country: Italy • Setting: single centre • Inclusion criteria: type 2 diabetic patients who were normotensive and had microalbuminuria while at rest; aged 40 to 65 years; known duration of diabetes > 12 months; HbA1c < 10%; stable BMI (35 kg/m^2); supine BP < 140/90 mm Hg; SCr < 106 µmol/L; 24-hour UAE 20 to 200 µg/min; no cardiovascular, hepatic or systemic disease before starting the study • Number (randomised/analysed): treatment group (16/15); control group (17/15) • Mean age ± SD (years): treatment group (56 ± 2); control group (57 ± 3) • Sex (M/F): treatment group (13/2); control group (13/2) • Exclusion criteria: presence of kidney or hepatic disease; ECG abnormalities at rest or exercise-induced; peptic ulcer disease or previous haemorrhage episodes; treatment with other antiplatelet agents or ACEi
Interventions	Treatment group • Picotamide: 300 mg, 3 times/day for 12 months Control group • Placebo: 3 times/day Cointerventions • The patients were treated with an isocaloric diet with no restriction on sodium intake and oral hypoglycaemic agents • All patients underwent submaximal physical exercise
Outcomes	• SCr • CrCl • UAE at rest and post-exercise • Adverse events • BP • Blood glucose • Serum picotamide • ECG abnormalities
Notes	• Funding: Grant of Regione Lombardia

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Giustina 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Central randomisation."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes were likely to be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "An overall number of 33 patients were enrolled in the study. Three patients spontaneously withdrew from the study during the first 3 months of follow-up due to lack of compliance. Two of these patients were in the placebo group, and the other was in the picotamide group." Comment: Although in total 9% were lost to follow-up, there were some differences between groups
Selective reporting (reporting bias)	High risk	Study did not report all outcomes expected for this type of study
Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

GLOBAL LEADERS 2018

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: 1 July 2013 to 9 November 2015 • Duration of follow-up: 24 months
Participants	• Country: multinational (18 countries) • Setting: multicentre (130 sites) • Inclusion criteria: ≥ 18 years; presence of one or more coronary artery stenoses of 50% or more in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation. The vessel should have a reference vessel diameter of at least 2.25 mm (no limitation on the number of treated lesions, vessels, or lesion length); able to provide informed consent and be willing to participate in 2-year follow-up period • Number (total population/CKD patients): treatment group (7992/428); control group (7999/410) • Mean age ± SD (years): not reported for CKD patients • Sex (M/F): not reported for CKD patients • Exclusion criteria: known intolerance to aspirin, P2Y12 inhibitors, bivalirudin, stainless steel or biolimus stent; known intake of a strong CYP3A4 inhibitor (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir), as co-administration may lead to a substantial increase in exposure to ticagrelor; known moderate to severe hepatic impairment (alanine-aminotransferase ≥ 3 times ULN); planned surgery, including CABG as a staged procedure (hybrid) within 12 months of the index procedure, unless dual antiplatelet therapy is maintained throughout the peri-surgical period; need for chronic oral anticoagulation therapy; active major bleeding or major surgery within the last 30 days; known history of intracranial haemorrhagic stroke or intracranial aneurysm; known stroke (any

GLOBAL LEADERS 2018 *(Continued)*

	type) within the last 30 days; known pregnancy at time of randomisation; female who is breastfeeding at time of randomisation; currently participating in another trial and not yet at its primary endpoint
Interventions	Treatment group • Dual-antiplatelet therapy: aspirin 75 to 100 mg once/day + ticagrelor 90 mg twice/day for one month • Ticagrelor monotherapy for 23 months Control group • Reference regimen (aspirin 75 to 100 mg daily in combination with either clopidogrel 75 mg once/day in patients with stable CAD or ticagrelor 90 mg twice/day in patients with acute coronary syndromes for 1 year, followed by aspirin 75 to 100 mg once/day alone for the following 12 months (from 12 to 24 months after PCI) Cointerventions • Not reported
Outcomes	• Composite endpoint of all-cause death or new Q-wave MI at 2 years. The POCE was defined as the composite of all-cause death, any stroke, site-reported MI and any revascularization, whereas NACE combined POCE with BARC type 3 or 5 bleeding events • Investigator-reported BARC type 3 or 5 bleeding • Individual components of the primary endpoint (all-cause death, new Q-wave MI), individual components of key secondary safety endpoint (BARC defined bleeding type 3 or type 5 bleeding) • Any stroke • Site-reported MI • Any revascularization • Target vessel revascularization • Definite stent thrombosis defined according to the Academic Research Consortium criteria
Notes	• Funding: European Clinical Research Institute, which received unrestricted grants from Biosensors International, AstraZeneca, and the Medicines Company • Note: Authors contacted on the 10/7/2021 but they did not reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote from Tomaniak 2020: "Open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Objective and subjective outcomes were reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote from Gao 2020: "All the analyses were performed by the intention-to-treat principle."

GLOBAL LEADERS 2018 *(Continued)*

		Comment: ITT analyses were performed however data on discontinuations were not clearly stated
Selective reporting (reporting bias)	High risk	Prespecified outcomes were reported. Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	Quote from Hiatt 2017: "The Duke Clinical Research Institute held the clinical database and conducted all analyses for publication independent of the sponsor." Comment: Baseline characteristics were not reported for patients with CKD and diabetes. Funding was likely to influence data analysis and interpretation

Goicoechea 2012

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study (recruitment): January 2007 to May 2007 • Duration of follow-up: mean follow-up 88.2 ± 40 months
Participants	• Country: Spain • Setting: single centre • Inclusion criteria: eGFR < 60 mL/min/1.73 m^2; stable clinical condition defined as no hospitalisations or cardiovascular events within the 3 months before screening and stable kidney function (baseline SCr had to have not increased by 50% in the 3 months before screening) • Number: treatment group (46); control group (45) • Mean age ± SD (years): treatment group (70 ± 14); control group (70 ± 8) • Sex (M/F): not reported • SCr (mg/dL): treatment group (1.7 ± 0.5); control group (1.7 ± 0.5) • Exclusion criteria: history of pentoxifylline hypersensitivity; already on pentoxifylline treatment; active infections or inflammatory diseases or HIV infection; chronic liver disease; received immunosuppressive therapy
Interventions	Treatment group • Pentoxifylline: 400 mg, twice/day Control group • Standard treatment, without antiplatelet agents Cointerventions • Not reported
Outcomes	• Dialysis therapy • Doubling SCr • ≥ 50% decrease in eGFR • Cardiovascular death • Death (any cause) • Cardiovascular events • Adverse events • Serious adverse events

Goicoechea 2012 *(Continued)*

Notes	• Funding: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned according to a computer-generated list". Comment: Computer-generation is considered as low risk of bias
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes were likely to be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were analysed
Selective reporting (reporting bias)	High risk	Study did not report all outcomes (bleeding event) expected for this type of study
Other bias	Low risk	No evidence of other sources of bias

Gonzalez 1995

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 3 years
Participants	• Country: Spain • Setting: single centre • Inclusion criteria: DKD and retinopathy (mild to moderate kidney impairment) • Number: 8; numbers per group not reported • Mean age SD: 51 ± 12 years; age per group not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Dipyridamole • Aspirin • ACEi Control group

Gonzalez 1995 *(Continued)*

	• ACEi without antiplatelet agents Cointerventions • Not reported
Outcomes	• Number reaching ESKD • Change in SCr • Metabolic control • Proteinuria • Adverse events
Notes	• Abstract-only publication • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Some outcomes were likely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	23/58 patients dropped out of study for different causes (not clearly reported)
Selective reporting (reporting bias)	High risk	Study did not report expected outcomes for this type of study
Other bias	Unclear risk	Insufficient information to permit judgement

Gröntoft 1985

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: 1980 to 1982 • Duration of follow-up: 4 weeks
Participants	• Country: Sweden • Setting: multicentre (2 sites) • Inclusion criteria: uraemic patients (HD) who were to undergo fistula surgery • Number: treatment group (19); control group (17)

Gröntoft 1985 *(Continued)*

- Mean age, range: 44.6 years, 24 to 72
- Sex (M/F): 28/14
- Exclusion criteria: bleeding tendency or thrombocytopenia and those who received anticoagulants, anti-inflammatory drugs or platelet aggregation inhibitors or other than heparin during dialysis

Interventions	Treatment group • Ticlopidine (oral): 250 mg twice/day from 2 days before surgery until 4 weeks after surgery Control group • Placebo Cointerventions • Not reported
Outcomes	• Fistula function • Patency of the fistula (clotting of the fistula) • Adverse events • Serious adverse events • Withdrawal from treatment • Number of patients with bleeding
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome adjudication may likely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	6/42 patients lost to follow-up
Selective reporting (reporting bias)	High risk	Study did not report all outcomes expected for this type of study
Other bias	Low risk	No evidence of other sources of bias

Gröntoft 1998

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 4 weeks
Participants	• Country: Sweden and Finland • Setting: multicentre (9 sites) • Inclusion criteria: CKD predialysis or when on dialysis who had been selected for surgery of an AV, saphenous, or artificial graft as HD site could be admitted to the study; patients in whom the first operation failed could be re-entered after randomisation after a washout period of 3 weeks • Number (randomise/analysed): treatment group (131/118); control group (136/124) • Mean age ± SD (years): treatment group (56 ± 15); control group (58 ± 15) • Sex (M/F): treatment group (75/43); control group (77/47) • Exclusion criteria: known antiplatelet agents or anticoagulant other than in connection with dialysis sessions or who had history or evidence of hepatic disease; severe or malignant hypertension; GI ulcer, haemorrhagic diathesis not due to uraemia, or any underlying lesion capable of causing severe haemorrhage, or who showed leukopenia, granulocytopenia, or thrombocytopaenia at screening
Interventions	Treatment group • Ticlopidine: 250 mg tablets twice/day for a target of 7 (minimum 3) days before the day of scheduled surgery and for 28 days postoperatively Control group • Placebo Cointerventions • None of the patients was treated with EPO before or during the study
Outcomes	• Fistula function • Serious adverse events • Early thrombosis events • Occlusions (dialysis access failure) • Death • Cardiovascular death, due to stroke or MI • Vascular events • Blood counts and biochemistry including electrolytes and liver function tests • Patients with haemostatic events
Notes	• Funding: Sanofi Recherche (Study No. C417A)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study

Gröntoft 1998 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome adjudication was likely to be influenced by knowledge of treatment outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "In total, 258 patients were randomised to placebo or ticlopidine for 285 operations. Of the 285 randomised operations, 16 first entries (5P:11T) and 2 re-entries (both T) were not evaluable, leaving 267 evaluable operations in 242 patients." Comment: 242/258 completed the study. Hoverer, outcome data related to death showed that there were 136 participants in the control group (124/136 completed the trial) and 131 participants in the treatment group (118/131 completed the trial). There were < 10% lost to follow-up, with no differences between groups
Selective reporting (reporting bias)	Low risk	Study outcomes included critical outcomes expected for this type of study
Other bias	High risk	No evidence of other sources of bias. The role of funding was not reported

Guo 1998

Study characteristics	
Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 4 weeks
Participants	• Country: Germany • Setting: single centre • Inclusion criteria: type I diabetic patients with persistent microalbuminuria (20 to 200 µg/min) and normal BP • Number: 11 • Mean age ± SD: 46.4 ± 14.3 years • Sex (M/F): 9/2 • Exclusion criteria: labile DM; congestive heart failure, MI, stroke or treatment for active gastric or duodenal ulcer within the last 6 months prior to the study; malignancy; severe allergies; pregnancy; non-DKD; UTI; NSAIDs including aspirin; hypersensitivity or contraindications against aspirin or other NSAIDs; mental illness or inability to consent; known positive tests of hepatitis B, C, or HIV; clinically significant laboratory abnormalities (haematology and biochemistry)
Interventions	Treatment group • Aspirin: 500 mg/day chewable tablets, daily for 4 weeks Control group • Placebo Cointerventions • Not reported
Outcomes	• Effects on kidney function • Urinary 6-keto-prostaglandin F1 alpha excretion

Guo 1998 *(Continued)*

- UAE rate
- Urinary thromboxane B2
- CrCl
- Urine beta-2 microglobulin
- Alpha1-microglobulin
- Urea nitrogen
- Blood fructosamine
- HbA1c
- Serum lipids
- Safety
- Adverse events
- BP
- Heart rate

Notes	• German paper with English abstract • Funding: Bayer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "The assignment sequences (ASA / PL or PL / ASA) for the two patient groups A and B were alternatively randomised." Comment: Alternation is considered as a high risk of bias
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes assessment may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study did not report expected outcomes for this type of study. Data were not appropriately reported for a cross-over RCT
Other bias	High risk	Insufficient information to permit judgement. The role of funding was not reported

Hansen 2000

Study characteristics

Methods	• Study design: cross-over RCT • Duration of study: not reported

Hansen 2000 *(Continued)*

	• Duration of follow-up: 4 weeks
Participants	• Country: Denmark • Setting: single centre • Inclusion criteria: type 1 diabetes; persistent microalbuminuria 30 to 300 mg/24 hours • Number: 17 • Mean age ± SD: 43 ± 9 years • Sex (M/F): 5/12 • Exclusion criteria: SBP > 200 mm Hg; cyclooxygenase inhibitor; acute gastritis or peptic ulcer; pregnant
Interventions	Treatment group • Aspirin: 150 mg/day Control group • Placebo Cointerventions • Patients drank 150 to 200 mL tap water/hour during the study period
Outcomes	• GFR • BP • UAE • HbA1c and blood glucose • Adverse events
Notes	• Funding: Danish Diabetes Association

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "AER (enzyme-linked immunosorbent assay), glomerular filtration rate (GFR) (plasma clearance of 51Cr-EDTA), blood pressure (BP) (Hawksley), and HbA1c (by high-performance liquid chromatography)." Comment: Outcomes generally were unlikely to be influenced by knowledge of treatment allocation. Adverse events may likely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients completed the study

Hansen 2000 *(Continued)*

Selective reporting (reporting bias)	High risk	Study did not report expected outcomes for this type of study. Data were not appropriately reported for a cross-over RCT
Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

Harter 1979

Study characteristics	
Methods	• Study design: parallel RCT • Durtion of study: 1 April 1977 to 1 December 1978 • Duration of follow-up: mean 4.7 months
Participants	• Country: USA • Setting: single centre • Inclusion criteria: consecutive HD patients receiving AV shunt • Number: treatment group (19); control group (25) • Mean age ± SD (years): treatment group (53.3 ± 14); control group (46 ± 16) • Sex (M/F): treatment group (11/8); control group (9/16) • Exclusion criteria: 2 patients excluded due to recent GI haemorrhage, 2 excluded due to possible allergy to aspirin, no other exclusion criteria reported
Interventions	Treatment group • Aspirin: 160 mg/day, for a mean of 4.6 months Control group • Placebo for a mean of 4.7 months Cointerventions • All patients were dialysed 3 times/week for 4 to hours with standard hollow-fibre or coil dialysers
Outcomes	• Death • Hospitalisation • Bleeding events • Number of patients with AV shunt thrombosis and number of thrombosis events • Kidney failure • Adverse events • HCT • Number of patients required transfusion
Notes	• Funding: Grant from the National Institute of Health, by an NIH Program Project Grant and by NIK Training Grant. Rexall Drug Company donated aspirin

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement

Harter 1979 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome adjudication may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	High percentage of patients left the study with some differences between groups
Selective reporting (reporting bias)	Low risk	Study outcomes included critical outcomes expected for this type of study
Other bias	High risk	There were some differences in baseline characteristics between groups. Funder was unlikely to influence data analysis and study reporting or interpretation

Hidaka 2013

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: August 2009 to October 2009 • Duration of follow-up: 24 weeks

Participants	• Country: Japan
	• Setting: multicentre (2 sites)
	• Inclusion criteria: HD patients who could stop the administration of antiplatelet agents except aspirin; peripheral arterial disease with at least one symptom:
	  ○ Cool limb sensation
	  ○ Intermittent claudication
	  ○ Skin perfusion pressure in instep or sole < 50 mm Hg
	  ○ ABI < 1.0
	  ○ Peripheral artery stenosis > 50% or identified by Doppler
	• Number: treatment group 1 (17); treatment group 2 (18)
	• Mean age ± SD (years): treatment group 1 (71.5 ± 3.5); treatment group 2 (71.1 ± 7.8)
	• Sex (M/F): treatment group 1 (8/9); treatment group 2 (13/5)
	• Exclusion criteria: HD within 3 months; worsening ischaemic symptoms; leg symptoms; chronic heart failure; bleeding disorders; hepatic disorder; malignancy; pregnancy; cerebrovascular disease; hypersensitivity to drugs

Interventions	Treatment group 1 • Sarpogrelate: 300 mg/day Treatment group 2 • Cilostazol: 200 mg/day

Hidaka 2013 *(Continued)*

	Cointerventions • Not reported
Outcomes	• Skin perfusion pressure • Oxidative stress biomarker • Adverse events • Major averse events (bleeding) • BP • CRP • Malondialdehyde-modified low-density lipoprotein • Fibrinogen and pentosidine
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome adjudication may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 35 patients completed the study
Selective reporting (reporting bias)	High risk	Study did not report expected outcomes for this type of study
Other bias	Low risk	No evidence of other sources of bias

HOT 1993

Study characteristics

Methods	• Study design: parallel RCT • Durtion of study: not reported • Duration of follow-up: 3.8 years
Participants	• Country: multinational (26 countries in Europe, North and South America, and Asia) • Setting: multicentre (number of sites not reported) • Inclusion criteria: 50 to 80 years; DBP between 100 and 115 mm Hg and CKD (eGFR < 60 mL/min/1.73 m^2)

HOT 1993 *(Continued)*

- Number: treatment group (1791); control group (1828)
- Mean age ± SD (years)*: treatment group (65.0 ± 7.5; 66.1 ± 8.2); control group (64.9 ± 7.5; 66.1 ± 7.9)
- Sex (M/F): treatment group (586/1205); control group (627/1201)
- Exclusion criteria: no exclusion on the basis of kidney function

* split into 2 groups based on eGFR: 45 to 59 and < 45 mL/min/1.73 m^2

Interventions	Treatment group • Aspirin: 75 mg/day Control group • Placebo Cointerventions • Not reported
Outcomes	• Composite of major cardiovascular events (MI, stroke, death), MI, stroke, cardiovascular death, death (any cause) • Change in GFR • Bleeding and bleeding events (major and minor) • Fatal bleeding
Notes	• Post-hoc analysis • Funding: National Health and Medical Research Council, European Commission Project InGenious HyperCare, Dutch Kidney Foundation. Sophia Zoungas has served as an advisory board member for Merck Sharpe and Dohme and NovoNordisk. Zanchetti has received lecture fees from Menarini International, Recordati, and Merck. The original HOT study was supported by AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation was computer-generated based on communications by fax between investigators and the Study Coordinating Centre at Östra Hospital, Göteborg, Sweden."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An independent clinical event committee evaluated all events (masked)."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up < 10% with no differences between groups
Selective reporting (reporting bias)	Low risk	The study reported all outcomes expected for this type of study
Other bias	High risk	No evidence of other sources of bias. The role of funding was not reported

IMPACT II 1997

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: 30 November 1993 to 9 November 1994 • Duration of follow-up: 6 months
Participants	• Country: USA • Setting: multicentre (82 sites) • Inclusion criteria: scheduled for elective, urgent, or emergency coronary intervention with a device approved by the Food and Drug Administration (balloon angioplasty, directional coronary atherectomy, rotational atherectomy, or excimer laser ablation): the protocol was specifically designed to enrol a representative cross-section of patients undergoing percutaneous revascularization (data reported for CKD patients) • Number (total population/CKD patients): treatment groups 1+2 (2682/547); control group (1328/259) • Median, IQR (years): treatment group 1 (62, 53 to 69); treatment group 2 (60, 52 to 68); control group (60, 52 to 69); not reported for CKD patients • Sex (M/F): treatment group 1 (984/365); treatment group 2 (1012/321); control group (997/331); not reported for CKD patients • Exclusion criteria: history of bleeding diathesis; severe hypertension (SBP > 200 mm Hg or DBP > 100 mm Hg on therapy); major surgery within the previous 6 weeks; history of stroke or other disorders of the central nervous system; pregnancy; GI or genitourinary bleeding within the previous 30 days, or other major illness
Interventions	Treatment group 1 • Eptifibatide (135/0.5 regimen): bolus of 135 µg/kg followed by an infusion of 0.5 µg/kg/min for 20 to 24 hours • Aspirin: 325 mg before the procedure, then continued indefinitely Treatment group 2 • Eptifibatide (135/0.75 regimen): bolus of 135 µg/kg followed by an infusion of 0.75 µg/kg/min for 20 to 24 hours • Aspirin: 325 mg before the procedure, then continued indefinitely Control group • Placebo bolus and placebo infusion • Aspirin: 325 mg before the procedure, then continued indefinitely Cointerventions • After vascular access had been established, a 100 U/kg bolus of heparin was given
Outcomes	• Occurrence within 30 days: death, MI, urgent or emergency repeat coronary intervention, urgent or emergency coronary artery bypass surgery, or index placement of an intracoronary stent for abrupt closure (a second assessment was also required after 5 months for ascertainment of long-term events) • Major bleeding and major bleeding events • Transfusion • Stroke • Platelet counts and measurement of creatine kinase concentration
Notes	• Funding: COR Therapeutics Inc and Schering-Plough Inc.
Risk of bias	

IMPACT II 1997 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The allocation schedule was generated by computer". Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All efficacy and safety events were adjudicated by consensus of the Clinical Events Committee from which treatment assignment was concealed during the trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	The study reported all outcomes expected for this type of study
Other bias	High risk	No evidence of other sources of bias. The role of funding were not reported

Jiao 2013

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 6 months
Participants	• Country: China • Setting: not reported • Inclusion criteria: diabetes; UAE 30 to 300 mg/24 hours • Number: treatment group (20); control group (20) • Mean age ± SD (years): not reported • sex (M/F): treatment group (11/9); control group (9/11) • Exclusion criteria: not reported
Interventions	Treatment group • Cilastazol (oral): 100 mg twice/day Control group • Placebo: 10 mg vitamin B twice/day Cointerventions • Not reported
Outcomes	• UACR

Jiao 2013 *(Continued)*

	• Urine cytokines • BP • Kidney function • HbA1c
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Outcome measurement adjudication unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study did not report outcomes expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias

JPAD 2008

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: December 2002 to May 2005 • Duration of follow-up: 4.37 years (median)
Participants	• Country: Japan • Setting: multicentre (163 sites) • Inclusion criteria: type 2 diabetes; 30 to 85 years; eGFR < 60 mL/min per 1.73 m^2 • Number: treatment group (342); control group (290) • Mean age ± SD (years): treatment group (68 ± 9); control group (69 ± 8) • Sex (M/F): treatment group (184/158); control group (150/140) • Exclusion criteria: ECG changes consisting of ischaemic ST-segment depression, ST-segment elevation, or pathologic Q waves; a history of coronary heart disease confirmed by coronary angiography; history of cerebrovascular disease consisting of cerebral infarction, cerebral haemorrhage, subarachnoid haemorrhage, and TIA; history of arteriosclerotic disease necessitating medical treatment; atrial fibrillation; pregnancy; use of antiplatelet or antithrombotic therapy, defined as aspirin, ticlopidine,

JPAD 2008 *(Continued)*

	cilostazol, dipyridamole, trapidil, warfarin, and argatroban; severe gastric or duodenal ulcer; severe liver dysfunction; severe kidney dysfunction; allergy to aspirin
Interventions	Treatment group • Aspirin: 81 mg or 100 mg once/day Control group • No antiplatelet agents Cointerventions • Not reported
Outcomes	• Any atherosclerotic event, which was a composite of sudden death • Death from coronary, cerebrovascular, and aortic causes • Non-fatal acute MI • Unstable angina • Newly developed exertional angina • Nonfatal ischaemic and haemorrhagic stroke • TIA; or nonfatal aortic and peripheral vascular disease (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis) • Each primary endpoint and combination of primary endpoints • Death from any cause • Adverse events analysed included GI events and any haemorrhagic events other than hemorrhagic stroke events
Notes	• Funding: Grant from the Ministry of Health, Labour and Welfare of Japan. Y.S. conducted the trial, interpreted and analysed data, and wrote the manuscript. T.M. performed all statistical analyses. H.O. conducted the trial, contributed to discussion, and reviewed and edited the manuscript. M.N., S.U., N.D., H.J., M.W., H.S., and S.S. researched data. S.O. contributed to discussion and reviewed and edited the manuscript. Y.A. reviewed and edited the manuscript

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation was performed as non stratified randomisation from a random number table." Comment: Random number table is considered as low risk of bias
Allocation concealment (selection bias)	Unclear risk	Quote: "The study centre prepared the sealed envelopes with random assignments and distributed them by mail to the physicians in charge at the study sites." Comment: Unclear whether envelopes were opaque and sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All potential primary end points, secondary end points, and adverse events were adjudicated by an independent committee on validation of data and events that was un-aware of the group assignments

JPAD 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants who were randomised were included in the primary efficacy and safety analyses
Selective reporting (reporting bias)	Low risk	Study outcomes included critical outcomes expected for this type of study
Other bias	Low risk	No evidence of other sources of bias. Funder did not influence data analysis and study reporting or interpretation. Subgroup analysis (post-hoc)

J-PADD 2014

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 24 weeks
Participants	• Country: Japan • Setting: multicentre (11 sites) • Inclusion criteria: HD; peripheral arterial disease; skin perfusion pressure < 40 mm Hg regardless of symptoms or < 50 mm Hg and symptoms • Number (randomised/analysed): treatment group (37/33); control group (35/35) • Mean age ± SD (years): treatment group (69.9 ± 9.2); control group (69.5 ± 12.3) • Sex (M/F): treatment group (24/9); control group (21/14) • Exclusion criteria: receiving treatment for peripheral arterial disease except for aspirin; prostaglandin treatment; heart failure; bleeding problems; malignancy; pregnancy; severe complication in organs of heart, liver, lung, GI tract, cerebrovascular system; within 6 months of revascularization procedure; within 3 months of starting HD; allergic reaction to treatment; involuntary leg movements
Interventions	Treatment group • Cilostazol 200 mg/day or sarpogrelate 300 mg/day Control group • Beraprost sodium: 120 µg/day Cointerventions • Not reported
Outcomes	• ABI • Skin perfusion pressure • Cardiovascular death • Cardiovascular events including cardiovascular death, acute MI, angina, heart failure, coronary intervention, and stroke • Peripheral arterial disease events • QoL • Adverse events and major adverse events • Peripheral arterial disease events included worsening from non-CLI to CLI, or additional treatments including revascularization, worsening of ulcer, or amputation for peripheral arterial disease
Notes	• Funding: not reported

J-PADD 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was conducted by permutated-block randomisation method, where block size was 6 and allocation ratio was 1:1." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome events were likely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "In Group B, one patient did not receive medication and three patients received both cilostazol and sarpogrelate instead of sarpogrelate, in violation of protocol. Finally, patients qualifying for analysis numbered 68 patients including: 35 from Group A (n = 35) and 33 from Group B (n = 33; cilostazol 15, sarpogrelate 18)." Comment: 0/35 patients in treatment group and 4/37 patients in control group were not included in analysis
Selective reporting (reporting bias)	Low risk	Study outcomes included critical outcomes expected for this type of study
Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

Kaegi 1974

Study characteristics

Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 6 months (first phase)
Participants	• Country: Canada • Setting: single centre • Inclusion criteria: chronic HD patients with straight AV shunt • Number (randomised/analysed at 6 months): treatment group (30/24); control group (32/28) • Mean age: treatment group (43 years); control group (44 years) • Sex (M/F): treatment group (16/8); control group (20/8) • Exclusion criteria: not reported
Interventions	Treatment group • Sulfinpyrazone: 200 mg 3 times/day

Kaegi 1974 *(Continued)*

	Control group • Placebo Cointerventions • All patients were interviewed monthly • Some of the patients were also treated with oral anticoagulants
Outcomes	• Number of patients with fistula thrombosis, fistula thrombosis events, number of arterial and venous fistula revisions • GI bleeding • Other side effects • Death • Withdrawal from the study • MI
Notes	• Funding: St. Joseph's Hospital Foundation and Ontario Heart Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This was a double blind crossover study, the allocation of the patients to treatment being made according to a prescribed randomised arrangement." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome adjudication was likely to be influenced by any knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	In the first phase, 52/62 completed the 6 months follow-up; 24/30 in the treatment group and 28/32 in the control group completed the study; > 10% lost to follow-up
Selective reporting (reporting bias)	Low risk	Study reported expected outcomes for a study of this type. Data were appropriately reported for a cross-over RCT
Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

Kamper 1997

Study characteristics

Methods	• Study design: parallel RCT

Kamper 1997 *(Continued)*

	• Duration of study: not reported • Duration of follow-up: 3 weeks
Participants	• Country: Belgium • Setting: single centre • Inclusion criteria: HD patients • Number: treatment group (13); control group (14) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: dialysis through a central catheter; already taking antiplatelet agents; not willing to participate
Interventions	Treatment group • Ticlopidine: 250 mg once/day • Nadroparin Control group • Nadroparin Cointerventions • Not reported
Outcomes	• Platelet aggregation • Minor and major haemorrhage events • Manual compression time after dialysis (bleeding time) • Presence of visible clots in the extracorporeal circulation • Number of packed cell transfusions and laboratory parameters • Plasma Hb • AXa • APTT • Thrombin time
Notes	• Funding: Sanofi

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome adjudication (due to nature of outcomes) was generally unlikely to be influenced by knowledge of treatment allocation. However, bleeding time may be influenced by the knowledge of the treatment assignment

Kamper 1997 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study
Selective reporting (reporting bias)	High risk	Study outcomes did not include all expected for this type of study
Other bias	High risk	Insufficient information to permit judgement. The role of funding was not reported

Kauffmann 1980

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 12 months
Participants	• Country: USA • Setting: single centre • Inclusion criteria: patients post kidney transplant • Number: treatment group (22); control group (20) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Dipyridamole: 100 mg 4 times/day Control group • Buffered aspirin (ascriptin): 5 mg twice/day Cointerventions • All patients received conventional antacids 4 times/day and more often if they had any epigastric distress
Outcomes	• GI bleeding • Graft loss • Transfusion • HCT • Adverse events • SCr
Notes	• Funding: not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "Randomization was achieved by whether the last digit of the patients' hospital number was odd or even".

Kauffmann 1980 *(Continued)*

		Comment: This method is considered as high risk of bias
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome adjudication likely to be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study did not report all outcomes that would be expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias

Kaufman 2003

Study characteristics	
Methods	• Study design: parallel RCT • Duration of follow-up: 24 months but terminated at 330 days (at the time of study termination, the average follow-up period was 196 ± 84 days (median 214 days; range 13 to 323 days) for the placebo-treated group and 202 ± 84 days (median 217 days; range 9 to 322 days) for the treatment group
Participants	• Country: USA • Setting: multicentre (30 sites) • Inclusion criteria: patients with PTFE graft in the arm; ≥ 21 years; undergoing HD 3 times/week • Number: treatment group (104); control group (96) • Mean age ± SD (years): treatment group (61 ± 13); control group (62 ± 11) • Sex (M): treatment group (100%); control group (99%) • Exclusion criteria: blood loss requiring transfusion or hospitalisation in the 3 months prior; advanced proliferative diabetic retinopathy; life expectancy of < 24 months; uncontrolled BP; platelet count < 100,000 mm^3; INR > 1.3; partial thromboplastin time 5 seconds longer than control; access thrombosis or operation in the previous 14 days; other conditions that would make antiplatelet therapy high risk; receiving warfarin, aspirin or other salicylates, dipyridamole, sulphinpyrazone, ticlopidine, clopidogrel, or NSAIDs
Interventions	Treatment group • Aspirin: 325 mg/day for 24 months • Clopidogrel: 75 mg/day for 24 months Control group • Double placebo Cointerventions

Kaufman 2003 *(Continued)*

	• Not reported
Outcomes	• Adverse events • Bleeding events (major, intermediate, minor) • First episode of fistula thrombosis • Death • Transfusion • Withdrawal from the study
Notes	• Funding: The Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development and by an unrestricted grant to Friends of Medical Research (a not-for-profit foundation) from Sanofi-Synthelabo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The randomisation was stratified according to medical centre with a permuted block scheme, with a block size of four and equal allocation." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed centrally, by the coordinating centre."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Assessment of the severity of bleeding episodes was performed by a panel blinded to the treatment assignments." Comment: Although assessment of bleeding episode was performed in an objective way, adverse events were likely to be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Participants were censored at the time of death, kidney transplantation, transfer to peritoneal dialysis, loss to follow-up monitoring, or withdrawal of consent. On the basis of intention-to-treat principles, all other participants for whom study medications were discontinued continued to be monitored according to the protocol." Comment: Reasons for exclusions listed and intention-to-treat analysis was performed
Selective reporting (reporting bias)	Low risk	Study reported expected outcomes for this type of study
Other bias	High risk	The study was terminated earlier because of a significantly increased bleeding risk in the active treatment arm. Sample size smaller than planned. The role of Sanofi was not reported

Khajehdehi 2002

Study characteristics

Khajehdehi 2002 *(Continued)*

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 2 months
Participants	• Country: Iran • Setting: multicentre (number of sites not reported) • Inclusion criteria: overt type 2 DKD (proteinuria > 500 mg/day), who had normal kidney function, well-controlled BP and blood sugars and not receiving ACEi • Number: treatment group 1 (19); treatment group 2 (19); treatment group 3 (19); control group (19) • Mean age ± SD (years): treatment group 1 (56.1 ± 7.5 years); treatment group 2 (56.8 ± 8.6); treatment group 3 (57.9 ± 7.0); control group (56.9 ± 6.9) • Sex (M/F): treatment group 1 (7/12); treatment group 2 (8/11); treatment group 3 (12/7); control group (9/10) • Exclusion criteria: SCr > 2 mg/dL and blood nitrogen > 20 mg/dL; bacteriuria; recurrent or relapsing UTI; active urine sediment
Interventions	Treatment group 1 • Aspirin: 1000 mg/day Treatment group 2 • Dipyridamole: 750 mg/day Treatment group 3 • Aspirin: 1000 mg/day • Dipyridamole: 750 mg/day Control group • Placebo Cointerventions • Not reported
Outcomes	• Change in 24-hour urinary protein • BP • Fasting blood sugar • Serum electrolytes (sodium, potassium, calcium, phosphorous, and uric acid) • CrCl • Protein-creatinine ratio • Creatinine excretion • Safety and side-effect profile of interventions • Adverse events (including bleeding) • Death was not a targeted outcome, but there were no deaths during the study period
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement

Khajehdehi 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not clear whether participants or trial personnel were blinded. A placebo is mentioned, but it is not clear whether this resulted in participants and personnel being unaware of treatment allocation. Hovewer, as the treatments were physically different, it was likely that participants and/or investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome assessment could have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were analysed
Selective reporting (reporting bias)	High risk	Study did not report all expected outcomes (cardiovascular disease) for this type of study
Other bias	Low risk	No evidence of other sources of bias

Kobayashi 1980

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 12 weeks
Participants	• Country: Japan • Setting: multicentre (30 sites) • Inclusion criteria: chronic HD patients with AV external shunts or vascular grafts who had experienced more than 1 episode of thrombosis of their fistula during the preceding 4 weeks • Number: treatment group (50); control group (57) • Mean age ± SD (years): not reported) • Sex (M/F): treatment group (17/33); control group (23/34) • Exclusion criteria: digestive ulcers; hepatic disorders; severe haematological disorders except anaemia of kidney insufficiency
Interventions	Treatment group • Ticlopidine: 100 mg twice/day Control group • Placebo Cointerventions • Not reported
Outcomes	• Frequency of clot removal from fistula and reconstructive surgery • Level of urea, creatinine, phosphoric acid, uric acid, platelet count, BP, pulse rate, BUN, Ca, Na, K, Cl, leukocyte count, RBC, Hb, HCT, GOT, GPT, alkaline phosphatase, total bilirubin, total cholesterol, triglyceride, total protein, A/G ratio

Kobayashi 1980 *(Continued)*

- Bleeding time
- Safety and side-effects (including bleeding and GI disturbances)
- Death was not a targeted outcome, but there were no deaths during the study period

Notes	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome adjudication may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of 107 patients, 5 patients were excluded from analytical data because of offence against protocol (4 A-V fistulas, 1 A-V external shunt without shunt trouble), and 2 patients because they were dosed with the test drug only for 4 days. Consequently, the efficacy was evaluated on 100 patients (T47, P53)." Comment: 100/107 patients included in analysis with no differences between groups
Selective reporting (reporting bias)	High risk	Study did not report all expected outcomes (cardiovascular disease) for this type of study
Other bias	Low risk	No evidence of other sources of bias

Kontessis 1993

Study characteristics

Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 1 week
Participants	• Country: UK • Setting: single centre • Inclusion criteria: type 1 diabetes with kidney disease • Number: 15 • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not available*

Kontessis 1993 *(Continued)*

	*The available electronic copy of this paper was incomplete and study data in this review are incomplete as a result
Interventions	Treatment group • Thromboxane synthase inhibitor FCE 22178: 400 mg 2 or 3 times/day Control group • Placebo Cointerventions • Not reported In 7 additional patients, the effect of the thromboxane synthase inhibitor given as 400 mg twice/day was compared with that of the thromboxane synthase inhibitor given as 400 mg 3 times/day
Outcomes	• Urinary thromboxane B2 • 2,3-dinor-thromboxane B2 • GFR • Effective renal plasma flow • Renal vascular resistance • Filtration fraction • Fractional clearance of albumin and immunoglobulin
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Outcome adjudication was unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study did not report all outcomes that would be expected for a study of this type. Data were not appropriately reported for a cross-over RCT
Other bias	Low risk	No evidence of other sources of bias

Kooistra 1994

Study characteristics	
Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 3 months (first phase)
Participants	• Country: Belgium • Setting: single centre • Inclusion criteria: ≥ 18 years with anaemia of CKD who were on chronic dialysis for more than 6 weeks • Number: treatment group (69); control group (68) • Mean age SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: uncontrolled hypertension, cardiac failure, angina pectoris above stage two; pregnancy; previous thrombovascular accidents other than thrombosis of fistula and treatment with NSAIDs or anticoagulants
Interventions	Treatment group • Aspirin: 30 mg/day for 3 months Control group • Placebo Cointerventions • Not reported
Outcomes	• Bleeding time • Bleeding events • Death (any cause) • Cardiovascular death • Systemic thrombovascular events • Fistula thrombosis • Thrombocyte count • HCT • Adverse events • Cardiovascular events (MI)
Notes	• Funding: Stichting Welzijn Nefrologiepatienten

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were assigned at random to group A or B by the monitor (MH), who was not in charge of the medical care for the patients." Comment: Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study

Kooistra 1994 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. The outcome adjudication may have been influenced by knowledge of the treatment type
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "One hundred and fifty-three patients were included in this study. Of these, 16 were withdrawn for further evaluation because of proven non-compliance to the ASA or placebo ingestion. From the remaining 137 patients, 68 had been randomised to group A (placebo-ASA) and 69 to group B (ASA-placebo). From the 68 group A patients, eight dropped out during the study. One patient, who suffered from chronic obstructive lung disease, died of progressive respiratory failure. Three patients received renal grafts, two patients had uncorrectable hypertension, and two stopped for unspecified personal reasons. From the 69 group B patients, 11 dropped out. Four patients died, one after a complicated hip fracture, one following a MI in the first week of the rHuEpo treatment, one from pulmonary embolism, and one from bacterial sepsis. Two patients received renal grafts, in one patient the Hct remained at target level after stopping rHuEpo administration, one proved to be a non-responder, and three stopped for personal reasons. In cases of drop-out, only data of completed study periods were used for evaluation." Comment: > 10% lost to follow-up
Selective reporting (reporting bias)	Low risk	Study reported expected outcomes for this type of study. Data were appropriately reported for a cross-over RCT
Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

Koyama 1990

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: January 1986 to March 1987 • Duration of follow-up: 24 weeks
Participants	• Country: Japan • Setting: multicentre (84 sites) • Inclusion criteria: primary glomerulonephritis • Number: 431 • Mean age ± SD: not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Dipyridamole: 300 mg/day for 6 months Control group • Placebo Cointerventions

Koyama 1990 *(Continued)*

	• Not reported
Outcomes	• Urinary protein excretion • CrCl
Notes	• Abstract-only publication • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Outcomes adjudication were unlikely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study did not report all outcomes that would be expected for a study of this type
Other bias	Unclear risk	Insufficient information to permit judgement

Liang 2015

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: February 2009 to July 2011 • Duration of follow-up: 30 days
Participants	• Country: China • Setting: single centre • Inclusion criteria: CKD; CAD; undergoing PCI with DES implantation • Number: treatment group 1 (184); treatment group 2 (186) • Mean age ± SD (years): treatment group 1 (65.0 + 10.5); treatment group 2 (64.6 + 10.3) • Sex (M/F): treatment group 1 (138/46); treatment group 2 (141/45) • Exclusion criteria: known contraindications to aspirin or clopidogrel; platelet count < 100,000/mm^3; active bleeding or bleeding diathesis; GI bleeding; cerebrovascular event within last 6 months; prior to PCI or coronary bypass grafting < 3 months ago; concomitant use of other antithrombotic drugs;

Liang 2015 *(Continued)*

	treatment with a glycoprotein IIb/IIIa antagonist; cardiac arrest; haemodynamic instability; HD; liver disease; concurrent; severe illness with an expected survival of < 1 month
Interventions	Treatment group 1 • Clopidogrel: 75 mg/day Treatment group 2 • Clopidogrel: 150 mg/day Cointerventions • 300 mg clopidogrel loading dose was administered at least 6 hours prior to PCI to all patients • All randomised patients were treated with aspirin 100 mg/day
Outcomes	• Maximal platelet aggregation • Stent thrombosis events • Major adverse cardiac events (included cardiovascular death, nonfatal MI and target lesion revascularization) • Bleeding events (minor and major) • Cardiovascular death
Notes	• Funding: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes adjudication were likely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patient was lost to follow-up
Selective reporting (reporting bias)	Low risk	Study reported expected outcomes for this type of study
Other bias	Low risk	No evidence of other sources of bias

Michie 1977

Study characteristics

Michie 1977 *(Continued)*

Methods	• Study design: RCT • Duration of study: not reported • Duration of follow-up: 3 months
Participants	• Country: USA • Setting: single centre • Inclusion criteria: adults with CKD scheduled to begin HD, prior to the creation of fistula or graft • Number: treatment group (8); control group (8) • Mean age: treatment group (49 years); control group (53 years) • Sex (M): treatment group (75%); control group (50%) • Exclusion criteria: not reported
Interventions	Treatment group • Sulfinpyrazone: 200 mg, 4 times/day for 3 months Control group • Placebo Cointerventions • Not reported
Outcomes	• Safety of intervention including death and nonfatal serious adverse events • Bleeding (minor and major) • Fistula thrombosis
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome adjudication may have been influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Data were not available for all patients
Selective reporting (reporting bias)	Low risk	Study reported expected outcomes for this type of study
Other bias	Low risk	No evidence of other sources of bias

Middleton 1992

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 18 months
Participants	• Country: not reported • Setting: not reported • Inclusion criteria: HD patients • Number: treatment group: number (451); control group (452) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Low-dose aspirin: 50 mg/day • Dipyridamole: 400 mg/day for 18 months Control group • Not reported Cointerventions • Not reported
Outcomes	• Death (any cause) • Cardiovascular death • Major bleeding
Notes	• Published results from an earlier systematic review ATT 2002 • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome adjudication may have been influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient information to permit judgement

Middleton 1992 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Study reported expected outcomes for this type of study
Other bias	High risk	Full study report not available

Milutinovic 1993

Study characteristics	
Methods	• Study design: cross-over RCT • Duariton of study: not reported • Duration of follow-up: 7 days
Participants	• Country: Croatia and Slovenia • Setting: multicentre (number of sites not reported) • Inclusion criteria: HD patients; tendency to blood clotting in fistula (> 25 fibres clotted/dialysis at least 3 times/month) • Number: 51 • Mean age ± SD: 47.2 ± 13.0 years • Sex (M/F): 33/18 • Exclusion criteria: no concurrent illness; no antirheumatic drugs or antipyretic drugs
Interventions	Treatment group • Ticlopidine: 250 mg/day Control group • Placebo Cointerventions • All patients were regularly dialysed using normal standard heparin 3 times/week for 4 hours on a standard cuprophan hollow fibre dialyser
Outcomes	• Dialysis clearances (urea, creatinine and phosphate) • Blood cell counts (leucocytes, erythrocytes, platelets) • Adverse events • Dialyser clotting • Bleeding (minor bleeding)
Notes	• Funding: not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Milutinovic 1993 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study did not report all outcomes that would be expected for a study of this type. Data were not appropriately reported for a cross-over RCT
Other bias	Low risk	No evidence of other sources of bias

Movchan 2001

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 1 month
Participants	• Country: Russia • Setting: not reported • Inclusion criteria: patients with acute (3 to 4 months of disease) streptococcal glomerulonephritis • Number: treatment group 1 (14); treatment group 2 (26); control group (10) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Dipyridamole: 150 to 400 mg Treatment group 2 • Pentoxifylline (Trental): 400 to 800 mg Control group • Standard care without antiplatelet agents Cointerventions • Not reported
Outcomes	• Platelet function activity • Platelet aggregation activity • Proteinuria • Haematuria
Notes	• Russian - partly translated

Movchan 2001 *(Continued)*

- Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. However, outcomes were unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study did not report all outcomes that would be expected for a study of this type
Other bias	Unclear risk	Insufficient information to permit judgement

Mozafar 2013

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: June 2009 to June 2010 • Duration of follow-up: perm-cath survival (primary outcome) was 5.3 months
Participants	• Country: Iran • Setting: single centre • Inclusion criteria: HD; AV access via a perm-cath; > 50 years • Number: treatment group (90); control group (90) • Mean age ± SD (years): treatment group (60 ± 1); control group (61 ± 1.3) • Sex (M/F): treatment group (55/35); control group (53/37) • Exclusion criteria: contraindication to aspirin
Interventions	Treatment group • Aspirin: 80 mg/day on the day following permanent catheter insertion Control group • Placebo Cointerventions

Mozafar 2013 *(Continued)*

	• Not reported
Outcomes	• Vascular access function • Major bleeding events (GI bleeding) • Survival time of catheter
Notes	• Funding: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study did not report all outcomes that would be expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias

Mozafar 2018

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: 2014 to 2016 • Duration of follow-up: 6 months
Participants	• Country: Iran • Setting: single centre • Inclusion criteria: HD; AV access via a perm-cath • Number: treatment group (50); control group (50) • Mean age ± SD (years): treatment group (55.5 ± 11.8); control group (55.7 ± 12.1) • Sex (M/F): treatment group (34/16); control group (30/20) • Exclusion criteria: poor blood flow following perm-cath insertion during HD; absolute contraindication to clopidogrel
Interventions	Treatment group

Mozafar 2018 *(Continued)*

	• Clopidogrel: 75 mg/day Control group • Placebo Cointerventions • All patients underwent standard preoperative assessments, including clinical examination
Outcomes	• Dialysis vascular access function • GI haemorrhage • Systemic infection • Catheter survival • Thrombosis • Bleeding events
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was carried out, using a computer-generated table of random numbers at a ratio of 1:1." Comment: Random number is considered as low risk of bias
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes may have been influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study did not report all outcomes that would be expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias

Nakamura 2001d

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 6 months

Nakamura 2001d *(Continued)*

Participants	• Country: Japan
	• Setting: not reported
	• Inclusion criteria: normotensive or hypertensive; ADPKD; microalbuminuria
	• Number
	  ○ Treatment group: normotensive (6); hypertensive (5)
	  ○ Control group: normotensive (6); hypertensive (5)
	• Mean age: normotensive (46.6 years); hypertensive (52.2 years)
	• Sex (M/F): normotensive (4/8); hypertensive (2/8)
	• Exclusion criteria: SCr > 1.5 mg/dL or CrCl < 70 mL/min

Interventions	Treatment group • Dilazep dihydrochloride: 300 mg/day Control group • Placebo Cointerventions • Not reported
Outcomes	• SCr • BUN • BP • CrCl • UAE
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Outcomes adjudication were unlikely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study outcomes did not include critical outcomes expected for this type of study
Other bias	Low risk	No evidence of other sources of bias

Nakamura 2002b

Study characteristics	
Methods	• Study design: parallel RCT • Duraiton of study: not reported • Duration of follow-up: 12 months
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: HD patients with ventricular hypertrophy; no symptoms of MI; clinically stable; adequate dialysis defined by Kt/V • Number: treatment group (20); control group (20) • Mean age ± SD (years): treatment group (57.6 ± 18.2); control group (56.8 ± 16.2) • Sex (M/F): treatment group (8/12); control group (9/11) • Exclusion criteria: infection; blood transfusion in previous 12 months
Interventions	Intervention group • Dilazep dihydrochloride: 300 mg/day Control group • Placebo Cointerventions • All patients were dialysed 3 times/week with a bicarbonate dialysate
Outcomes	• Cardiac troponin T • BP • Hb • Left ventricular mass index • Average ultrafiltration • Ultrafiltration
Notes	• Funding: not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Outcomes adjudication were unlikely to be influenced by knowledge of the treatment allocation

Nakamura 2002b *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study outcomes did not include critical outcomes expected for this type of study
Other bias	Low risk	No evidence of other sources of bias

NCT01252056

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: March 2010 to December 2012 • Duration of follow-up: 96 weeks
Participants	• Country: China • Setting: not reported • Inclusion criteria: 40 to 75 years; type 2 DM above 6 months; HbA1c ≤ 8%; twice (above 2-week interval) confirmed UACR 30 to 3000 µg/mg; receive routine dosage ACEI or ARB treatment above 2 months, and the dosage has been fixed for at least 1 month; LDL cholesterol > 100 mg/dL (2.60 mmol/L) and/or hyperlipidaemia patients with statins treatment • Number: 353 • Mean age ± SD (years): not reported • Sex (M/F): mot reported • Exclusion criteria: allergic history to investigational drugs; receive antilipaemic agents (except statins) within the latest 2 months, including probucol; receive antiplatelet or anticoagulation agents (except aspirin) within the latest 2 months, including cilostazol; rapid progression of nephropathy within the latest 3 months; kidney disease caused by other reasons according to medical history; serum potassium < 3.5 mEq/L or > 5.5 mEq/L; haemorrhagic tendency or haemorrhagic disease; MI, angina pectoris, or cerebral infarction within the latest 3 months; congestive heart failure; pregnant, potentially pregnant, or lactating woman; severe hepatic inadequacy (AST or ALT is 2.5 times > ULN); SCr 1.5 times > ULN; persistent or hardly controlled hypertension; severe ventricular arrhythmia; medical history of cardiac syncope or primary syncope; condition that may prolong QT interval or for men QT interval > 450 msec, for women QT interval> 470 msec; severe complications; other clinical trials within the latest 3 months; other conditions that would be excluded from this study according to doctors' judgment
Interventions	Treatment group • Probucol: 250 mg twice/day • Cilostazol: 50 to 100 mg twice/day Control group • Probucol: 250 mg twice/day Cointerventions • Not reported
Outcomes	• IMT • Atherosclerosis-related biomarker • Urine albumin • Doubling SCr • HD-free survival

NCT01252056 *(Continued)*

	• Adverse events
Notes	• Funding: Otsuka Beijing Research Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. The outcome adjudication may have been influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study outcomes did not included critical outcomes expected for this type of study
Other bias	Unclear risk	Insufficient information to permit judgement (only available information is entry in www.clinicaltrials.gov). Funder was unlikely to influence data analysis and study reporting or interpretation

Nyberg 1984

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 1 year
Participants	• Country: Sweden • Setting: single centre • Inclusion criteria: insulin-dependent diabetes (DKD patients); proteinuria; treated for hypertension; GFR < 60 mL/min/1.73 m^2 • Treatment group: number (11); control group (11) • Age range: 24 to 47 years • Sex (M/F): (14/9) • Exclusion criteria: not reported
Interventions	Treatment group • Ticlopidine: 250 mg twice/day

Nyberg 1984 *(Continued)*

	Control group • Placebo Cointerventions • All patients were treated for arterial hypertension
Outcomes	• Platelet studies (beta-TG and platelet aggregation) • HbA1c • BP • Kidney function (slope 1/creatinine, SCr and GFR) • Bleeding (major retinal bleeding included) • Death • Platelet and leucocyte counts • Adverse events
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. The outcome adjudication may have been influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	22/23 participants were included in analyses
Selective reporting (reporting bias)	Low risk	Study outcomes included critical outcomes expected for this type of study
Other bias	Low risk	No evidence of other sources of bias

Ogawa 2008

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 16 weeks

Ogawa 2008 *(Continued)*

Participants	• Country: Japan • Setting: single centre • Inclusion criteria: DKD and arteriosclerosis obliterans; maximum internal carotid medial thickness > 1 mm; UACR > 30 mg/g; HbA1c < 8.0%; BP < 180/110 mm Hg; no serious retinopathy • Number: treatment group 1 (20); treatment group 2 (20) • Mean age ± SD (years): treatment group 1 (68.7 ± 1.61); treatment group 2 (67.4 ± 1.54) • Sex (M/F): treatment group 1 (11/9); treatment group 2 (10/10) • Exclusion criteria: treated with antiplatelet or anticoagulant agents; hospitalised in the past 12 months for any reason and those who had their drugs changed in the past 12 months
Interventions	Treatment group 1 • Sarpogrelate: 300 mg/day Treatment group 2 • Aspirin: 100 mg/day Cointerventions • Not reported
Outcomes	• Change in UACR levels • SCr • eGFR • Plasma monocyte chemoattractant protein-1 • Plasma adiponectin • UACR • Plasma IL-6
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Outcomes adjudication were unlikely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study outcomes did not include critical outcomes expected for this type of study

Ogawa 2008 *(Continued)*

Other bias	Low risk	No evidence of other sources of bias

OPT-CKD 2018

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: October 2015 to December 2016 • Duration of follow-up: 30 days
Participants	• Country: China • Setting: single centre • Inclusion criteria: ADP P2Y12 inhibitor-naive patients; > 18 years; Non-ST elevation coronary syndrome; eGFR < 60 mL/min/1.73 m^2 • Number: treatment group 1 (30); treatment group 2 (30) • Mean age ± SD (years): treatment group 1 (69.7 ± 7.7); treatment group 2 (65.1 ± 10.9) • Sex (M/F): treatment group 1 (17/13); treatment group 2 (18/12) • Exclusion criteria: cardiogenic shock; thrombolytic therapy administered before randomisation; active bleeding or bleeding pre-disposition, including retinal or vitreous haemorrhage, GI or urinary tract haemorrhage, or a history of intracranial haemorrhage or cerebral infarction hypersensitivity to ticagrelor or to any of its excipients; deep puncture or major surgery within the previous month; untreated or uncontrolled hypertension with a BP > 180/110 mm Hg; known Hb < 10 g/dL or platelet count < 100 x 10^9/L; known moderate or severe hepatic impairment; known aminotransferase level > 3 ULN; known allergy to any of the study drugs or devices; pregnancy or lactation; any condition which might interfere with study compliance, or otherwise unsuitable for study participation, as judged by the investigators; unwilling or unable to undergo a repeat platelet assay or clinical follow-up
Interventions	Treatment group 1 • Ticagrelor: 180 mg loading dose, followed by 90 mg twice/day • Aspirin: 100 mg/day Treatment group 2 • Clopidogrel: 600 mg loading dose, followed by 75 mg once/day • Aspirin: 100 mg/day Cointerventions • All patients received aspirin unless they were intolerant
Outcomes	• Platelet aggregation • Death (any cause and cardiovascular) • Nonfatal MI • Stroke • Bleeding • eGFR
Notes	• Funding: National Key Research and Development programme of China (grant number: 2016YFC1301300), the Natural Science Foundation of Liaoning Province (grant number: 201 602 777) and a grant of external sponsored research grant from AstraZeneca Co. Ltd
Risk of bias	

OPT-CKD 2018 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Some outcomes adjudication were likely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, 57/60 patients included in outcome assessment (28/39 in the ticagrelor group and 29/30 in the clopidogrel group)
Selective reporting (reporting bias)	Low risk	Study outcomes included critical outcomes expected for this type of study
Other bias	High risk	No evidence of other sources of bias. The role of AstraZeneca was not reported

Ota 1996

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 3 weeks
Participants	• Country: Japan • Setting: not reported • Inclusion criteria: patients undergoing HD • Number (randomised/analysed): treatment group 1 (111/106); treatment group 2 (113/98) • Mean age ± SD (years): not reported • Sex (M/F): treatment group 1 (58/48); treatment group 2 (49/49) • Exclusion criteria: not reported
Interventions	Treatment group 1 • Satigrel (E5510) (oral): 1 mg for 3 weeks Treatment group 2 • Ticlopidine (oral): 100 mg twice/day for 3 weeks Cointerventions • Not reported
Outcomes	• Clotting in the extracorporeal circuit • Residual blood in the circuit

Ota 1996 *(Continued)*

- Adverse events
- BUN
- Uric acid
- Creatinine
- Phosphorous
- Improving rating
- Safety rating
- Utility rating
- Bleeding events
- Death (any cause)
- Cardiovascular death

Notes	• Japanese • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Improvement and utility rate were assessed by steering committee". Comment: Some outcomes adjudication were likely to be influenced by knowledge of the treatment allocation (not reported if steering committee was blind)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "204 patients (106 in the group E and 98 in group T) were assessed for general improving rating, 223 (110 in the group E and 113 in group T) were assessed for overall safety rating, and 206 (106 and 100) were assessed for general utility rating" Comment: < 10% were lost to follow-up with not differences between groups (only one patient in group E was completely excluded from the analysis)
Selective reporting (reporting bias)	Low risk	Study outcomes included critical outcomes expected for this type of study
Other bias	Unclear risk	Insufficient information to permit judgement

PEGASUS-TIMI 54 2014

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: commenced 29 October 2010

PEGASUS-TIMI 54 2014 *(Continued)*

	• Duration of follow-up: 3 years

Participants	• Country: multinational (31 countries)
	• Setting: multicentre (1145 sites)
	• Inclusion criteria: ≥ 50 years; spontaneous MI 1 to 3 years prior; taking aspirin 75 to 150 mg/day; contraception in women of child-bearing potential; eGFR < 60 mL/min/1.73 m^2; at least one of the following risk factors:
	  ○ ≥ 65 years
	  ○ DM on medication
	  ○ Second prior MI
	  ○ Multivessel CAD ≥ 50% in 2+ coronary territories
	  ○ Chronic kidney dysfunction non-end stage (CrCl < 60 mL/min)
	• Number (GFR < 60 mL/min/1.73 m^2): 4849
	• Mean age: 70 years
	• Sex (M/F): 3071/1778
	• Exclusion criteria: planned use of adenosine-diphosphate receptor blockers, dipyridamole or cilostazol Planned revascularization (coronary, peripheral, cerebrovascular); Potent inducer/inhibitor/substrate of CYP3A use; chronic anticoagulation; known bleeding diathesis or coagulation disorder; increased risk of bleeding (history of intracranial bleed at any time, central nervous system tumour or intracranial vascular abnormality at any time, Intracranial or spinal cord surgery within 5 years, or GI bleed within the past 6 months, or major surgery within 30 days); history of ischaemic stroke; at risk of bradycardic events unless already treated with a permanent pacemaker; coronary-artery bypass grafting in the last 5 years; known severe liver disease; kidney failure requiring dialysis; pregnancy or lactation; life-expectancy < 1 year; any condition judged by the investigator to make participation unsafe for the patient; concern for inability to comply with the protocol; prior participation in a trial with ticagrelor (if treated with active ticagrelor)

Interventions	Treatment group 1 • Ticagrelor: 90 mg twice/day Treatment group 2 • Ticagrelor: 60 mg twice/day Control group • Placebo Cointerventions • Not reported
Outcomes	• Cardiovascular death • Major adverse cardiovascular events (MI and stroke) • Death (any cause) • Coronary or cerebrovascular arterial thrombosis • Hospitalisation (defined as MI, stroke, or hospitalisation for urgent coronary revascularization, unstable angina, or TIA) • Coronary stent thrombosis • QoL as measured using the Euro QoL-5 • Bleeding (major or minor) events • Fatal bleeding events • Adverse events (including kidney adverse events)
Notes	• Funding: Grant from AstraZeneca. Advisory board obtained modest fees from Merck, AstraZeneca, Pfizer, Amgen

PEGASUS-TIMI 54 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed using a central computerized telephone or web based system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Adjudication for each event is performed according to definitions in the PEGASUS-TIMI 54 Clinical Endpoints Committee Charter (online Appendix B) by an independent, blinded, and trained Clinical Endpoints Committee with board certification in either Cardiology or Neurol-ogy depending on the event type."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Ascertainment of the primary outcome was complete for 99.2% of the potential patient years of follow-up
Selective reporting (reporting bias)	Low risk	Study reported all critical outcomes expected for a study of this type
Other bias	High risk	No evidence of other sources of bias. The role of funding was not reported

PIANO-2 CKD 2011

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: September 2009 to June 2011 • Duration of follow-up: 14 days
Participants	• Country: Korea • Setting: not reported • Inclusion criteria: patients with CKD undergoing HD and PCI for stable CAD • Number: treatment group 1 (24); treatment group 2 (25); treatment group 3 (25) • Mean age ± SD (years): treatment group 1 (53.5 ± 12.8); treatment group 2 (51.6 ± 10.2); treatment group 3 (53.9 ± 6.6) • Sex (M/F): treatment group 1 (13/11); treatment group 2 (10/15); treatment group 3 (15/10) • Exclusion criteria: known allergies to aspirin, clopidogrel, or cilostazol; thienopyridine use before enrolment; concomitant use of other antithrombotic drugs (oral anticoagulants and dipyridamole); platelet count < 100 x 10^6/μL; HCT < 25%; liver disease (bilirubin > 2 mg/dL); active bleeding or bleeding diathesis; GI bleeding within the last 6 months; haemodynamic instability; acute coronary or cerebrovascular event within 3 months; malignancy; concomitant use of a cytochrome P450 inhibitor or NSAIDs; recent treatment (< 30 days) with a glycoprotein IIb/IIIa antagonist
Interventions	Treatment group 1 • Clopidogrel: loading dose 300 mg then 75 mg/day for 14 days

PIANO-2 CKD 2011 *(Continued)*

	Treatment group 2 • Clopidogrel: loading dose 300 mg then 150 mg/day for 14 days Treatment group 3 • Cilostazol: 200 mg/day for 14 days • Xlopidogrel 75 mg/day for 14 days Cointerventions • All patients received aspirin (100 mg/day) for ≥ 1 week before coronary intervention
Outcomes	• Platelet function • Platelet activation markers (soluble CD40 ligand and soluble P-selectin) • High on-treatment platelet reactivity • Inhibition of platelet aggregation • P2Y12 reaction units • Differences in sCD40L and sP-selectin levels before and after antiplatelet agents
Notes	• Funding: Kyung Hee University for the young researcher in medical science (KHU-20100741). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "CKD patients were randomly assigned using a computer-generated randomisation sequence."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes adjudication were unlikely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study did not report all critical outcomes expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias. Funder did not influence data analysis and study reporting or interpretation

PIANO-3 2015

Study characteristics

PIANO-3 2015 *(Continued)*

Methods	• Study design: cross-over RCT • Duration of study: January 2013 to August 2013 • Duration of follow-up: 14 days (first phase)
Participants	• Country: Korea • Setting: single centre • Inclusion criteria: kidney failure undergoing regular (≥ 6 months) maintenance HD; ongoing (≥ 2 months) treatment with clopidogrel; treated with clopidogrel with or without aspirin because of moderate coronary stenosis by coronary angiography or because they were at high risk (Framingham heart risk score ≥ 20%) for CAD • Number: treatment group 1 (12); treatment group 2 (13) • Mean age ± SD (years): treatment group 1 (51.9 ± 11.4); treatment group 2 (50.4 ± 12.0) • Sex (M/F): treatment group 1 (6/6); treatment group 2 (10/3) • Exclusion criteria: known allergies to aspirin, clopidogrel, or ticagrelor; concomitant use of other antithrombotic drugs (oral anticoagulants and dipyridamole); previous coronary intervention, thrombocytopenia (platelet count < 100,000/mL); HCT < 25%; uncontrolled hyperglycaemia (HbA1c > 10%); liver disease (bilirubin > 2 mg/dL); symptomatic severe pulmonary disease; active bleeding or bleeding diathesis; GI bleeding within the past 6 months; haemodynamic instability; acute coronary or cerebrovascular event within the past 3 months; pregnancy; any malignancy; concomitant use of a cytochrome P450 inhibitor or NSAID; recent treatment (< 30 days) with a glycoprotein IIb/IIIa antagonist
Interventions	Treatment group 1 • Ticagrelor: loading dose of 180 mg and then 90 mg twice/day for 14 days • Aspirin: 100 mg Treatment group 2 • Clopidogrel: loading dose of 300 mg then 75 mg once/day for 14 days • Aspirin: 100 mg Cointerventions • Not reported
Outcomes	• Platelet function and aggregation • Adverse events • Number of patients with major and minor bleeding • Heart rate, respiratory rate, and arterial oxygen saturation • Differences in Agg_{max} and IPA • Death was not a targeted outcome, but there were no deaths during the study period
Notes	• Funding: Bio Research & Development program through the National Research Foundation of Korea funded by grant 2010-0019913 from the Ministry of Education, Science and Technology. The founders of this study were not involved in study design, collection, data analysis, data interpretation, writing the report, or the decision to submit the report for publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients with HTPR were randomly assigned at a 1:1 ratio by an independent investigator to the clopidogrel or ticagrelor groups using computerized random-number generation." Comment: Ramdon number is considered as low risk of bias

PIANO-3 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "Patients with HTPR were randomly assigned by an independent investigator to the clopidogrel or ticagrelor groups." Comment: Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes adjudication were likely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	As reported in Figure 1, at the end of the first phase 4/13 in the clopidogrel group and 4/12 in the ticagrelor group did not complete the first phase of treatment (due to adverse event or non-adherence)."
Selective reporting (reporting bias)	High risk	Study did not report all expected outcomes (cardiovascular disease) for a study of this type. Data were not appropriately reported for a cross-over RCT
Other bias	Low risk	No evidence of other sources of bias. Funder did not influence data analysis and study reporting or interpretation

PIANO-6 2017

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 14 days
Participants	• Country: Korea • Setting: single centre • Inclusion criteria: patients on regular (≥ 6 months) maintenance HD; took low-dose aspirin (100 mg/day) and clopidogrel (75 mg once/day) for at least 14 days as part of their standard treatment regimens • Number (randomised/analysed): treatment group 1 (18/17); treatment group 2 (21/18); treatment group 3 (13/13) • Mean age ± SD (years): treatment group 1 (47.7 ± 9.8); treatment group 2 (49.2 ± 11.4); treatment group 3 (54.6 ± 12.8) • Sex (M/F): treatment group 1 (12/5); treatment group 2 (13/5); treatment group 3 (7/6) • Exclusion criteria: known allergy to aspirin, clopidogrel, or ticagrelor; concomitant use of other antithrombotic drugs (oral anticoagulants, dypiridamole); liver disease (serum bilirubin level > 2 mg/dL); symptomatic severe pulmonary disease; active bleeding or bleeding diathesis; GI bleeding within the last 6 months; haemodynamic instability; acute coronary or cerebrovascular event within the last 3 months; pregnancy; malignancy; concomitant use of a cytochrome P450 inhibitor or an NSAID; recent treatment (within 30 days) with a glycoprotein IIb/IIIa antagonist
Interventions	Treatment group 1 • Clopidogrel: 300 mg loading dose, then 75 mg/day for 14 days Treatment group 2 • Ticagrelor (standard dose): 180 mg loading dose, then 90 mg twice/day for 14 days

PIANO-6 2017 *(Continued)*

	Treatment group 3 • Ticagrelor (low dose): 90 mg twice/day for 14 days Cointerventions • All patients were prescribed aspirin (100 mg once/day)
Outcomes	• Platelet function • Platelet aggregation • Bleeding events • Adverse events • Death was not a targeted outcome, but there were no deaths during the study period • Treatment withdrawal
Notes	• Funding: Bio & Medical Technology Development Program of the National Research Foundation of the Ministry of Education, Science and Technology (No. 2012M3A9C6050507). The funding of this study were not involved in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the report for publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An independent investigator randomised the patients in a 1:1:1 ratio to one of three treatment groups. The investigator employed a computerized random number generation method." Coment: Random number method is considered as a low risk of bias
Allocation concealment (selection bias)	Unclear risk	Quote: "An independent investigator randomised the patients in a 1:1:1 ratio." Comment: Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The study was not conducted in a double-blinded manner."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes adjudication were likely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of 52 participants, four patients discontinued their drugs because of adverse events, as follows: one patient with BARC type 1 bleeding (gum bleeding) in the clopidogrel group; two patients with BARC type 1 and 2 bleeding (gum bleeding and arteriovenous fistula bleeding, respectively) in the standard-dose ticagrelor group; and one patient with dyspnoea in the standard-dose ticagrelor group. [...] A total of 52 patients underwent randomisation, and 48 completed the study protocol." Comment: 17/18 in the clopidogrel group, 18/21 in the standard-dose ticagrelor group, and 13/13 in the low-dose ticagrelor group completed the study. There were differences between groups (> 10% lost to follow-up)
Selective reporting (reporting bias)	High risk	Study did not reported all expected outcomes (cardiovascular events) for a study of this type

PIANO-6 2017 *(Continued)*

Other bias	Low risk	No evidence of other sources of bias. Funder did not influence data analysis and study reporting or interpretation

Pierucci 1989

Study characteristics

Methods	• Study design: cross-over RCT • Duration of study: February 1986 to March 1988 • Duration of follow-up: 48 hours
Participants	• Country: Italy • Setting: single centre • Inclusion criteria: aged 18 to 70 years; diffuse proliferative nephritis (lupus nephritis); deteriorating kidney function • Number: 6 • Age range: 21 to 63 years • Sex (M/F): 1/5 • Exclusion criteria: not reported
Interventions	Treatment group • BM13.177 (sulphonamide derivative) IV Control group • Placebo Cointerventions • Not reported
Outcomes	• Urinary TXB2 excretion • Inulin clearance • Para-aminohippurate excretion • Bleeding time • BP
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study

Pierucci 1989 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes adjudication were generally unlikely to be influenced by knowledge of the nature of the treatment allocation. However, bleeding time could be influenced by the knowledge of the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study outcomes did not include critical outcomes expected for this type of study. Data were not appropriately reported for a cross-over RCT
Other bias	Unclear risk	Insufficient information to permit judgement

PLATO 2009

Study characteristics	
Methods	• Study design: parallel RCT (post-hoc analysis) • Duration of study: October 2006 to July 2008 • Duration of follow-up: 12 months
Participants	• Country: multinational (43 countries) • Setting: multicentre (800 sites) • Inclusion criteria: patients with acute coronary syndrome with onset during the previous 24 hours; CrCl < 60 mL/min • Number (total population/CKD patients): 15,202/3237 • Median age, range (CKD patients): 74 years, 68 to 79) • Sex (M/F): 1948/1289 • Exclusion criteria: contraindication against the use of clopidogrel; fibrinolytic therapy within 24 hours before randomisation; need for oral anticoagulation therapy; increased risk of bradycardia; concomitant therapy with a strong cytochrome P-450 inhibitor or inducer; patients with ESKD requiring dialysis
Interventions	Treatment group 1 • Ticagrelor: 180 mg loading dose, followed by 90 mg twice/day (the median duration of study treatment was 9.1 months) Treatment group 2 • Clopidogrel: 300 mg loading dose, followed by 75 mg/day (the median duration of study treatment was 9.1 months) Cointerventions • All participants consumed one tablet of placebo
Outcomes	• Death from vascular causes (stroke, cardiovascular or any other with unknown cause) • MI • Stroke • Number with bleeding (major, minor, fatal) • Other adverse effects • Increase in SCr percentage

PLATO 2009 *(Continued)*

Notes	• Funding: AstraZeneca. Support for the analysis and interpretation of results and preparation of the manuscript was provided through funds to the Uppsala Clinical Research Center and Duke Clinical Research Institute as part of the Clinical Study Agreement

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomised 1:1 ratio using a randomisation schedule blocked by site." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	An independent central adjudication committee adjudicated all suspected primary and secondary efficacy end points as well as major and minor bleeding events. Hovewer, outcome adjudication (adverse events) may have been influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Vital status was available for all participants (except 5 participants that had missing vital status follow-up)
Selective reporting (reporting bias)	Low risk	Study reported all critical outcomes expected for a study of this type
Other bias	High risk	FDA reporting identified a minimum of 106 participants without outcome data (instead of the 5 reported in the primary study report). There may have been an imbalance between study groups with significantly more patients allocated to ticagrelor that had incomplete vital status at follow-up. Funder was unlikely to influence data analysis and study reporting or interpretation

PREDIAN 2011

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 12 months
Participants	• Country: Spain • Setting: not reported • Inclusion criteria: diabetic patients with stage 3–4 CKD • Number: treatment group (82); control group (87) • Mean age ± SD (years): treatment group (70.2 ± 8.9); control group (69.5 ± 9.5) • Sex (M/F): treatment group (45/37); control group (46/41) • Exclusion criteria: not reported

PREDIAN 2011 *(Continued)*

Interventions	Treatment group • Pentoxifylline: 600 mg daily (extended-release tablets) for 1 month, then increased to 600 mg twice/day Control group • No pentoxifylline treatment Cointerventions • Not reported
Outcomes	• Progression to DKD (change in eGFR) • Reduction in eGFR ≥ 25% • Urinary TNF-a at 1 year • Klotho levels at 1 year • Phosphorous at 1 year
Notes	• Trial registration number was not reported. Funding: Instituto de Salud Carlos III (ISCIII) (Ref. EC07/90021) (Spanish Ministry of Economy, Industry and Competitiveness). This work was supported by Fondo de Investigaci´on en Salud PI15/00298, CP14/00133, PI16/02057,PI16/00024, ISCIII-Redes Tematicas de Investigaci ´on Cooperativa en Salud (RETIC)-REDINREN RD16/0009, Sociedad Espanola de Nefrologıa, and Asociacion Cienıfitca para la Investigaci on Nefrologica. The authors acknowledge co-funding by Fondo Europeo de Desarrollo Regional, Uni´on Europea ("Una forma de hacer Europa"). M.D.S.-N. is recipient of a Miguel Servet Research Contract. J.D.-C. is recipient of a Sara Borrel Contract (CD16/00165). E.M.-N. is recipient of a research contract from the ISCIII (FI14/00033). C.F. is recipient of a research contract from the ISCIII-RETIC-REDINREN (RD16/0009/ 0022).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. However, participants and/or investigators could be aware of treatment assigned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only subjective outcomes were reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Of the 169 patients in the PREDIAN trial, 166 (85 control group, 81 pentoxifylline group) who completed 1-year follow-up were included in this analysis." Comment: 166/169 participants completed the study (< 5% loss to follow-up). However, no clear data were reported by the treatment group
Selective reporting (reporting bias)	High risk	Prespecified outcomes were reported. Clinically-relevant outcomes that would be expected for this type of intervention were not reported

PREDIAN 2011 *(Continued)*

Other bias	Unclear risk	Quote: "The founders played no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript." Comment: Baseline characteristics were not reported. Funder did not influence data analyses and interpretation

PRISM-PLUS 1998

Study characteristics	
Methods	• Study design: parallel RCT (post-hoc analysis) • Duration of study: November 1994 to September 1996 • Duration of follow-up: 6 months
Participants	• Country: multinational (14 countries) • Setting: multicentre (72 sites) • Inclusion criteria: patients with acute coronary syndrome; CrCl < 60 mL/min data reported • Number: total population (1537); treatment groups 1+2 (CKD patients: 300); control group (CKD patients: 311) • Mean age ± SD (years): < 30 mL/min (79.4 ± 6.7); 30 to 60 mL/min (71.1 ± 8.0) • Sex (M): < 30 mL/min (35.0%); 30 to 60 mL/min (54.1%) • Exclusion criteria: severe kidney insufficiency (SCr ≥ 2.5 mg/dL); ST-segment elevation < 20 min; thrombolysis in the previous 48 hours; cardiac angiography in the previous 6 months; bypass operation in the previous 1 month; angina caused by identifiable factors; history of platelet disorder or thrombopenia; active bleeding; high risk of bleeding; stroke in the previous year; platelet count < 150,000/m^3
Interventions	Treatment group 1 • Tirofiban: 0.4 µg/kg/min for 30 minutes, followed by an infusion of 0.1 µg/kg/min • Aspirin: 325 mg/day Treatment group 2 • Tirofiban: 0.6 µg/kg/min for 30 minutes, followed by an infusion of 0.15 µg/kg/min • Aspirin: 325 mg/day • Heparin placebo Control group • Placebo • Aspirin: 325 mg/day Cointerventions • Heparin administered as an IV bolus of 5000 U, followed by an infusion of 1000 U/h
Outcomes	• Death (any cause) • MI or refractory ischaemia • Number with bleeding (major, minor, fatal) and bleeding events • Adverse events
Notes	• Funding: not reported
Risk of bias	

PRISM-PLUS 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomisation was performed locally by means of sealed envelopes." Comment: It was not clear if envelopes were opaque and numbered. Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All events had been evaluated by the end-points committee. The investigators remained blinded to treatment until after the six-month visit
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Study reported all critical outcomes expected for a study of this type
Other bias	High risk	The tirofiban + placebo arm was terminated earlier than planned and not included in the final analysis due to excess death at seven days. An independent data and safety monitoring board reviewed unblinded data in two interim analyses

PURSUIT 1997

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: November 1995 to January 1997 • Duration of follow-up: 6 months
Participants	• Country: multinational (28 countries; USA and Europe) • Setting: multicentre (number of sites not reported) • Inclusion criteria: symptoms of ischaemic chest pain at rest, lasting ≥ 10 minutes within the previous 24 hours, with transient ST-segment elevation > 0.5 mm, transient or persistent ST-segment depression > 0.5 mm, T-wave inversion >1 mm within 12 hours before or after chest pain, or a serum concentration of creatine kinase MB isoenzyme that was above ULN for the hospitals where they were evaluated; eGFR < 60 mL/min • Number (total population/eGFR < 60 mL/min): treatment group (4722/1434); control group (4739/1183) • Median age, IQR (years): not reported for CKD patients • Sex (M/F): not reported for CKD patients • Exclusion criteria: persistent ST-segment elevation > 1 mm; active bleeding or a history of bleeding diathesis; GI or genitourinary bleeding within 30 days before enrolment; SBP > 200 mm Hg or DBP >110 mm Hg; history of major surgery within the previous 6 weeks; history of non- haemorrhagic stroke within the previous 30 days or any history of haemorrhagic stroke; kidney failure; pregnancy; planned

PURSUIT 1997 *(Continued)*

	administration of a platelet glycoprotein IIb/IIIa receptor inhibitor or thrombolytic agent; receipt of thrombolytic therapy within the previous 24 hours
Interventions	Treatment group • Eptifibatide: bolus dose of 180 µg/kg, followed by an infusion of 2.0 µg/kg/min • Aspirin: 80 to 325 mg/day Control group • Placebo: bolus and infusion until discharge from the hospital or for 72 hours • Aspirin: 80 to 325 mg/day Cointerventions • Aspirin was administrated at the discretion of the treating physicians; patients who were allergic to or intolerant of aspirin could receive ticlopidine • Heparin bolus dose of 5000 U, followed by an infusion at a rate of 1000 U/hour
Outcomes	• Composite of death from any cause or nonfatal MI at 30 days • Death from all causes within 30 days after the index event, a first or recurrent MI within 30 days, the composite endpoint (death or non-fatal MI) at 96 hours and 7 days, and measures of the safety and efficacy of treatment in patients undergoing percutaneous revascularization • Safety endpoint included mild, moderate and severe bleeding events and life-treating bleeding • Stroke, classified as haemorrhagic, ischaemias, or ischaemias with haemorrhagic conversion • Platelet count
Notes	• Funding: COR Therapeutics and Schering-Plough Research Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed, in a double-blind manner, by coordinating centres in the United States or the Netherlands."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluated by a masked clinical events committee
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Study reported all critical outcomes expected for a study of this type
Other bias	High risk	Quote: "It was specified in the protocol that the study would be stopped in the lower-dose group after the independent data safety and monitoring committee had conducted an interim review of safety data, provided the higher dose had an acceptable safety profile. After 3218 patients had been randomly as-

PURSUIT 1997 *(Continued)*

	signed to treatment groups, the committee recommended dropping the lower dose." Comment: Percentage of discontinuation of study drug due to early discharge from hospital not balanced across groups. The role of funding was not reported

Quarto Di Palo 1991

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 12 months
Participants	• Country: Italy • Setting: single centre • Inclusion criteria: cadaveric kidney transplant recipients with SCr < 140 µmol/L (good kidney function) • Number: treatment group (18); control group (18) • Mean age ± SD (years): treatment group (37 ± 5); control group (37 ± 7) • Sex (M/F): treatment group (13/5); control group (12/6) • Exclusion criteria: SCr ≥ 140 µmol/L
Interventions	Treatment group • Picotamide: 600 mg/day Control group • Placebo Cointerventions • All patients were on triple immunosuppressive regimen with CSA, AZA, and steroids
Outcomes	• Change in SCr • Urinary thromboxane B2 • Blood CSA • Adverse events • BP • Blood counts • Death was not a targeted outcome, but there were no deaths during the study period
Notes	• Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Quarto Di Palo 1991 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. The outcome adjudication may have been influenced by knowledge of the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote. "There was no rejections or major complications making it necessary to interrupt the trial." Comments: All participants completed the study
Selective reporting (reporting bias)	High risk	Study outcomes did not included critical outcomes expected for this type of study
Other bias	Low risk	No evidence of other sources of bias

RAPPORT 1998

Study characteristics	
Methods	• Study design: parallel RCT • Duraiton of study (enrolment): 16 November 1995 to 2 February 1997 • Duration of follow-up: 6 months
Participants	• Country: USA • Setting: multicentre (36 sites) • Inclusion criteria: patients within 12 hours of the onset of acute MI, referred for primary angioplasty (data reported for CKD patients) • Number (total population/CKD patients): treatment group (241/27); control group (242/30) • Mean age, IQR (total population): treatment group (60 years, 52 to 70); control group (62 years, 53 to 71) • Sex (M) (total population): treatment group (73%); control group (72%) • Exclusion criteria: severe thrombocytopenia; baseline prothrombin time > 1.2 times control; ongoing internal bleeding or recent major surgery; previous stroke; severe uncontrolled hypertension; PTCA of the infarct artery within 3 months; cardiogenic shock or prolonged resuscitation; vasculitis; prior administration of abciximab or fibrinolytic therapy; inability to give written informed consent
Interventions	Treatment group • Abciximab: 0.25 mg/kg bolus followed by a 12 hours infusion of 0.125 µg/kg/min (maximum 10 µg/min) • Aspirin Control group • Placebo • Aspirin Cointerventions • Heparin: 100 U/kg bolus was given before angioplasty, followed by additional weight-adjusted doses to maintain an activated clotting time > 300 seconds • The rest of the medical regimen was left to the investigator's discretion

RAPPORT 1998 *(Continued)*

Outcomes	• Death (any cause) • MI • Urgent target vessel revascularization • Major bleeding (including intracranial haemorrhage) • Minor bleeding events • Revascularisation • Reinfarction
Notes	• Unpublished data provided for individuals with CKD defined as GFR < 60 mL/min/1.73 m^2 • Funding: Centocor, Malvern, Pa, and Eli Lilly and Company, Indianapolis, Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All clinical end points were independently adjudicated by a clinical events committee, who reviewed the case report forms, hospital records, and ECG and enzymatic data. All angiograms were reviewed by a central angiographic laboratory."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low percentage of lost to follow-up. Intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Study reported all critical outcomes expected for a study of this type
Other bias	High risk	No evidence of other sources of bias. The role of funding was not reported

Reams 1985

Study characteristics

Methods	• Study design: parallel-group RCT • Duration of study: not reported • Duration of follow-up: 8 days
Participants	• Country: USA • Setting: single centre • Inclusion criteria: males and females with endogenous CrCl < 5 mL/min (with the exception of one patient with normal kidney function undergoing PD for psoriasis); > 18 years; maintenance PD; considered haemodynamically stable • Number: Treatment group (7); control group (7)

Reams 1985 *(Continued)*

- Mean age (years): treatment group (50); control group (42)
- Sex (M/F): treatment group (4/3); control group (4/6
- Exclusion criteria: acute infection; unstable circulatory conditions; uncontrolled hypertension

Interventions	Treatment group • Dipyridamole (oral): 75 mg 3 times/day Control group • Placebo (oral): 3 times/day Cointerventions • Following a series of 3 to 4 in and out exchanges, a series of 36 hourly peritoneal exchanges was attempted and standard manual technique was used
Outcomes	• Glucose • Urea • SCr • Insulin • Protein • Alteration in peritoneal clearance • Adverse events
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Some outcomes adjudication (adverse events) were likely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	High risk	Study outcomes did not included critical outcomes expected for this type of study
Other bias	Unclear risk	Insufficient information to permit judgement

RESIST 2008

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 1 month
Participants	• Country: USA • Setting: multicentre (7 sites) • Inclusion criteria: atherosclerotic renal artery stenosis 50% and 100% treatable with the embolic protection devices undergoing stenting; history of hypertension; renal insufficiency, heart failure, or angina with poorly controlled hypertension • Number: treatment group 1 (25); treatment group 2 (25); treatment group 3 (22); control group (28) • Mean age ± SD (years): treatment group 1 (72 ± 9); treatment group 2 (72 ± 6); treatment group 3 (71 ± 11); control group (75 ± 7) • Sex (M/F): treatment group 1 (11/14); treatment group 2 (12/13); treatment group 3 (9/13); control group (12/16) • Exclusion criteria: < 18 years; pregnancy; life expectancy ≤ 6 months; dialysis or kidney transplant; stenosis not amenable to stent; allergy to study agents; unrelated kidney disease; untreated aortic aneurysm; kidney size < 8 cm; restenosis; vessel dimensions out of range for study devices; treatment of a side branch or distal stenosis; active bleeding; stroke within 2 years or with a significant residual neurological deficit; INR > 1.2 times control; thrombocytopenia; major surgery or trauma within 6 weeks; intracranial neoplasm; AV malformation or aneurysm, vasculitis, or a non-study procedure within 24 hours
Interventions	Treatment group 1 • Abciximab Treatment group 2 • Abciximab • Angioguard Treatment group 3 • Angioguard Control group • Placebo Cointerventions • Antihypertensive medications were continued during the evaluation except for diuretics, which were held that morning. NSAIDs (except aspirin), cimetidine, ranitidine, and trimethoprim were withheld for 7 days • Patients were instructed to drink at least 1 L of water the day before and at least 500 mL of water on the morning of the assessment
Outcomes	• Creatinine • Clotts • GFR • Embolic protection • BP • Platelet aggregates • Platelet inhibition • Bleeding events (major and minor) • Transfusions

RESIST 2008 *(Continued)*

	• Activated clotting times • Occurrence of platelet-rich thrombi • Capture of atheromatous debris • Fibrin-based thrombi • ESKD requiring dialysis • Death was not a targeted outcome, but there were no deaths during the study period
Notes	• Funding: University of Toledo, Centocor Inc and Cordis Corp, and Johnson & Johnson companies. Hovewer, the study conduct, analysis, and reporting were performed independently of the sponsors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The 2x2 randomisation plan was generated from computer-based pseudo random number generators with the following allocations: half to Angioguard and half to no Angioguard, and half to abciximab and half to placebo infusion. This yielded 4 groups: control, Angioguard only, abciximab only, and Angioguard with abciximab. Randomization was stratified by baseline creatinine >=1.6 mg/dL and enrolling centre." Comment: Insufficient information to permit judgement (pseudo random number)
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind use of a platelet glycoprotein IIb/IIIa inhibitor."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Some outcomes adjudication were likely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient data on CKD patients to permit judgement
Selective reporting (reporting bias)	High risk	Study did not report all critical outcomes (cardiovascular events) expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias. Funder did not influence data analysis and study reporting or interpretation

Rouzrokh 2010

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: December 2003 to August 2007 • Duration of follow-up: 6 months
Participants	• Country: Iran

Rouzrokh 2010 *(Continued)*

- Setting: single centre
- Inclusion criteria
- ESKD treated with HD requiring AVF
- Number (randomised/analysed): 501/390; treatment group 1 (130); treatment group 2 (130); control group (130)
- Mean age ± SD (years): not reported
- Sex (M/F): treatment group 1 (52/78); treatment group 2 (65/65); control group (65/65)
- Exclusion criteria: bleeding disorder; pregnancy; lactation; active or suspected bleeding tendency; active peptic ulcer disease; severe hepatic insufficiency; receiving anti-coagulation and regular NSAIDs

Interventions	Treatment group 1 • Aspirin: 100 mg/day Treatment group 2 • Dipyridamole: 75 mg/day Control group • Placebo Cointerventions • All patients received anti-platelet drugs for at least 6 months
Outcomes	• Fistula patency
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcome adjudication may have been influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "At least in six month period, 390 patients out of 501 (130 cases randomised in each group) remained and 111 patients were excluded, because they had failed to follow up, whose AVFs had failed within the first 72 h after the surgery or drugs discontinuity." Comment: > 10% lost of follow-up
Selective reporting (reporting bias)	High risk	Study did not reported all expected outcomes for a study of this type

Rouzrokh 2010 *(Continued)*

Other bias	Low risk	No evidence of other sources of bias

Rubin 1982

Study characteristics

Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 8 days (first phase)
Participants	• Country: USA • Setting: single centre • Inclusion criteria: patients undergoing intermittent PD at 2 L/hour • Number: treatment group (5); control group (5) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Dipyridamole: 75 mg 3 times/day Control group • Placebo: 3 times/day Cointerventions • All dialyses were carried out using a cycle machine and tubing
Outcomes	• SCr • Uric acid • Inulin • Clearance of creatinine, inulin and urea • Protein • Sodium • Glucose • BP • Withdrawal treatment
Notes	• Funding: The United States Public Health grant MO/RR006260

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "The initial patient medication was determined by the flip of a coin. The next patient received the opposite to the first patient. The next patient's medication was chosen by coin flip, and so on." Comment: Flip of a coin is considered as a high risk of bias because it was used in alternate way
Allocation concealment (selection bias)	Unclear risk	Quote: "The study was balanced (by the pharmacist) so that five patients received the drug and five patients received the placebo during the first period."

Rubin 1982 *(Continued)*

		Comment: Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Peritoneal clearances of creatinine, urea, and inulin were calculated by multiplying the volume of dialysate effluent by the concentration of dialysate effluent and dividing this product by the plasma concentration multiplied by the time of the study exchanges. The plasma concentration used in the calculations was the average of values obtained at the start and close of the 8-hr period. Sodium losses into dialysate were calculated by subtracting the amount infused from the amount in the dialysate effluent (concentration multiplied by effluent volume)." Comment: Outcomes were generally unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data related to the first period were not reported in sufficient detail to perform an adjudication
Selective reporting (reporting bias)	High risk	Study outcomes did not include all expected for this type of study. Data were not appropriately reported for a cross-over RCT
Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

Salter 1984

Study characteristics	
Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 7 days (first period)
Participants	• Country: UK • Setting: single centre • Inclusion criteria: long-term HD patients; been on dialysis for periods in excess of 6 months and were in a clinically stable state • Number: 17 • Mean age ± SD (years): not reported • Sex (M/F): 15/2 • Exclusion criteria: antithrombotic treatment for at least 21 days prior to starting the study
Interventions	Treatment group 1 • Low-dose aspirin: 100 mg 3 times/day • Dipyridamole: 75 mg 3 times/day Treatment group 2 • High-dose aspirin: 330 mg 3 times/day • Dipyridamole 75 mg 3 times/day

Salter 1984 *(Continued)*

	Control group • Placebo Cointerventions • Each dialysis lasted 4 hours, 3 times/week • The heparin protocol used was an initial loading dose of 5,000 IU sodium heparin and an hourly maintenance dose of 1,000 IU
Outcomes	• Platelet count • Platelet aggregates • Fibrin deposition • Enmeshed erythrocytes • Thrombosis • Plasma heparin concentration • Adverse events • Withdrawal of treatment
Notes	• Funding: Yorkshire Kidney Research Fund

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Platelet counts were made using 0.1% ammonium oxalate as a diluent under phase contrast microscopy. Plasma heparin concentrations were measured chromo genically by the method of Teien, employing activated Factor X." Comment: Outcomes were generally unlikely to be influenced by knowledge of treatment allocation. However, adverse events may be influenced by the knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study outcomes did not include all expected for this type of study. Data were not appropriately reported for a cross-over RCT
Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

Schnepp 2000

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: not reported
Participants	• Country: Germany • Setting: single centre • Inclusion criteria: HD patients • Number: treatment group 1 (10); treatment group 2 (10); control group (10) • Mean age ± SD: 69.4 ± 12.2 years • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • Aspirin: 100 mg/day Treatment group 2 • Ticlopidine: 250 mg twice/day Control group • Clopidogrel: 75 mg/day Cointerventions • Not reported
Outcomes	• Platelet aggregation time
Notes	• Abstract-only publication • Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Outcomes adjudication were unlikely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Schnepp 2000 *(Continued)*

Selective reporting (reporting bias)	High risk	Study outcomes did not include critical endpoints that might be expected for a study of this type
Other bias	Unclear risk	Insufficient information to permit judgement

Schulze 1990

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: February 1985 to February 1986 • Duration of follow-up: 12 months
Participants	• Country: Germany • Setting: single centre • Inclusion criteria: cadaveric kidney transplant recipients • Number: treatment group (32); control group (32) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Dipyridamole (oral): 150 mg 3 times/day Control group • No treatment with antiplatelet agents Cointerventions • AZA and prednisolone
Outcomes	• Loss of graft function • GI bleeding • Adverse events • Thrombosis
Notes	• German • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation

Schulze 1990 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. The outcome adjudication may have been influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study outcomes did not include critical endpoints that might be expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias

Sreedhara 1994

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: April 1982 to February 1988 • Duration of follow-up: 18 months or until the first thrombotic episode
Participants	• Country: USA • Setting: multicentre (3 sites) • Inclusion criteria: patients who required a new expanded PTFE graft for chronic HD (type I) or patients on chronic HD who had expanded PTFE graft who developed thrombosis and required revision or thrombectomy (type II) • Number: treatment group 1 (29); treatment group 2 (26); treatment group 3 (29); control group (24) • Mean age ± SD (years): treatment group 1 (Type I: 56.6 ± 15.0; Type II: 62.2 ± 16.7); treatment group 2 (Type I: 56.7 ± 14.5; Type II: 43.0 ± 17.5); treatment group 3 (Type I: 51.3 ± 17.8 years; Type II: 48.5 ± 22.2 years); control group (Type 1: 55.3 ± 10.6; Type II: 57.0 ± 15.8) • Sex (M/F): treatment group 1 (7/22); treatment group 2 (16/10); treatment group 3 (9/20); control group (13/11) • Exclusion criteria: uncontrolled hypertension (sitting DBP of > 110 mm Hg); history of active peptic ulcer disease; haemophilia, Von Willebrand's disease or other bleeding disorders; neoplastic disorders and hypersensitivity to aspirin or dipyridamole
Interventions	Treatment group 1 • Dipyridamole: 75 mg 3 times/day for 18 months or until the first episode of thrombosis • Aspirin placebo Treatment group 2 • Dipyridamole placebo • Aspirin: 325 mg/day for 18 months or until the first episode of thrombosis Treatment group 3 • Dipyridamole: 75 mg 3 times/day • Aspirin 325 mg once/day for 18 months or until the first episode of thrombosis Control group • Dipyridamole placebo • Aspirin placebo for 18 months or until the first episode of thrombosis

Sreedhara 1994 *(Continued)*

	Cointerventions • None of the patients received EPO during the study period as the drug was not available for general use at that time interval • There was no attempt to change any parameters of dialysis prescription during the study period
Outcomes	• Expanded PTFE graft thrombosis • Adverse events • Blood counts • Cardiovascular events • Bleeding events (GI bleeding) • Death (any cause)
Notes	• Funding: Boehringer Ingeiheim Pharmaceutical

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was done using a predetermined schedule." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Thrombosis was detected by the lack of blood flow by palpation and auscultation or the presence of thrombus detected during introduction of the dialysis needle into the graft." Comment: Some outcomes adjudication may have been influenced by knowledge of the treatment type due to the nature of the outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Eleven patients did not complete the protocol. Two of them were lost to follow-up and the remaining were dropped from the study because of transplantation or patient refusal to continue. [...] Thirty-four patients were discontinued from the study due to adverse events." Comment: Lost to follow-up > 10%
Selective reporting (reporting bias)	Low risk	Study reported all critical outcomes expected for a study of this type
Other bias	High risk	No evidence of other sources of bias. The role of funding was not reported

Steiness 2018

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reprorted

Steiness 2018 *(Continued)*

	• Duration of follow-up: 28 days
Participants	• Country: Germany • Setting: not reported • Inclusion criteria: type 2 diabetic patients with DKD (i.e. UACR > 30 mg/g Cr) • Number: treatment group 1 (24); treatment group 2 (25); control group (23) • Mean age, range (years): treatment group 1 (67, 33 to 78); treatment group 2 (64, 40 to 77); control group (67, 52 to 81) • Sex (M/F): treatment group 1 (18/7); treatment group 2 (19/5); control group (18/5) • Exclusion criteria: not reported
Interventions	Treatment group 1 • SER150 (oral): 15 mg twice/day (novel anti-thromboxane) Treatment group 2 • SER150 (oral): 30 mg twice/day Control group • Placebo Cointerventions • Patients regular medication
Outcomes	• Safety and tolerability, including bleeding time during 28 days • Change from baseline in UACR, assessed at 28 days
Notes	• Abstract-only publication • Trial registration number was not reported • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double-blind." Comment: Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated
Blinding of outcome assessment (detection bias) All outcomes	High risk	Objective and subjective outcomes were reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient information to permit judgement

Steiness 2018 *(Continued)*

Selective reporting (reporting bias)	High risk	Prespecified outcomes were reported. Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	Unclear risk	Similar baseline characteristics were reported. Funding was not reported

STOP 1995

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 12 months
Participants	• Country: Italy • Setting: multicentre (12 sites) • Inclusion criteria: HD patients (HD treatment started at least 60 days earlier) with permanent internal stabilised vascular access (autologous AVF or AVF with prosthetic graft) • Number: treatment group: number (416); control group (416) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: history of relevant bleeding; serious hepatic insufficiency; chronic treatment with antiplatelet agents or with NSAIDs; hypersensitivity to study drug
Interventions	Treatment group • Picotamide Control group • Placebo Cointerventions • Not reported
Outcomes	• Acute occlusions of vascular access • Death (any cause) • Cardiovascular death (including vascular death) • Major cardiovascular events (nonfatal stroke, nonfatal MI) • Major bleeding • Thrombotic occlusions events • BP • Laboratory parameters • Serious adverse events
Notes	• Published results from an earlier systematic review ATT 2002 (protocol published) • Funding: Sandoz

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

STOP 1995 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Assignment of the randomisation codes is organized in blocks and the patients are enrolled according to the sequential order designated for each centre." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomisation key relative to each individual patient is contained in a sealed envelope that must be opened in case of emergency." Comment: Not reported if envelopes were opaque and numbered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Members of the coordinating group take part in the steering committee of the study that validate outcomes events approve final results." Comment: It was not clear if these members of coordinating group were aware of treatment assigned. Outcome adjudication may have been influenced by knowledge of the treatment type due to the nature of the outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Study endpoints included critical outcomes for this type of study
Other bias	High risk	Baseline characteristics were not provided. The role of funding was not reported

Storck 1996

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 21 days
Participants	• Country: Germany • Setting: single centre • Inclusion criteria: patients with transplanted kidney graft • Number: treatment group: (9); control group (5) • Mean age ± SD (years): treatment group (48 ± 3); control group (42 ± 4) • Sex (M/F): treatment group (6/3); control group (3/2) • Exclusion criteria: not reported
Interventions	Treatment group • Intraoperative aspisol: 1 g IV in a central venus line 5 minutes before kidney reperfusion (15 minutes of intervention) Control group

Storck 1996 *(Continued)*

	• Placebo Cointerventions • Not reported
Outcomes	• Thromboxane B_2 • Leukotrine B_4 • Protaglandin $F1_a$ • SCr
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. However, outcomes were unlikely to be influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study
Selective reporting (reporting bias)	High risk	Study did not report all outcomes that would be expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias

Taber 1992

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 3 months
Participants	• Country: USA • Setting: not reported • Inclusion criteria: patients who underwent a new HD vascular graft placement • Number: treatment group 1 (12); treatment group 2 (10); treatment group 3 (8); control group (15) • Mean age ± SD (years): not reported • Sex (M/F): not reported

Taber 1992 *(Continued)*

	• Exclusion criteria: not reported
Interventions	Treatment group 1 • Aspirin: started 2 days before and given for 14 days after graft placement Treatment group 2 • Low molecular weight dextran: started 30 minutes pre-operatively and continued post-operatively to complete the total infusion on 10 mg dextran 40 Treatment group 3 • Low molecular weight dextran • Aspirin Control group • No antiplatelet agents Cointerventions • Not reported
Outcomes	• Graft with at least 50% stenosis • Cholesterol
Notes	• Abstract-only publication • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes adjudication were likely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study outcomes did not include critical endpoints that might be expected for a study of this type
Other bias	Unclear risk	Insufficient information to permit judgement

Tang 2014

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: April 2008 to April 2010 • Duration of follow-up: 52 weeks
Participants	• Country: Taiwan • Setting: single centre • Inclusion criteria: type 2 diabetes (DKD) with HbA1c between 7.0% and 12.0% and stable medication during the preceding 3 months; 35 to 80 years; ABI < 0.9, a symptom with intermittent claudication and peripheral arterial occlusion disease in one or both limbs; dyslipidaemia or hypertension with stable medication during the preceding 3 months • Number: treatment group (45); control group (45) • Mean age ± SD (years): treatment group (67.3 ± 8.9); control group (65.2 ± 8.0) • Sex (M/F): treatment group (17/28); control group (15/30) • Exclusion criteria: type 1 DM; females of childbearing potential or those who were lactating; history of heart failure, MI, coronary vascular disease or unstable angina pectoris within the past 6 months; CKD (on dialysis of any kind, or kidney implantation); any history of clinically significant bleeding or haemorrhagic tendencies within the previous year; malignancy of any kind; use of an investigational drug within the past 3 months; impaired liver function (AST and/or ALP (2 times the ULN); any uncontrolled or untreated systemic disease; ABI > 1.3
Interventions	Treatment group • Cilostazol: 100 mg twice/day Control group • Placebo Cointerventions • Not reported
Outcomes	• Serious adverse events (including death, danger to life, disability, or hospitalisation requiring intervention to prevent permanent impairment or damage) • Adverse events • SCr • eGFR • Microalbuminuria and macroalbuminuria (including change in UACR) • Lipids • BP • Fasting glucose • ABI • Changes in plasma inflammatory markers (TNF-a and high-sensitivity CRP) • Endothelial markers (selectin, soluble intercellular adhesion molecule-1 and vascular cell adhesion molecule-1) • MCP-1 • Urinary albumin concentration • HbA1c • Withdrawal from the study
Notes	• Funding: Grants from the National Science Council (NSC 101-2314-B-016-032) and the Tri-Service General Hospital (TSGH-C97-S04 and TSGH-C102-118)
Risk of bias	

Tang 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. The outcome adjudication may have been influenced by knowledge of the treatment type due to the nature of the outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/45 in treatment group and 1/45 in control group did not complete follow-up and were not included in analysis
Selective reporting (reporting bias)	High risk	Study outcomes did not include critical endpoints (bleeding) that might be expected for a study of this type
Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

TARGET 2000

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study (enrolment): 30 December 1999 to 25 august 2000 • Duration of follow-up: 6 months (MI), 1 year (death (any cause))
Participants	• Countries: multinational (18 countries) • Setting: multicentre (149 sites) • Inclusion criteria: scheduled to undergo a coronary stenting procedure of a newly stenotic or restenotic atherosclerotic lesion in a native vessel or bypass graft (lesions with stenosis > 70% on angiography); undergoing an elective procedure or one performed urgently; eGFR < 60 mL/min/1.73 m^2 • Number (total population/CKD patients); treatment group 1 (2647/388); treatment group 2 (2411/402) • Mean age ± SD (years): not reported for CKD patients • Sex (M/F): not reported for CKD patients • Exclusion criteria: cardiogenic shock or an acute MI with ECG evidence of ST-segment elevation; SCr level ≥ 2.5 mg/dL; ongoing bleeding or a bleeding diathesis, including platelet count < 120,000 mm^3
Interventions	Treatment group 1 • Tirofiban: bolus dose of 10 µg/kg followed by an infusion of 0.15 kg/min for 18 to 24 hours • Aspirin: 250 to 500 mg before the procedure Treatment group 2 • Abciximab: bolus dose of 0.25 mg/kg followed by an infusion of 0.125 mg/kg/min (maximum 10 µg/min) for 12 hours

TARGET 2000 *(Continued)*

	• Aspirin: 250 to 500 mg before the procedure Cointerventions • All patients received, when possible, a loading dose of clopidogrel of 300 mg 2 to 6 hours before the procedure • All patients received pre-procedural unfractionated heparin with an initial IV bolus of 70 U/kg, and a nomogram was used to reach a targeted activated clotting time of 250 seconds • All patients received the active formulation of one of the GP IIb/IIIa inhibitor treatments and the placebo formulation of the other
Outcomes	• Death (any cause) • Non-fatal MI • Urgent target vessel revascularization • Major and minor bleeding • Ischaemic outcomes • Creatine kinase
Notes	• Unpublished data provided by investigators for individuals with CKD. Unpublished data available for death at 12 months and MI at 6 months • Funding: Merck and several of their cardiovascular medical specialists provided scientific input for the study design, analysis and interpretation of data, and final review of the paper. The masked data were collected and adjudicated by an independent company. The prespecified statistical plan and decision for this submission were made by the international steering committee

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was stratified according to the presence or absence of diabetes." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Patients who met the eligibility criteria were randomly assigned with the use of a central interactive system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "An independent Clinical Events Committee reviewed and adjudicated all investigators reported ischemics endpoints." Comment: Hovewer, some outcomes adjudication may have been influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall, 499/5308 participants were excluded from analysis. However, data on CKD population were Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Study endpoints included critical outcomes for this type of study
Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

Tayebi 2018

Study characteristics	
Methods	• Study design: parallel RCT • Duraiton of study: 10 September 2015 to 5 July 2016 • Duration of follow-up: 12 months
Participants	• Country: Iran • Setting: single centre • Inclusion criteria: ESKD (HD patients); new brachial AV graft • Number: treatment group 1 (20); treatment group 2 (20); control group (20) • Mean age ± SD: 55.69 ± 13.9 years • Sex (M/F): 33/27 • Exclusion criteria: < 20 years; pregnancy; comorbidities in which antiplatelet agents were contraindicated
Interventions	Treatment group 1 • Aspirin: 80 mg/day Treatment group 2 • Aspirin: 80 mg/day • Dipyridamole: 75 mg/day Control group • Placebo Cointerventions • Not reported
Outcomes	• Primary unassisted patency time (occurrence of graft thrombosis or stenosis of 50%) • Loss of graft patency • Graft infection • Bleeding events • Haemorrhagic events • Successful dialysis using the graft • Survival • Treatment discontinuation
Notes	• Funding: Research Department of Mashhad University of Medical Sciences

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Tayebi 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. The outcome adjudication may have been influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	The study outcomes did not include those considered critical (cardiovascular events) to this type of study
Other bias	Low risk	No evidence of other sources of bias. Funder was unlikely to influence data analysis and study reporting or interpretation

Teng 2018

Study characteristics	
Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: 48 hours (first phase)
Participants	• Country: USA • Setting: multicentre (2 sites) • Inclusion criteria: Men or women aged 18 to 80 years; body weight ≥ 50 kg; BMI 18 to 40 kg/m^2; ESKD requiring maintenance HD • Number: 14 • Mean age ± SD: 50.6 ± 12.5 years • Sex (M/F): 12/2 • Exclusion criteria: pregnancy; lactation; indication for oral anticoagulant or antiplatelet agents during the study period (low-dose aspirin was allowed); history of acute coronary syndrome within 12 months of study start; contraindication to ticagrelor; increased bleeding risk (platelet count < 100,000/µL); Hb < 9 g/dL; concomitant therapy with strong cytochrome P450 3A (CYP3A) inhibitors, inducers, or substrates with a narrow therapeutic index within 14 days of study initiation; history of alcohol, substance, or drug abuse within the year preceding the study; clinically significant laboratory abnormalities as judged by the investigator
Interventions	Treatment group 1 • Ticagrelor: 90 mg 1-day post-HD session Treatment group 2 • Ticagrelor: 90 mg before HD Cointerventions • All subjects were required to fast (2 hours for HD subjects, 8 hours overnight for healthy patients) prior to ticagrelor administration and for 2 hours post-dose
Outcomes	• Pharmacokinetics

Teng 2018 *(Continued)*

- Pharmacodynamics P2Y12 reaction units
- Inhibition of platelet aggregation
- Platelet reactivity
- Adverse events
- Laboratory testing
- Vital signs
- 12-lead ECG

Notes	• Funding: AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes were generally unlikely to be influenced by knowledge of treatment allocation but adverse events could be influenced by the knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Three haemodialysis subjects discontinued treatment (two who received the pre-haemodialysis regimen first and one who received the post-haemodialysis regimen first". Comment: However author reported that 3/14 patients discontinued, data were not reported for the fist phase. Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	The study outcomes did not include those considered critical to this type of study
Other bias	High risk	Funder was likely to influence data analysis and study reporting or interpretation

TRA 2P-TIMI 50 2009

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: median of 30 months
Participants	• Country: multinational (32) • Setting: multicentre (1032 sites) • Inclusion criteria: patients with impaired kidney function with stable atherosclerosis (history of MI, ischaemic stroke or peripheral artery disease)

TRA 2P-TIMI 50 2009 *(Continued)*

- Number (total population/eGFR < 68 mL/min/1.73 m^2): 19,932/4983
- Median age, IQR: 67 years, 60 to 73
- Sex (F): 31.7%
- Exclusion criteria: revascularization procedure; history of bleeding diathesis; recent active abnormal bleeding; concomitant or anticipated use of warfarin; oral factor Xa inhibitor; oral direct thrombin inhibitor; active hepatobiliary disease and platelet count of < 100,000/mm^3

Interventions	Treatment group • Vorapaxar: 2.5 mg/day Control group • Placebo Cointerventions • Not reported
Outcomes	• eGFR • Cardiovascular death • Stroke • Severe or moderate bleeding • MI • MACE • Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) moderate or severe bleeding • Composite of CV death, MI, stroke or recurrent ischaemias requiring urgent revascularization • TIMI major bleeding • TIMI minor bleeding • Intracranial haemorrhage • Fatal bleeding • Death (any cause)
Notes	• Funding: Supported by Schering-Plough Research Institute. However, Dr. Bonaca reports grant support from Amgen, AstraZeneca, Merck, MedImmune and Pfizer; and receipt of consulting fees from Amgen, Aralez, AstraZeneca, Bayer, Janssen, Merck and Sanofi. Dr. Scirica reports research grants via Brigham and Women's Hospital from AstraZeneca, Eisai, Novartis, and Merck; consulting fees from AstraZeneca, Biogen Idec, Boehringer Ingelheim, Covance, Dr. Reddy's Laboratory, Eisai, Elsevier Practice Update Cardiology, GlaxoSmithKline, Lexicon, Merck, NovoNordisk, Sanofi, St. Jude's Medical; and equity in Health [at] Scale. Dr. Morrow reports receipt of consulting fees from Abbott Laboratories, Aralez, AstraZeneca, DiaDexus, GlaxoSmithKline, Merck and Company, Peloton, Roche Diagnostics, Verseon; and research grants from Abbott, Amgen, Astra-Zeneca, Daichii Sankyo Ltd, GlaxoSmithKline, Merck and Company, Pfizer, Novartis Pharmaceuticals, Roche Diagnostics. Dr. O'Donoghue reports research grants from GlaxoSmithKline, Eisai, AstraZeneca, Merck, Janssen, The Medicines Company. Dr Simon Correa, Erica Goodrich and Sabina Murphy have nothing to disclose

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "Central computerised system"

TRA 2P-TIMI 50 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: "All deaths, ischaemic and bleeding endpoints were adjudicated by a blinded Clinical Events Committee"
Incomplete outcome data (attrition bias) All outcomes	High risk	2477/4983 reported outcomes data
Selective reporting (reporting bias)	Low risk	The study outcomes included those considered critical to this type of study
Other bias	High risk	Funder was likely to influence data analysis and study reporting or interpretation. After completion of enrolment and a median of 24 months of follow-up, the data and safety monitoring board reported an excess of intracranial haemorrhage in patients with a history of stroke. The board recommended continuation of the trial in patients without a history of stroke

TRACER 2013

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 24 months

Participants	• Country: multinational (37 countries)
	• Setting: multicentre (818 sites)
	• Inclusion criteria: acute symptoms of coronary ischaemias within 24 hours before hospital presentation and at least one of the following findings:
	  ○ Cardiac troponin (I or T) or creatine kinase MB level that was > ULN or new ST-segment depression of more than 0.1 mV or transient ST-segment elevation (< 30 minutes) of more than 0.1 mV in at least two contiguous leads (data reported for CKD patients)
	• Also required were one or more of the following four criteria:
	  ○ Age of at least 55 years
	  ○ Previous MI
	  ○ PCI
	  ○ Coronary-artery bypass grafting
	  ○ DM
	  ○ Peripheral arterial disease
	• Number: total population (12,944); moderate kidney impairment (1477); severe kidney impairment (190)
	• Mean age ± SD (years): not reported
	• Sex (M/F): not reported
	• Exclusion criteria: concurrent or anticipated treatment with warfarin (or derivatives, e.g., phenprocoumon), oral factor Xa inhibitor, or oral direct thrombin inhibitor after enrolment; concurrent or anticipated treatment with a potent inducer (e.g., rifampin) or potent inhibitor (e.g., ketoconazole, erythromycin) of CYP3A4 isoenzymes (a more detailed list will be supplied in separate instructions to the investigator): history of a bleeding diathesis, or evidence of active abnormal bleeding within 30 days before enrolment: history at any time of intracranial haemorrhage (except “micro-haemorrhage”), in-

TRACER 2013 *(Continued)*

	tracranial or spinal cord surgery, or a central nervous system tumour or aneurysm; documented sustained severe hypertension (SBP >200 mm Hg or DBP > 110 mm Hg) at enrolment or within the previous 10 days: severe valvular heart disease, as defined by the American College of Cardiology/American Heart Association; history within 2 weeks prior to enrolment of major surgery other than mentioned above or of ischaemic (presumed thrombotic) stroke; known history of thrombocytopenia (conventionally defined as platelet count <100,000/mm^3) occurring within 30 days before enrolment; known active hepatobiliary disease, or known unexplained persistent increase in serum ALT or AST activity to ≥ 2 times ULN; any serious illness or any condition that the investigator feels would (a) pose a significant hazard to the subject if investigational therapy were initiated, or (b) would limit the prognosis of the subject, regardless of investigational therapy; any serious medical comorbidity (e.g., active malignancy) such that the subject's life expectancy is < 24 months; previous participation in the current study; current participation in any other study of investigational therapy, or participation in such a study within the last 30 days; known hypersensitivity to any component of the current investigational product; woman who is breast-feeding, pregnant, or who intends to become pregnant; subject is part of the staff personnel directly involved with this study, or is a family member of the investigational staff; known current substance abuse at the time of enrolment
Interventions	Treatment group • Vorapaxar: loading dose of 40 mg and a daily maintenance dose of 2.5 mg thereafter Control group • Placebo Cointerventions • Not reported
Outcomes	• Composite of death from cardiovascular causes, MI, stroke, recurrent ischaemias with re-hospitalisation or urgent revascularization • Other efficacy endpoints were exploratory • Composite of moderate or severe bleeding events • Adverse events • Fatal bleeding events
Notes	• Abstract-only publications • Funding: Merck. Analyses presented in this article were performed independently at the Duke Clinical Research Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Quote: "24-hour automated voice-response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A central clinical-events committee, whose members were unaware of the study-group assignments, assessed all suspected efficacy and bleeding events

TRACER 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Overall, only 15 patients (0.1%) were lost to follow-up." Comment: Lost to follow-up < 10%
Selective reporting (reporting bias)	Low risk	The study reported all critical outcomes that might be expected for this type of study
Other bias	High risk	After an unplanned safety review on January 8 2011, the data and safety monitoring board recommended that the trial be stopped rather than continue as planned. The protocol-defined target number of primary efficacy endpoints had been reached. Funder was unlikely to influence data analysis and study reporting or interpretation

TRITON-TIMI 38 2006

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: November 2004 to September 2007 • Duration of follow-up: median 14.5 months
Participants	• Country: multinational (30 countries) • Setting: multicentre (707 sites) • Inclusion criteria: patients with acute coronary syndromes (both patients with moderate-to-high-risk unstable angina or non–STEMI and patients with STEMI); ischaemic symptoms lasting 10 minutes or more and occurring within 72 hours before randomisation; TIMI risk score 19 of 3 or more, and either ST-segment deviation ≥1 mm or elevated levels of a cardiac biomarker of necrosis; patients with STEMI could be enrolled within 12 hours after the onset of symptoms if primary PCI was planned or within 14 days after receiving medical treatment for STEMI; eGFR < 60 mL/min/1.73 m^2 • Number (total population/eGFR < 60 mL/min/1.73 m^2): treatment group 1 (6813/717); treatment group 2 (6795/773) • Mean age ± SD: 74.4 ± 8.3 years • Sex (M): 51.5% • Exclusion criteria: increased risk of bleeding; anaemia; thrombocytopenia; history of pathologic intracranial findings; Use of thienopyridines (any) within 5 days before enrolment; cardiogenic shock; recent fibrinolytic administration
Interventions	Treatment group 1 • Prasugrel: loading dose of 60 mg. After PCI, patients received maintenance doses of prasugrel 10 mg/day, (median 12 months of treatment for a maximum of 15 months) • Aspirin daily Treatment group 2 • Clopidogrel: loading dose of 300 mg. After PCI, patients received maintenance doses of clopidogrel 75 mg/day, (median 12 months of treatment for a maximum of 15 months) • Aspirin daily Cointerventions • Not reported
Outcomes	• Composite of the rate of death from cardiovascular causes, nonfatal MI, or nonfatal stroke • Urgent target-vessel revascularization

TRITON-TIMI 38 2006 *(Continued)*

	• Stent thrombosis and a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, or re-hospitalisation due to a cardiac ischaemic event • Major bleeding not related to coronary-artery bypass graft • Non–coronary-artery bypass graft-related TIMI life-threatening bleeding • Major (including intracranial haemorrhage) or minor bleeding • Serious adverse events • Adverse events • Thrombosis • Transfusions
Notes	• Unpublished data for participants with eGFR < 60 mL/min/1.73 m^2 • Funding: Eli Lilly and Company and Daiichi Sankyo Co. The trial is monitored by an independent data monitoring committee (DMC) empowered to assess safety, futility, or overwhelming efficacy. The DMC is supported by an independent statistician

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All components of the primary, secondary, and key safety end points were adjudicated by members of an independent clinical events committee that was unaware of the group assignments."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Overall, a total of 14 patients (0.1%) were lost to follow-up." Comment: < 10% of lost to follow-up
Selective reporting (reporting bias)	Low risk	The study reported all critical outcomes that might be expected for this type of study
Other bias	Low risk	No evidence of other sources of bias. Funder did not influence data analysis and study reporting or interpretation

UK-HARP-I 2005

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: October 1999 to March 2001 • Duration of follow-up: 12 months
Participants	• Country: UK • Setting: multicentre (number of sites not reported)

UK-HARP-I 2005 *(Continued)*

- Inclusion criteria: men or women ≥18 years; predialysis patient with the most recent SCR ≥ 1.7 mg/dL (150 mol/L), HD or PD patient, or had a functioning kidney transplant (with any creatinine level); their own nephrologist and primary care physician did not consider there was a definite indication for (or contraindication to) cholesterol-lowering therapy or aspirin
- Number: treatment group 1 (112); treatment group 2 (112); treatment group 3 (113); control group (111)
- Mean age ± SD (years): treatment group 1 (54 ± 14); treatment group 2 (52 ± 15); treatment group 3 (52 ± 16); control group (54 ± 15)
- Sex (M/F): treatment group 1 (78/34); treatment group 2 (79/33); treatment group 3 (81/32); control group (76/35)
- Exclusion criteria: there was no upper limit to blood cholesterol levels, but patients were not to be randomised if their own doctor considered that cholesterol-lowering therapy should be prescribed; evidence of a recent history of acute uraemia, history of chronic liver disease, inflammatory muscle disease (i.e. dermatomyositis or polymyositis) or creatine kinase level > 3 times ULN; previous adverse reaction to a statin or history of aspirin hypersensitivity (e.g. aspirin-induced asthma or angioedema); concurrent treatment with a contraindicated drug (i.e. non-study statin, fibrate, niacin, macrolide antibiotic; systemic azole antifungal, nefazodone, or oral anticoagulant therapy); high immediate risk for bleeding (e.g. active peptic ulceration, recent injury, or haemophilia); child-bearing potential in the absence of a reliable method of contraception; life-threatening condition other than CKD or vascular disease (e.g. non skin cancer or acquired immunodeficiency syndrome); frequent nonattendance at clinics or known noncompliance with drug treatments; alcohol or substance abuse

Interventions	Treatment group 1 • Simvastatin: 20 mg/day • Aspirin: 100 mg/day for 12 months Treatment group 2 • Simvastatin: 20 mg/day for 12 months • Aspirin placebo Treatment group 3 • Aspirin: 100 mg/day for 12 months • Simvastatin placebo Control group • Simvastatin placebo • Aspirin placebo for 12 months Cointerventions • Not reported
Outcomes	• Lipids • Death (any cause and cardiovascular death) • Number of patients with serious adverse events (including cardiovascular and renal events) • Hospitalisation • Initiation of dialysis therapy • Vascular access procedure • Kidney transplantation • Number of patients with bleeding (major and minor) • Vascular events • SCr • Albumin • Hb • Urate levels

UK-HARP-I 2005 *(Continued)*

	• CK and alanine transaminase • Apolipoprotein A_1 and apolipoprotein B • Fatal bleeding • Withdrawal the treatment
Notes	• Funding: Grant from Merck & Co

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Minimized randomisation was used to balance the treatment groups with respect to eligibility criteria and other major prognostic factors." Comment: Minimized randomisation is considered as low risk of bias
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. The outcome adjudication may have been influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of 448 randomised patients, 71 patients stopped both treatments (that is, simvastatin [or matching placebo] and aspirin [or matching placebo]), 19 patients (4%) stopped aspirin (or matching placebo) only, and 11 patients (2%) stopped simvastatin (or matching placebo) only. [...] Although there was no excess of patients stopping among those allocated to active aspirin compared with placebo aspirin overall (44 patients, aspirin versus 46 patients, placebo aspirin), allocation to aspirin therapy was associated with an excess of adverse effects resulting in treatment discontinuation (20 versus 5 patients)." Comment: > 10% loss to follow-up
Selective reporting (reporting bias)	Low risk	The study reported all critical outcomes that might be expected for this type of study
Other bias	High risk	Premature discontinuation of study due to insufficient bleeding events. The role of funding was not reported

Waseda 2016

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: not reported
Participants	• Country: Japan • Setting: not reported • Inclusion criteria: HD patients; coronary artery stenting

Waseda 2016 *(Continued)*

- Number: treatment group (16); control group (17)
- Mean age ± SD (years): not reported
- Sex (M/F): not reported
- Exclusion criteria: not reported

Interventions	Treatment group • Prasugrel Control group • Clopidogrel Cointerventions • Not reported
Outcomes	• Platelet aggregation • Frequency of CYP2C19 genotype
Notes	• Abstract-only publication • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Outcomes adjudication were unlikely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study outcomes did not include critical endpoints that might be expected for a study of this type
Other bias	Unclear risk	Insufficient information to permit judgement

Watanabe 2011b

Study characteristics

Methods	• Study design: parallel RCT

Watanabe 2011b *(Continued)*

	• Duration of study: not reported • Duration of follow-up: median 5.1 years
Participants	• Country: Japan • Setting: not reported • Inclusion criteria: stable angina; diabetes; CKD stage 3 or 4 • Number: treatment group (26); control group (27) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Sarpogrelate Control group • Standard care without antiplatelet agents Cointerventions • Not reported
Outcomes	• Flow-mediated dilatation brachial artery • Pulse wave velocity • Exercise tolerance • eGFR • Major adverse cardiovascular events, or hospitalisation for revascularization
Notes	• Abstract-only publication • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Some outcomes adjudication were likely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study outcomes did not include critical endpoints that might be expected for a study of this type

Watanabe 2011b *(Continued)*

Other bias	Unclear risk	Insufficient information to permit judgement

Weseley 1982

Study characteristics	
Methods	• Study design: cross-over RCT • Duration of study: not reported • Duration of follow-up: not reported (overall 20 exchange PD, but data were not reported for the first period)
Participants	• Country: USA • Setting: not reported • Inclusion criteria: stable long-term PD with severe hypertension • Number: 16 • Mean age: 57.1 years • Sex (M/F): 11/5 • Exclusion criteria: vasculitis and uncontrolled hypertension
Interventions	Treatment group • Dipyridamole: 75 mg Control group • Placebo Cointerventions • Not reported
Outcomes	• BUN • SCr • Clearance of urea and creatinine • Platelet aggregation
Notes	• Abstract-only publication • Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study

Weseley 1982 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Outcomes adjudication were unlikely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study outcomes did not include critical endpoints that might be expected for a study of this type. Data were not appropriately reported for a cross-over RCT
Other bias	Unclear risk	Insufficient information to permit judgement

Xydakis 2004

Study characteristics	
Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 5 days
Participants	• Country: Greece • Setting: single centre • Inclusion criteria: non-diabetic; HD patients; diagnosis of acute coronary syndrome • Number: treatment group 1 (19); treatment group 2 (19) • Mean age ± SD (years): treatment group 1 (64.8 ± 7.2); treatment group 2 (65.2 ± 7) • Sex (M/F): treatment group 1 (15/4); treatment group 2 (14/5) • Exclusion criteria: not reported
Interventions	Treatment group 1 • Clopidogrel: 300 mg loading dose followed by 75 mg/day • Aspirin: 325 mg/day Treatment group 2 • Aspirin: 325 mg/day Cointerventions • Not reported
Outcomes	• Troponin I • CRP • Cardiac enzymes • Platelet activation plasma • Beta-thromboglobulin
Notes	• Abstract-only publication • Funding: not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Xydakis 2004 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Outcomes adjudication were unlikely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study outcomes did not include critical endpoints that might be expected for a study of this type
Other bias	Unclear risk	Insufficient information to permit judgement

Yang 2016b

Study characteristics	
Methods	• Study design: quasi-RCT • Duration of study: not reported • Duration of follow-up: 18 months

Participants	• Country: China
	• Setting: single centre
	• Inclusion criteria: undergoing HD for at least 3 months; plan for receiving HD for at least 2 years
	• Number
	  ○ Antibody-negative: treatment group (29); control group (11)
	  ○ Antibody-positive: treatment group (23); control group (21)
	• Mean age ± SD (years): not reported
	• Sex (M/F): not reported
	• Exclusion criteria: already had antiplatelet agents before the starting point; patients were not able to undergo dialysis therapy; plan for transplantation; thrombocytopaenia for at least 5 years

Interventions	Treatment group • Aspirin Control group • Clopidogrel Cointerventions • All patients underwent bicarbonate HD with a polysulfone low-flux filter

Yang 2016b *(Continued)*

Outcomes	• All-cause thrombotic events (MI, cerebral infarction, AVF embolism, semi-permanent dialysis catheter embolism) • Bleeding time • Platelet aggregation • Survival • Platelet count
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All anti-positive patients were subdivided into three groups by randomly selecting ID numbers of patients using the statistic software CHISS. All anti-negative patients were divided into three groups by the same method." Comment: Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes adjudication were likely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Large proportion of patients did not complete evaluate or switched treatment groups
Selective reporting (reporting bias)	Low risk	Study reported all critical outcomes that might be expected for this type of study
Other bias	Low risk	No evidence of other sources of bias

Yuto 2012

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 8 weeks
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: HD patients requiring forearm AVF • Number: treatment group (33); control group (46) • Mean age ± SD (years): not reported • Sex (M/F): not reported

Yuto 2012 *(Continued)*

	• Exclusion criteria: not reported
Interventions	Treatment group • Sarpogrelate: 300 mg/day Control group • Standard care without antiplatelet agents Cointerventions • Not reported
Outcomes	• Blood flow rate • Diameter of shunt vessel • Patency failure
Notes	• Abstract-only publication • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported. Outcomes adjudication were generally unlikely to be influenced by knowledge of the nature of the treatment allocation. However, patency failure could be influenced by the knowledge of the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	Study did not report many critical outcomes that would be expected for this type of study
Other bias	Unclear risk	Insufficient information to permit judgement

Zäuner 1994

Study characteristics

Methods	• Study design: parallel RCT • Duration of study: not reported • Duration of follow-up: 36 months

Zäuner 1994 *(Continued)*

Participants	• Country: Germany • Setting: single centre • Inclusion criteria: patients with biopsy-proven MPGN and nephrotic syndrome, requiring dialysis • Number: treatment group (10); control group (8) • Mean age ± SD (years): treatment group (48.0 ± 5.7); control group (41.4 ± 5.6) • Sex (M/F): treatment group (8/2); control group (3/5) • Exclusion criteria: not reported
Interventions	Treatment group • Acetylsalicylic acid: 500 mg/day • Dipyridamole: 75 mg/day for 36 months Control group • Antihypertensive agents without antiplatelet agents Cointerventions • Protein restriction diet (0.8 g/kg/day)
Outcomes	• Change in SCr • Change in 24-hour urine protein excretion • % of nephrotic patients • BP • Death was not a targeted outcome, but there were no deaths during the study period
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. As the treatments were physically different, it was likely that participants and investigators were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported. Outcomes adjudication were unlikely to be influenced by knowledge of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	High risk	Study did not report many critical outcomes that would be expected for this type of study
Other bias	Low risk	No evidence of other sources of bias

ABI - ankle-brachial index; ACEi - angiotensin-converting enzyme inhibitors; ACR - albumin/creatinine ratio; ADPKD - autosomal dominant polycystic kidney disease; ALT - alanine aminotransferase; ARB - angiotensin receptor blocker; ASP - aspartate aminotransferase; AV - arteriovenous; AVF - arteriovenous fistula; AZA - azathioprine; BACE - Bleeding Academy Research consortium; BMI - body mass index; BP - blood pressure; BUN - blood urea nitrogen; CABG - coronary artery bypass graft; CAD - coronary artery disease; CKD - chronic kidney disease; CrCl - creatinine clearance; CRP - C-reactive protein; CSA - cyclosporin; CVA - cerebrovascular accident; CVC - central venous catheter; DBP - diastolic BP; DES - drug-eluting stents; DKD - diabetic kidney disease; DM - diabetes mellitus; ESKD - end-stage kidney disease; ECG - electrocardiogram; EPO - erythropoietin; ESR - erythrocyte sedimentation rate; GI - gastrointestinal; (e)GFR - (estimated) glomerular filtration rate; Hb - haemoglobin; HbA1c - haemoglobin A1c; HCT - haematocrit; HD - haemodialysis; HIV - human immunodeficiency virus; IgAN - IgA nephropathy; INR - international normalised ratio; IQR - interquartile range; IV - intravenous; KRT - kidney replacement therapy; LDL - low-density lipoprotein; MACE - major adverse cardiovascular events; MDRD-4 - four-variable Modification of Diet in Renal Disease; M/F - male/female; MAP - mean arterial BP; MI - myocardial infarction; MPGN - membranoproliferative glomerulonephritis; NACE - net adverse clinical events; NSAID - non-steroidal anti-inflammatory drug; NYHA - New York Heart Association; PCTA - percutaneous transluminal coronary angioplasty; PCI - percutaneous coronary intervention; PD - peritoneal dialysis; POCE - patient-oriented composite endpoint; PTFE - polytetrafluoroethylene; QoL - quality of life; RBC - red blood cell; RCT - randomised controlled trial; rHuEPO - recombinant human erythropoietin; SBP - systolic BP; SCr - serum creatinine; SD - standard deviation; SEM - standard error of the mean; SLE - systemic lupus erythematosus; STEMI - ST-elevation MI; TIA - transient ischaemic attack; TIMI - thrombolysis in MI; TNF-a - tumour necrosis factor-a; UACR - urinary albumin/creatinine ratio; UAE - urinary albumin excretion; ULN - upper limit of normal; UTI - urinary tract infection; WBC - white blood cells

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
AVERROES 2010	Wrong comparator: antiplatelet agent versus anticoagulant
Bang 1994	Wrong population: IgAN patients with normal kidney function
Caravaca 1995a	Unclear study design: patients randomly assigned to antiplatelets or not, however 3 different antiplatelet agents were used and it was not reported how these were assigned
Changjiang 2015	Wrong comparator: antiplatelet agent versus anticoagulant
Coli 2006	Wrong intervention: early warfarin therapy after tunnelled cuffed catheter placement versus warfarin therapy after tunnelled cuffed catheter thrombosis or malfunction
EXCITE 2000	Wrong population: CKD patients excluded
Foroughinia 2017	Wrong intervention: omega-3 supplements versus placebo
Gorter 1998	Wrong comparator: antiplatelet agent versus anticoagulant
Lee 1997	Wrong intervention: antiplatelet agent + anticoagulant versus control
Lindsay 1972	Wrong comparator: antiplatelet agent versus pyrimido-pyrimidine compound RA 233
NITER 2005	Wrong intervention and comparator: medical treatment (included antiplatelet agents) versus medical treatment + percutaneous transluminal renal artery stenting
Perkovic 2004	Wrong intervention: targeted risk factor modification
POISE-2 2013	Wrong population: all patients undergoing elective and urgent/emergent noncardiac surgery
PRODIGY 2010	Wrong population: all patients undergoing PCI
RAS-CAD 2009	Wrong population: patients with ischaemic heart disease undergoing cardiac catheterization
REPLACE-2 2003	Wrong population: patients undergoing PCI

Study	Reason for exclusion
Sakai 1991	Wrong comparator: dipyridamole versus urokinase
SPS3 2018	Wrong population: patients with impaired kidney function were excluded
STENO-2 1999	Wrong intervention: antiplatelet agent + multiple non-antiplatelet agents versus control
Swan 1995a	Wrong intervention: diaspirin cross-linked Hb versus placebo
TRILOGY ACS 2010	Wrong population: all patients with acute coronary syndromes
Woo 1987	Wrong population: IgAN patients with normal kidney function
Wu 2018a	Wrong population: all patients undergoing emergency PCI for MI; no CKD data available (author contacted)
Yang 2014a	Wrong study design: stratified according to PF4/H antibodies (positive or negative) then assigned to control or intervention; numbers per group not even so unsure if truly randomised
Yeh 2017	Wrong study design: states it is quasi-RCT (by days of the week), however numbers per group are very different indicating the recruitment could have been subverted and there was a very high dropout/lost to follow-up
Yoshikawa 1999	Wrong intervention and comparator: prednisolone, AZA, heparin-warfarin, and dipyridamole versus heparin-warfarin and dipyridamole
Zhang 2009a	Wrong intervention: platelet activation inhibitor (Lipo-PGE_1 or low-dose heparin) versus control
Zibari 1995	Wrong comparator: aspirin versus heparin
Zimmerman 1983	Wrong population: MPGN patients with normal kidney function

AZA - azathioprine; CKD, chronic kidney disease; Hb - haemoglobin; IgAN - IgA nephropathy; MI - myocardial infarction; MPGN - membranoproliferative glomerulonephritis; PCI - percutaneous coronary intervention; RCT - randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

A-CLOSE 2019

Study name	A randomized comparison of CLOpidogrel monotherapy versus extended dual-antiplatelet therapy beyond 12 months after implantation of drug-eluting StEnts in high-risk lesions or patients; A-CLOSE Trial
Methods	• Study design: RCT • Duration of follow-up: 24 months
Participants	• Country: Korea • Setting: not reported • Inclusion criteria: > 19 years; underwent DES implantation 12 months (+5 months) previously; high-risk characteristics (clinical or lesion) for ischaemic events (must at least one); high-risk patients; clinical criteria including acute coronary syndrome, previous history of CVAs, history of peripheral artery intervention, heart failure (left ventricular ejection fraction ≤ 40%), diabetes treated with medication, chronic kidney insufficiency including ESKD; high-risk lesions; angiographic or procedural criteria including left main diseases, bifurcation lesions, chronic total occlusion instent lesions, graft lesions, diffuse long lesions requiring total stent length ≥ 28 mm, calcified le-

A-CLOSE 2019 *(Continued)*

	sions requiring atherectomy, multivessel CAD with multiple stents, small vessel disease requiring stent diameter of ≤ 2.5 mm • Baseline characteristics: not reported for CKD patients • Exclusion criteria: > 80 years; pregnant women or women with potential childbearing; life expectancy < 1 year; refusal or inability to understand informed consent
Interventions	Treatment group 1 • Clopidogrel: 75 mg Treatment group 2 • Clopidogrel: 75 mg • Aspirin: 100 mg Cointerventions • Not reported
Outcomes	• MACE including death (any cause), MIs, stent thrombosis, or stroke • Adverse events • Death (any cause) • Major bleeding • Minor bleeding
Starting date	August 2019
Contact information	Byeong-Keuk Kim Phone: 82-2-2228-8460 Email: mailto:kimbk%40yuhs.ac?subject=NCT03947229, 4-2019-0234, A Randomized Comparison of CLOpidogrel Monotherapy Versus Extended Dual-antiplatelet Therapy Beyond 12 Months After Implantation of Drug-eluting StEnts in High-risk Lesions or Patients; A-CLOSE Trial
Notes	• ClinicalTrials.gov Identifier: NCT03947229 • Funding: Yonsei University • Study status: ongoing

ALTIC 2016

Study name	A randomized, pharmacodynamic comparison of Low dose TIcagrelor to Clopidogrel in patients with prior myocardial infarction (ALTIC)
Methods	• Study design: Cross-over RCT • Duration of follow-up: 14 days (first phase)
Participants	• Country: Greece • Setting: Single centre (Cardiology Department Patras University Hospital Rio, Achaia) • Inclusion criteria: > 50 years with MI 1 to 3 years earlier and at least one high-risk feature (age > 65 years, DM, a second MI, multivessel disease, or kidney dysfunction) • Baseline characteristics: not reported for CKD patients • Exclusion criteria: planned use of a P2Y12 receptor antagonist, dipyridamole, cilostazol, or anticoagulant therapy during the study period; known allergy, intolerance, hypersensitivity to ticagrelor or clopidogrel or any excipients; active pathological bleeding, severe hepatic impairment, a bleeding disorder or a history of an ischaemic stroke or intracranial bleeding, a central ner-

ALTIC 2016 *(Continued)*

	vous system tumour, or an intracranial vascular abnormality; GI bleeding within the previous 6 months or major surgery within the previous 30 days; concomitant use of potent CYP3A4 inhibitors (atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole, grapefruit juice over 1 litre daily), CYP3A substrates with narrow therapeutic indices (CSA, quinidine), or inducers (carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, and rifapentine); increased risk of bradycardic events (e.g. known sick sinus syndrome or third degree AV block or previous documented syncope suspected to be due to bradycardia unless treated with a pacemaker); inability to adhere to the follow-up requirements or any other reason or condition that the investigator feels would place the patient at increased risk if the investigational therapy is initiated
Interventions	Treatment group 1 • Copidogrel: 75 mg for 14 days • Aspirin 100 mg/day Treatment group 2 • Ticagrelor: 60 mg for 14 days • Aspirin: 100 mg/day Cointerventions • All patients received standard secondary prevention medication
Outcomes	• Platelet reactivity • Platelet function • Major bleeding events
Starting date	January 2017
Contact information	Dimitrios Alexopoulos Phone: not reported Email: not reported
Notes	• Abstract • Funding: not reported • Study was completed on June 2017

ALTIC-2 2018

Study name	Low dose ticagrelor versus low dose prasugrel in patients with prior myocardial infarction (ALTIC-2)
Methods	• Study design: cross-over RCT • Duration of follow-up: 14 days
Participants	• Country: Greece • Setting: Single centre (Attikon University Hospital Chaidari) • Inclusion criteria: provision of informed consent prior to any study-specific procedures; postmenopausal female or male aged > 50 years; spontaneous MI 1 to 3 years before enrolment; at least one of the following high-risk features: ≥ 65 years, DM requiring medication, a second prior spontaneous MI, multivessel CAD, or non-ESKD (estimated CrCl of < 60 mL/min) • Exclusion criteria: planned use of a P2Y12 receptor antagonist, dipyridamole, cilostazol, or anticoagulant therapy during the study period; known allergy, intolerance, hypersensitivity to tica-

ALTIC-2 2018 *(Continued)*

	grelor or prasugrel or any excipients; active pathological bleeding, severe hepatic impairment, a bleeding disorder or a history of an ischaemic stroke or intracranial bleeding, a central nervous system tumour, or an intracranial vascular abnormality; GI bleeding within the previous 6 months or major surgery within the previous 30 days; concomitant use of potent CYP3A4 inhibitors (atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole, grapefruit juice over 1 litre daily), CYP3A substrates with narrow therapeutic indices (CSA, quinidine), or inducers (carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, and rifapentine); increased risk of bradycardic events; inability to adhere to the follow-up requirements or any other reason or condition that the investigator feels would place the patient at increased risk • Estimated enrolment: not reported for patients with CKD
Interventions	Treatment group 1 • Ticagrelor: 60 mg Treatment group 2 • Prasugrel: 5 mg Cointerventions • All patients will receive concomitant aspirin (100 mg/day) and standard secondary prevention medication
Outcomes	• Platelet reactivity • Platelet function
Starting date	January 2018
Contact information	Dimitrios Alexopoulos Phone: not reported Email: not reported
Notes	No results posted

ATTACK 2018

Study name	Aspirin to target arterial events in chronic kidney disease (ATTACK) protocol
Methods	• Study design: RCT • Duration of follow-up: 2.5 years
Participants	• Country: UK • Setting: mUlticentre • Inclusion criteria: adults with CKD who do not have pre-existing cardiovascular disease including decreased eGFR for at least 90 days (defined as eGFR < 60 mL/min/1.73 m^2), and/or albuminuria or proteinuria for at least 90 days (defined as UACR ≥ 3 mg/mmol, and/or UPCR ≥ 15 mg/mmol, and/or + protein or greater on reagent strip; and in all cases where the most recent qualifying result is UACR ≥ 3mg/mmol); willing to give permission for their paper and electronic medical records to be accessed by trial investigators and are willing to be contacted and interviewed by trial investigators; can communicate well with the investigator or designee, understand the requirements of the study and understand and sign the written informed consent • Baseline characteristics: not reported

ATTACK 2018 *(Continued)*

	• Exclusion criteria: CKD GFR category 5; pre-existing cardiovascular disease (angina, MI, stroke, TIA, significant peripheral vascular disease, coronary or peripheral revascularization for atherosclerotic disease); current pre-existing condition associated with increased risk of bleeding other than CKD; currently prescribed anticoagulants or antiplatelet agent, or taking over the counter aspirin continuously; currently and regularly taking other drugs with a potentially serious interaction with aspirin; known allergy to aspirin or definite previous clinically important adverse reaction; poorly controlled hypertension (SBP ≥ 180 mm Hg and/or DBP ≥ 105 mm Hg); anaemia (Hb < 90g/L; or Hb < 100g/L with mean cell volume ≤ 75 fL); pregnant or likely to become pregnant during the study period; malignancy that is life-threatening or likely to limit prognosis, other life-threatening co-morbidity, or terminal illness; behaviour or lifestyle would render them less likely to comply with study medication; in prison; currently participating in another interventional clinical trial or who have taken part in a trial in the last 3 months
Interventions	Treatment group • Aspirin: 75 mg Control group • No aspirin Cointerventions • Usual medication
Outcomes	• Non-fatal MI, non-fatal stroke and cardiovascular death (excluding confirmed intracranial haemorrhage) • Death (any cause) • Composite outcome of major vascular event or revascularization (coronary and non-coronary) • Individual components of the primary composite endpoint • HRQoL • Composite outcome of intracranial haemorrhage (fatal and non-fatal), fatal extracranial haemorrhage and non-fatal major extracranial haemorrhage (adjudicated) • Fatal and non-fatal (reported individually and as a composite) intracranial haemorrhage comprising: i) primary haemorrhagic stroke (to distinguish from the haemorrhagic transformation of ischaemic stroke); ii) other intracranial haemorrhages (adjudicated) • Fatal and non-fatal (reported individually and as a composite) major extracranial haemorrhage: i) vascular-procedural; ii) vascular-nonprocedural; iii) GI; iv) genitourinary; v) respiratory; vi) pericardial; vii) ocular; viii) other; ix) undetermined (adjudicated) • Clinically relevant non-major bleeding • TIA • Unplanned hospitalisation • New diagnosis of cancer (colorectal/other) • CKD progression • New diagnosis of dementia
Starting date	September 2018
Contact information	Hugh Gallagher Phone: not reported Email: hugh.gallagher1@nhs.net
Notes	• Funding: National Institute for Health Research (NIHR) Health Technology Assessment • (HTA) Programme (Ref: 16/31/127) • Study status: ongoing

ChiCTR1900021393

Study name	Antiplatelet therapy for prevention of atherosclerosis in chronic kidney disease: a perspective, multi-center randomized controlled trial
Methods	• Study design: RCT • Duration of follow-up: 36 months
Participants	• Country: China • Setting: multicentre • Inclusion criteria: 14 and 65 years; kidney impairment 3 months, with or without decreased GFR; renal damage refers to the abnormal structure or function of the kidney, manifested as one of the following: 1) pathological examination abnormalities; 2) eGFR < 60 mL/min/1.73 m^2 3 months, with or without renal damage; ultrasound of the cervical blood vessels showed no cervical vascular plaque and no atherosclerosis; signed informed consent • Baseline characteristics: not reported • Exclusion criteria: unable or unwilling to complete the required process for the research; participating in other interventional clinical trials; pregnant or lactating; previous diagnosis of CKD with cardiovascular disease or previous cardiovascular disease patients, it shall clearly diagnosis MI, heart failure, cerebral haemorrhage and other serious cardiovascular and cerebrovascular complications; NYHA level III or IV heart failure; cirrhosis; HIV infection or AIDS; in the past 2 years due to malignant tumour chemotherapy or alkylation agent treatment; kidney transplant patients; existence of deep venous thromboembolism before inclusion; long-term use of aspirin or hydro clopidogrel, or in the recent three months in the short use of aspirin or hydro clopidogrel; active bleeding or coagulation dysfunction
Interventions	Treatment group • Aspirin: 100 mg or hydro clopidogrel 75 mg (if aspirin was not tolerated) Control group • No aspirin or hydro clopidogrel Cointerventions • Usual medications
Outcomes	• Atherosclerosis • Complex cardiovascular events • Death (any cause) • 50% drop in eGFR • Bleeding
Starting date	February 2018
Contact information	Zhao Jinghong Phone: +86 13668007369 Email: zhaojh@tmmu.edu.cn
Notes	• Funding: University • Study status: ongoing

IRCT2013012412256N1

Study name	Evaluation the effect of clopidogrel in prevention of access graft thrombosis in upper extremity in patients undergoing haemodialysis in Emam Reza's Hospital - Kermanshah, 2012-2013
Methods	• Study design: RCT • Duration of follow-up: 6 months
Participants	• Country: Iran • Setting: single centre (Emam Reza Hospital) • Inclusion criteria: HD patients with vascular access graft in upper extremity • Baseline characteristics: not reported • Exclusion criteria: history of coagulation disorders and malignancies; history of venous access thrombosis; thrombocytopenia (< 100,000/mL); thrombocytosis (> 450,000/mL); erythrocytosis (HCT > 55%); receiving warfarin, aspirin or other salicylates, dipyridamole, sulphinpyrazone and ticlopidine or other conditions that antiplatelet agents are contraindicated
Interventions	Treatment group • Clopidogrel: 75 mg Control group • Placebo Cointerventions • Not reported
Outcomes	• Thrombosis
Starting date	June 2012
Contact information	Bahman Alinejad Phone: +98 83 1427 6311 Email: dr.bh.alinejad@kums.ac.ir
Notes	• Funding: not reported • Study was completed on May 2013

IRCT2013100114333N8

Study name	Study of effects use and without use of aspirin on Permcath function in dialysis patients
Methods	• Study design: RCT • Duration of follow-up: 6 months
Participants	• Country: Iran • Setting: single centre (Imam Reza Hospital) • Inclusion criteria: adult dialysis patients; allowed to receive aspirin; matched for age, sex, diabetes, cardiovascular disease and written informed consent • Baseline characteristics: not reported • Exclusion criteria: coagulation disorders or use anticoagulant drugs; suffering from cancer or GI bleeding
Interventions	Treatment group

IRCT20131001114333N8 *(Continued)*

	• Aspirin: 80 mg after placing Permcath Control group • No antiplatelet agents Cointerventions • Not reported
Outcomes	• Infection • Bleeding (including GI bleeding) • Lifetime of Permcath
Starting date	June 2017
Contact information	Feizollah Foroughi Phone: +98 83 1821 4653 Email: fforoughi@kums.ac.ir
Notes	• Funding: Kermanshah University of Medical Sciences • No results posted

IRCT20171023036953N1

Study name	The effect of cilostazol on the mean time of arteriovenous fistula maturation and its comparison to control group in patients with chronic renal failure referring to Emam Reza hospital of Mashhad University of Medical Sciences
Methods	• Study design: RCT • Duration of follow-up: 12 weeks
Participants	• Country: Iran • Setting: single centre (Emam Reza Hospital) • Inclusion criteria: HD patients • Baseline characteristics: not reported • Exclusion criteria: not reported
Interventions	Treatment group • Cilostazol: 50 mg for 2 weeks, then 100 mg for 10 weeks or until fistula maturation Control group • No antiplatelet agents Cointerventions • Not reported
Outcomes	• Fistula maturation • Fistula flow rate
Starting date	December 2018
Contact information	Contact name: not reported

IRCT20171023036953N1 *(Continued)*

	Phone: not reported Email: not reported
Notes	• Funding: not reported • No results posted

LEDA 2017

Study name	Effect of aspirin on renal disease progression in patients with type 2 diabetes: A multicenter, double-blind, placebo-controlled, randomised trial. The renaL disEase progression by aspirin in Diabetic pAtients (LEDA) trial. Rationale and study design
Methods	• Study design: double-blind RCT • Duration of follow-up: 1 year
Participants	• Country: Italy • Setting: multicentre • Inclusion criteria: type 2 diabetes, random blood glucose ≥ 200 mg/dL, fasting blood glucose ≥ 126 mg/dL, blood glucose 2 hours after oral glucose tolerance test (75 g) ≥ 200 mg/dL, treatment with glucose-lowering agents • Exclusion criteria: history of cardiovascular or cerebrovascular events; HbA1c ≥ 8%; type 1 diabetes; kidney impairment in G4 stage (eGFR < 30 mL/min); chronic active infection or evidence of malignancy in the last 5 years; autoimmune systemic disease; cardiac arrhythmia; use of NSAIDs, vitamin supplements, or other antiplatelet agents in the previous 30 days; liver failure (e.g. cirrhosis); use of anticoagulants; life expectancy < 1 year; known allergy to aspirin • Estimated enrolment: not reported for patients with renal failure
Interventions	Treatment group • Aspirin: 100 mg/day Control group • Placebo Cointerventions • Not reported
Outcomes	• eGFR • Kidney function • Change of kidney function class after • Urinary excretion 11-dehydro-TxB2 • Adverse events • Major and minor bleeding • Cardiovascular events
Starting date	January 2017
Contact information	Francesco Violi Phone: +390649970893 Email: francesco.violi@uniroma1.it
Notes	• Protocol

LEDA 2017 *(Continued)*

- No results posted

Lemos Cerqueira 2018

Study name	The use of aspirin to reduce the risk of thrombotic events in patients with end-stage renal disease: protocol for a randomised controlled trial
Methods	• Study design: triple-blind RCT • Duration of follow-up: 12 months
Participants	• Country: Belgium • Setting: single centre • Inclusion criteria: adults with ESKD who have started chronic intermittent HD in the previous 3 months • Exclusion criteria: any contraindications to aspirin; concurrent treatment with anticoagulants or platelet aggregation inhibitors; pregnancy or lactation; life-threatening conditions other than kidney or vascular disease; patients on other modalities of KRT • Estimated enrolment: 342 participants (171 per arm)
Interventions	Treatment group • Aspirin: 100 mg/day Control group • Placebo Cointerventions • Not reported
Outcomes	• Thrombotic events, namely nonfatal stroke, nonfatal MI, AVF thrombosis, and cardiac death • Major bleeding events • Effect modification of treatment by the presence of type 2 diabetes or platelet hyperreactivity • Minor bleeding
Starting date	Not reported
Contact information	Nathalie Monique Vandevelde Phone: 32026425589 Email: nathalie.vandervelde@wiv-isp.be
Notes	• Protocol • No results posted

NCT00272831

Study name	The use of cilostazol in patients with diabetic nephropathy
Methods	• Study design: double-blind RCT • Duration of follow-up: 12 months

NCT00272831 *(Continued)*

Participants	• Country: Hong Kong • Setting: not reported • Inclusion criteria male or female patients aged 20 and 70 years; type 2 DM and mild to moderate kidney impairment; fasting UACR ≥ 30 mg/mmol or 24-hour UAE ≥ 300 mg/day in 2 urine collections; 2 consecutive SCr (women: 80 to 250 µmol/L; men: 105 to 250 µmol/L); written informed consent • Exclusion criteria: pregnancy; known allergy to cilostazol or aspirin; congestive heart failure (NYHA class III to IV); severe liver impairment (≥ 3 times ULN of ALT); serum potassium ≥ 5.5 mmol/L on 2 consecutive specimens • Estimated enrolment: 60 participants
Interventions	Treatment group • Cilostazol: 100 mg twice/day Control • Placebo Cointerventions • Not reported
Outcomes	• Progression of DKD • Decline in GFR • SCr • UAE rate • Doubling of SCr • 50% reduction in GFR • GFR < 15 mL/min/1.73 m^2 • Need for dialysis • Death related to renal causes • Fatal or severe bleeding • Composite cardiovascular endpoints (acute MI, revascularization procedures, heart failure or unstable angina or arrhythmia) requiring hospital admissions • Lower extremity amputation • Number of hospital admissions, total number of days of hospital stay and attendance at the Accident and Emergency Department
Starting date	December 2005
Contact information	Peter CY Tong Phone: not reported Email: not reported
Notes	• No results posted

NCT01198379

Study name	Aspirin in the prevention of cardiovascular events in haemodialysis patients
Methods	• Study design: double-blind RCT • Duration of follow-up: 3 years

NCT01198379 *(Continued)*

Participants	• Country: Taiwan • Setting: Veterans General Hospital, Taipei • Inclusion criteria: patients with ESKD who are undergoing long-term HD • Exclusion criteria: recent history of acute uraemia; previous adverse reaction to aspirin or history of aspirin hypersensitivity; concurrent treatment with other antiplatelet agents (clopidogrel or ticlopidine), steroidal drugs, or NSAIDs; high immediate risk for bleeding (e.g., active peptic ulceration, recent injury, or haemophilia), or life-threatening condition other than ESKD or vascular disease (e.g., non-skin cancer) • Estimated enrolment: 250 participants
Interventions	Treatment group • Aspirin: 100 mg for 3 years Control group • Matching placebo for 3 years Cointerventions • Not reported
Outcomes	• Aspirin resistance • Incidence of vascular events (MI, cardiac death, stroke, vascular access thrombosis, or revascularization procedure)
Starting date	February 2010
Contact information	Ying-Hwa Chen Phone: not reported Email: not reported
Notes	• No results posted

NCT01743014

Study name	Ramipril and clopidogrel in oxidative stress, vascular inflammation and endothelial dysfunction in type 2 diabetes and diabetic nephropathy
Methods	• Study design: open-label, cross-over RCT • Duration of follow-up: 12 weeks
Participants	• Country: Greece • Setting: not reported • Inclusion criteria: patients with DM type 2 and DKD in the range of micro- or macro albuminuria; HbA1c < 7%; BP ≤ 130/80 mm Hg; LDL < 100 mg/dL; informed consent • Exclusion criteria: patients with DKD and eGFR < 30 mL/min with MDRD equation; potassium > 5.2 mEq/L; nephrotic proteinuria defined as UACR > 3.5 g/g or as proteinuria > 3.5 g/1.73 m^2/24 hours; non-DKD; stroke, peripheral artery disease, CAD; secondary form of hypertension; severe hepatic failure, malignancy, severe endocrinopathy, autoimmune disease or chronic inflammatory disease; any known bleeding or platelet disorder or platelets < 100.000/µL heart failure in NYHA functional class II-IV; inability or unwillingness on the part of the patient to sign the Patient Consent Form; known hypersensitivity to ramipril or to clopidogrel; women of child-bearing potential use of oral anticoagulants or other antithrombotic treatment use of glitazones; patients receiving statins should be on a stable dose of at least 3 months prior to study initiation and dose

NCT01743014 *(Continued)*

	should be constant during the study; any surgical or medical condition which in the opinion of the investigator may expose the patient to a higher risk • Estimated enrolment: 60 participants
Interventions	Treatment group • Clopidogrel: 75 mg • Ramipril: 10 mg Control group • Ramipril:10 mg Cointerventions • Not reported
Outcomes	• Change in asymmetric dimethyl arginine • Change in high-sensitivity CRP • Change in soluble CD40 ligand • Change in urine 8-isoprostane-F2 levels • Reduction in UACR • Increase of GFR • Change from baseline in carotid intima-media thickness
Starting date	July 2012
Contact information	Fotios S Iliadis Phone: +306974960728 Email: iliadis@med.auth.gr
Notes	• No results posted

NCT02394145

Study name	Genotype and platelet reactivity in patients on haemodialysis
Methods	• Study design: RCT • Duration of follow-up: 14 days
Participants	• Country: Korea • Setting: not reported • Inclusion criteria: ESKD patients undergoing regular (≥ 6 months) maintenance HD; matching patients with normal kidney function; documented CAD or high risk (Framingham heart risk score ≥ 20%) of CAD • Exclusion criteria: known allergies to aspirin, clopidogrel, or ticagrelor; concomitant use of other antithrombotic drugs (oral anticoagulants, dipyridamole); thrombocytopenia (platelet count < 100,000/mm^3); HCT < 25%; HbA1c > 10%; liver disease (bilirubin level > 2 mg/dL); symptomatic severe pulmonary disease; active bleeding or bleeding diathesis; GI bleeding within the last 6 months; haemodynamic instability; acute coronary or cerebrovascular event within the last 3 months; pregnancy; any malignancy; concomitant use of a CYP3A4 inhibitor or NSAIDs; recent treatment (< 30 days) with a glycoprotein IIb/IIIa antagonist • Estimated enrolment: 20 participants

NCT02394145 *(Continued)*

Interventions	Treatment group 1 • Ticagrelor: initial dose of 180 mg and maintenance dose of 90 mg twice/day Treatment group 2 • Clopidogrel: initial dose 300 mg and maintenance dose 150 mg once/day Cointerventions • Not reported
Outcomes	• Difference of antiplatelet effects according to genotype • The difference of antiplatelet effects according to kidney function
Starting date	September 2009
Contact information	Weon Kim Phone: 82-2-958-8170 Email: mylovekw@hanmail.net
Notes	• No results posted

NCT02459288

Study name	Platelet resistance with ticagrelor or standard-dose clopidogrel among CKD and ACS patients (APROVE-CKD)
Methods	• Study design: cross-over RCT • Duration of follow-up: 2 weeks
Participants	• Country: Taiwan • Setting: not reported • Inclusion criteria: provision of informed consent prior to any study specific procedures; female and male, 20 to 75 years; stage 3-5 CKD (eGFR < 60 mL/min) patients or ESKD; taking standard treatment dose of clopidogrel (75mg/day) for more than 1 week; hospitalised for an acute coronary syndrome, with or without ST-segment elevation, with an onset of symptoms during the past 6 months; for patients who had an acute coronary syndrome without ST-segment elevation, at least 2 of the following 3 criteria had to be met 1) ST-segment changes on electrocardiography, indicating ischaemias 2) a positive test of a biomarker, indicating myocardial necrosis; or 3) one of several risk factors (age ≥ 60 years; previous MI or coronary-artery bypass grafting; CAD with stenosis of ≥50% in at least two vessels; previous ischaemic stroke, TIA, carotid stenosis of at least 50%, or cerebral revascularization; DM; peripheral arterial disease); for patients who had an acute coronary syndrome with ST-segment elevation, the following two inclusion criteria had to be met: 1) persistent ST-segment elevation of at least 0.1 mV in at least two contiguous leads, or 2) a new left bundle-branch block • Exclusion criteria: oral anticoagulation therapy that cannot be stopped; increased risk of bradycardia; concomitant use of strong CYP3A inhibitor/inducers; unwilling to sign informed consent; allergic or contraindicated to any study medications • Estimated enrolment: 80 participants
Interventions	Treatment group 1 • Ticagrelor (Brilinta): 90 mg Treatment group 2

NCT02459288 *(Continued)*

	• Clopidogrel (Plavix): 75 mg Cointerventions • Not reported
Outcomes	• Platelet changes • Major bleeding events • MI • Emergent condition with hospitalisation
Starting date	January 2014
Contact information	Ping-Yen Liu Phone: +88662353535 Email: larry@mail.ncku.edu.tw
Notes	• No results posted

NCT03039205

Study name	Platelet aggregation in patients with coronary artery disease and kidney dysfunction taking clopidogrel or ticagrelor
Methods	• Study design: RCT • Duration of follow-up: not reported
Participants	• Country: Brazil • Setting: not reported • Inclusion criteria: CrCl < 60 mL/min/m^2; use of aspirin for at least 7 days prior to randomisation; documented obstructive CAD by angiography; at least 12 months from the last episode of MI; agree to sign the Informed Consent • Exclusion criteria: prior ischaemic or haemorrhagic stroke; prior intracranial bleeding; use of oral anticoagulant in the past month; use of dual antiplatelet agents in the last 30 days; use of NSAIDs and/or dipyridamole in the past month; mandatory use of proton pump inhibitor; known platelet dysfunction or platelets < 100,000 or > 450,000/µL; ESKD undergoing HD; terminal illness; known liver disease or coagulation disorder; known pregnancy, breast-feeding, or intend to become pregnant during the study period; hypersensitivity to clopidogrel, ticagrelor or any excipients; refusal to sign informed consent; active pathological bleeding • Estimated enrolment: 112 participants
Interventions	Treatment group 1 • Clopidogrel: 600 mg loading dose + 75 mg for 7 to 9 days Treatment group 2 • Ticagrelor: 180 mg loading dose + 90 mg for 7 to 9 days Cointerventions • Not reported
Outcomes	• Platelet aggregation • Adenosine plasma concentration

NCT03039205 *(Continued)*

- Lipoprotein-a
- Hb
- Leukocytes
- Platelet count
- Prothrombin time
- Activated partial thromboplastin time
- SCr
- Urea
- Total and free cholesterol
- Free fatty acids
- Cholesterol ester transfer protein activity
- LDL
- HDL
- Triglycerides
- Fasting glucose
- HbA1c
- Ultra-sensitive CRP
- Interleukin-6
- Plasminogen activator inhibition
- Compare platelet aggregation
- Analyze the influence of ACEi or angiotensin receptor subtype 1 (AT1) blockers on platelet aggregation
- Analyze the influence of oral hypoglycaemic agents on platelet aggregation
- Analyze the influence of insulin on platelet aggregation
- Analyze the influence of beta-blockers on platelet aggregation
- Analyze the influence of proton pump inhibitors on platelet aggregation
- Analyze, in the studied groups with or without renal dysfunction, the incidence of dyspnoea

Starting date	November 2017
Contact information	André Franci Phone: 551126615850 Email: not reported
Notes	• No results posted

NCT03150667

Study name	Study comparing treatment effectiveness of guideline indicated APT for ACS in patients with CKD (CPRS-CKD)
Methods	• Study design: RCT • Duration of follow-up: 1 year
Participants	• Country: USA • Setting: not reported • Inclusion criteria: hospital admission with non-emergent acute coronary symptoms qualifying diagnosis (chest pain, unstable angina or non-STEMI); decision to prescribe clopidogrel or ticagrelor in addition to aspirin by the attending physician; eGFR < 60 mL/min/1.73 m^2 • Exclusion criteria: diagnosis of STEMI at admission; history of intracranial haemorrhage; bleeding requiring hospitalisation, surgery, or transfusion within the past 3 months; life expectancy in the

NCT03150667 *(Continued)*

	opinion of the provider < 6 months; chronic antithrombotic therapy; known allergy to clopidogrel or ticagrelor; patients on HD • Estimated enrolment: 220 participants
Interventions	Treatment group 1 • Ticagrelor: dose not reported Treatment group 2 • Clopidogrel: dose not reported Cointerventions • Not reported
Outcomes	• Death (any cause), non-fatal MI (MI), or ischaemic stroke • Bleeding • Incidence of BARC > 3 bleeding over a period of 1 year from hospital admission • Need for ischaemia-driven urgent coronary revascularization • MACE events • Length of hospital stay and readmission
Starting date	April 2017
Contact information	Subhash Banerjee Phone: 214-867-1608 Email: subhash.banerjee@utsouthwestern.edu
Notes	• No results posted

NCT03649711

Study name	Chronic kidney disease (CKD) platelet study
Methods	• Study design: double-blind RCT • Duration of follow-up: not reported
Participants	• Country: USA • Setting: not reported • Inclusion criteria: males and females, aged 18 to 91 years; ability to understand and sign informed consent; non-dialysis CKD patients eGFR of < 30 mL/min/1.73 m^2 for a period of ≥ 3 months • Exclusion criteria: no healthcare power of attorney to sign informed consent; unwillingness or inability to participate in the protocol or comply with any of its components; subjects unable or unwilling to stop taking aspirin and other antithrombotic agents, glycoprotein IIb/IIIa antagonist, NSAIDs and proton pump inhibitors, or fish oil, vitamin E and herbal supplements; AKI superimposed on CKD; kidney transplant or any other solid organ transplant recipient; ESKD on maintenance dialysis (PD or HD); nephrotic syndrome defined as nephrotic range proteinuria, hypoalbuminaemia, hyperlipidaemia and generalized oedema; recent hospitalisation or surgery < 3 months; acute coronary or cerebrovascular event in the last 12 months; blood dyscrasias, active bleeding, or bleeding diathesis; GI bleeding in the last 6 months; recent treatment (< 30 days) with a glycoprotein IIb/IIIa antagonist; HCT < 25%, WCC > 20,000/µL, or platelet count < 50,000/µL; any active malignancy or liver disease; pregnancy or positive urine pregnancy test; Has not undergone a hysterectomy or bilateral oophorectomy, not been naturally postmenopausal for at

NCT03649711 *(Continued)*

	least 12 consecutive months; must not be nursing due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants • Estimated enrolment: 81 participants
Interventions	Treatment group 1 • Ticagrelor: 90 mg twice/day Treatment group 2 • Clopidogrel: 75 mg/day in the morning and a matching placebo in the evening Cointerventions • Aspirin: 81 mg/day
Outcomes	• Adensosine diphosphate-induced platelet aggregation • Platelet surface P-selectin expression
Starting date	November 2018
Contact information	Jain Nishank Phone: 501-686-5295 Email: njain2@uams.edu
Notes	• No results posted

Park 2010

Study name	The prevention of contrast induced nephropathy by sarpogrelate in patients with chronic kidney disease: a study protocol for a prospective randomised controlled clinical trial
Methods	• Study design: open-label RCT • Duration of follow-up: not reported
Participants	• Country: Korea • Setting: not reported • Inclusion criteria: 20 to 85 years with a clinical diagnosis of CKD (eGFR < 60 mL/min/1.72 m^2) scheduled for coronary angiogram • Exclusion criteria: < 20 years or > 85 years; liver cirrhosis ≥ Child class B; decreased serum platelet level (< 100,000/μL); received or are scheduled to receive percutaneous kidney intervention; currently are taking anticoagulation drugs; unable to give informed consent • Estimated enrolment: 268 participants
Interventions	Treatment group 1 • Sarpogrelate: a fixed-flexible dose of 300 mg/day for 4 weeks Treatment group 2 • Sarpogrelate: for 4 weeks Cointerventions • Not reported

Park 2010 *(Continued)*

Outcomes	• Contrast-induced nephropathy • SCr • Performance of HD or haemofiltration • Bleeding
Starting date	December 2009
Contact information	Woo-Young Chung Phone: not reported Email: wychung@paran.com
Notes	• No results posted

PRASTO-III 2018

Study name	PRASTRO-III: a double-blind study of CS-747S versus clopidogrel sulfate in patients with thrombotic stroke having risk factors for stroke recurrence
Methods	• Study design: RCT • Duration of follow-up: 48 weeks
Participants	• Country: Japan • Setting: multicentre (43 sites) • Inclusion criteria: ≥ 50 years with thrombotic stroke having risk factors for stroke recurrence; evidence of infarct lesion that may have caused the last episode of attack on head imaging; subtype of stroke is either large-artery atherosclerosis or small-artery occlusion; at least one of the following risk factors 1) Hypertension: SBP and DBP of ≥ 140 mm Hg and ≥ 90 mm Hg; 2) DM: HbA1c ≥ 6.5%; 3) CKD: eGFR < 60 mL/min/1.73 m^2 or urine protein rated as ≥ 1+; 4) dyslipidaemia: LDL cholesterol ≥ 120 mg/dL, HDL cholesterol < 40 mg/dL, and triglyceride ≥ 150 mg/dL. If none of these are met in the presence of pharmacotherapy patients having at least two risk factors from among hypertension, DM, CKD, and dyslipidaemia are eligible for the study; history of stroke before the last episode of attack; able to start treatment with the study drug during the period from 7 days to 26 weeks after onset of the last episode of ischaemic attack • Exclusion criteria: symptomatic non-traumatic intracerebral haemorrhage or a known history of bleeding or a high risk of bleeding; scheduled to undergo cerebral revascularization for the latest ischaemic attack; severe hepatic disorder; severe renal disorder requiring dialysis therapy; received clopidogrel sulfate for at least 22 days during the period from the last episode of ischaemic attack to the start of treatment with the study drug • Baseline characteristics: not reported for CKD patients
Interventions	Treatment group 1 • Prasugrel Treatment group 2 • Clopidogrel Cointerventions • Not reported
Outcomes	• Ischaemic cerebrovascular and cardiovascular events (stroke, MI, and death from other vascular cause)

PRASTO-III 2018 *(Continued)*

	• Bleeding events
Starting date	June 2017
Contact information	Contact name: not reported Phone: +81-95-819-7200 Email: dsclinicaltrial@daiichisankyo.co.jp
Notes	• Funding: DAIICHI SANKYO Co.,Ltd. and Ube Industries,Ltd • No results posted

SERENADE 2015

Study name	Study design of the influence of SErotonin inhibition on patients with RENAl impairment or diabetes undergoing drug-eluting stent implantation (SERENADE) study: A multicenter, open-label, prospective, randomised study
Methods	• Study design: open-label RCT • Duration of follow-up: 1 year
Participants	• Country: Korea • Setting: multicentre • Inclusion criteria: symptomatic CAD (including acute coronary syndrome) or positive stress test and a native coronary lesion (> 50% diameter stenosis by visual estimation on coronary angiogram and reference diameter > 2.5 mm) and CKD or diabetic patients; ≥ 18 years; ability to acknowledge verbally the risks, benefits and treatment ramifications in receiving the sarpogrelate; written informed consent given by legally authorized agent prior to any study-related treatment; indication for use of DES based on ACC/AHA/SCAI and ESC/EACTS guidelines and/or clinical judgment of interventional cardiologist; target lesions amenable to PCI; previous diagnosis of DM; DM-specific treatment administration (oral or insulin); FBS > 126 mg/dL in at least 2 repeated determinations; HbA1c > 6.5%; eGFR < 60 mL/min/1.73 m^2 • Exclusion criteria: HD patients or with eGFR < 30 mL/min/1.73 m^2; known hypersensitivity or contraindication to any of the following agents: heparin, aspirin, clopidogrel, sarpogrelate or contrast media; inability to tolerate aspirin, clopidogrel or sarpogrelate for the 1-year duration of the study; KRT; females with childbearing potential; history of bleeding diathesis, known coagulopathy or refusal of blood transfusion; GI or genitourinary bleeding within prior 3 months or major surgery within 2 months; planned major non-cardiac surgery within designated study period; cardiogenic shock (Killip class IV); symptomatic heart failure, precluding coronary angiography in a supine position; non-cardiac co-morbid conditions limiting life expectancy (to < 1 year) or potentially undermining protocol compliance; active participation in another drug or device-related investigational study where the primary endpoint follow-up is ongoing; unwillingness or inability to comply with protocol procedures • Estimated enrolment: not reported for patients with kidney failure
Interventions	Treatment group • Aspirin: 100 mg twice/day • Clopidogrel: 75 mg twice/day • Sarpogrelate: 100 mg twice/day Control group • Placebo Cointerventions

SERENADE 2015 *(Continued)*

	• All patients will be recommended to undergo follow-up angiography at 9 month
Outcomes	• Late lumen loss measured by quantitative coronary angiography • Death (any cause) • Cardiac death • Nonfatal MI • Target lesion revascularization • Major bleeding using the TMI bleeding classification • Hepatic impairments as measured by increased serum glutamyl oxaloacetic transaminase level or glutamyl pyruvic transaminase level, increased serum glutamyl oxaloacetic transaminase level or glutamyl pyruvic transaminase level • Kidney impairment as measured by increased microalbuminuria or decreased CrCl
Starting date	April 2009
Contact information	Dong-Ju Choi Phone: not reported Email: djchoi@snubh.org
Notes	• No results posted

SONATA 2013

Study name	Effect of sarpogrelate on the nephropathy in type 2 diabetes (SONATA Study)
Methods	• Study design: double-blind RCT • Duration of follow-up: not reported
Participants	• Country: Korea • Setting: not reported • Inclusion criteria: ≥ 20 years who signed an informed consent form; Type 2 DM patient who have microalbuminuria or overt proteinuria; In case of hypertension patients, who keep the same medication steadily over the last 4 weeks • Exclusion criteria: hypersensitivity on sarpogrelate or another salicylic acid; should keep the antiplatelet agent because of acute cardiac disease or peripheral vein disease; took another anticoagulant agent within 1 month; ACEi OR ARB but not controlled (over 150/100 mm Hg); type 1 diabetes patients; cardiac or liver problem; SCr > 1.8 mg/dL or GFR < 40 mL/min; malignant tumour patients • Estimated enrolment: 166 participants
Interventions	Treatment group • Sarpogrelate: 100 mg, 2 tablets Control group • Placebo: 100 mg, 2 tablets Cointerventions • Not reported
Outcomes	• Safety • UACR

SONATA 2013 *(Continued)*

	• Urinary 5-hydroxyindoleacetic acid • SCr • UPCR
Starting date	February 2013
Contact information	D.S Choi Phone: not reported Email: not reported
Notes	• No results posted

TROUPER 2020

Study name	TicagRelor Or Clopidogrel in severe and terminal chronic kidney disease patients undergoing PERcutaneous coronary intervention for an acute coronary syndrome (TROUPER)
Methods	• Study design: open-label RCT • Duration of follow-up: 1 year
Participants	• Country: France • Setting: not reported • Inclusion criteria: not be of child-bearing potential (1 year post-menopausal, contraceptive or surgically sterile), non-ST-segment elevation ACS defined by the presence of at least 2 of the following criteria: (1) symptoms of myocardial ischaemia, (2) ECG ST-segment abnormalities (depression or transient elevation of at least 0.1 mV) or T-wave inversion in at least in 2 contiguous leads, or (3) an elevated cardiac troponin value (above the ULN) or ST-segment elevation ACS scheduled for primary PCI defined as a history of chest discomfort or ischaemic symptoms of > 20 minutes duration at rest ≤ 14 days prior to entry into the study with one of the following present on at least one ECG prior to randomisation: 1) ST-segment elevation ≥1 mm in two or more contiguous ECG leads; 2) new or presumably new left bundle branch block; 3) ST-segment depression ≥ 1 mm in two anterior precordial leads (V1 through V4) with clinical history and evidence suggestive of true posterior infarction • Exclusion criteria: minors, pregnant or breast-feeding women; chronic anticoagulant; thrombolytic therapy during the preceding 24 hours; bleeding; participating in another research protocol; not agreeing to participate; contraindication to clopidogrel or ticagrelor; severe hepatic failure ischaemic; stroke within one month or a history of haemorrhagic stroke; bradycardia; platelet count < 100,000; major surgery or trauma within 10 days; life expectancy < 1 year; known significant bleeding risk according to the physician judgment • Estimated enrolment: 514 participants
Interventions	Treatment group 1 • Clopidogrel: 600 mg loading dose of clopidogrel as pretreatment followed by 75 mg/day for 12 months Treatment group 2 • Ticagrelor: 180 mg loading dose as pretreatment of PCI followed by 90 mg twice/day for 12 months Cointerventions • Not reported
Outcomes	• MACE

TROUPER 2020 *(Continued)*

	• Bleedings • MI • Cardiovascular death • Urgent revascularization • Death (any cause) • Hospital re-admission • Probable and definite stent thrombosis (ARC definition)
Starting date	28 October 2018
Contact information	Laurent Bonello Phone: 330491968683 Email: laurent.bonello@ap-hm.fr
Notes	• No results posted

TWILIGHT 2016

Study name	TWILIGHT Study: The anti platelet therapy with both ticagrelor and aspirin for 3 months after coronary intervention followed by ticagrelor only for a year rather than both aspirin and ticagrelor is better in reducing the ischaemic events in high risk patients
Methods	• Study design: RCT • Duration of follow-up: 12 months
Participants	• Country: multinational (Brazil, Bulgaria, Canada, Denmark, Egypt, France, Hungary, India, Israel, Italy, New Zealand, Poland, South Africa, UK, USA) • Setting: multicentre • Inclusion criteria: > 65 years; females; troponin positive ACS; established vascular disease defined as previous MI, documented PAD or CAD/PAD revascularization; DM treated with medications (oral hypoglycaemic, subcutaneous injection of insulin); CKD defined as an eGFR < 60 mL/min/1.73 m^2 or CrCl < 60 mL/min; at least one angiographic inclusion criteria: multivessel CAD, target lesion requiring total stent length > 30 mm, thrombotic target lesion, bifurcation lesions with Medina X,1,1 classification requiring at least 2 stents, left main or proximal LAD lesion, calcified target lesion(s) requiring atherectomy • Exclusion criteria: < 18 years; contraindication to aspirin or ticagrelor; planned surgery within 90 days; planned coronary revascularization (surgical or percutaneous) within 90 days; need for chronic oral anticoagulation; prior stroke; dialysis-dependent kidney failure; active bleeding or extreme-risk for major bleeding (e.g. active peptic ulcer disease, GI pathology with a raised risk for bleeding, malignancies with a raised risk for bleeding); salvage PCI or STEMI presentation; liver cirrhosis; life expectancy < 1 year; unable or unwilling to provide informed consent; women of childbearing potential (as determined by hospital standard of care); fibrinolytic therapy within 24 hours of index PCI; concomitant therapy with a strong CYP3A4 inhibitor or inducer; platelet count < 100,000 mm^3; requiring ongoing treatment with aspirin 325 mg/day • Baseline characteristics: not reported
Interventions	Treatment group 1 • Aspirin: 81 mg/day Treatment group 2 • Ticagrelor: 90 mg twice/day Cointerventions

TWILIGHT 2016 *(Continued)*

	• Not reported
Outcomes	• Bleeding • Death (any cause) • Non-fatal MI • Stroke
Starting date	August 2016
Contact information	Upendra Kaul Phone: 011268250014243 Email: upendra.kaul@fortishealthcare.com
Notes	• Funding: Astra zeneca • No results posted

UMIN000003891

Study name	Examination concerning utility and safety of cilostazol use in patients with PAD complicated to CKD
Methods	• Study design: RCT • Duration of follow-up: not reported
Participants	• Country: Japan • Setting: not reported • Inclusion criteria: patients with PAD; ≥ 20 years; eGFR < 60 mL/min/1.73 m^2, or continues protein urea for 3 months or more; ABI < 0.9 or TBI < 0.7; patients with agreement by document • Exclusion criteria: nephrotic syndrome; active bleeding; allergy for cilostazol and aspirin; platelet dysfunction • Baseline characteristics: not reported
Interventions	Treatment group 1 • Cilostazol Treatment group 2 • Aspirin Cointerventions • Not reported
Outcomes	• Kidney function (eGFR, SCr) • Albuminuria • Endothelial dysfunction • Intima-media thickness, ABI, TBI • Serum lipid marker
Starting date	June 2017
Contact information	Yukio Yuzawa Phone: 052-744-5502

UMIN000003891 *(Continued)*

	Email:
Notes	• Funding: not reported • No results posted

VA PTXRx 2018

Study name	Pentoxifylline in diabetic kidney disease
Methods	• Study design: RCT • Duration of follow-up: 5 years
Participants	• Country: USA • Setting: multicentre (40 sites) • Inclusion criteria: ESKD with type 2 diabetes • Exclusion criteria: not reported • Baseline characteristics: not reported
Interventions	Treatment group • Pentoxifylline Control group • Placebo Cointerventions • Usual care
Outcomes	• Time to ESKD • Death • HRQoL (Kidney Disease Quality of Life Short Form (KDQoL-SF)) • Time until doubling of SCr • Hospitalisation for congestive heart failure • MACE • Peripheral vascular disease • 50% reduction in UACR from baseline • Rate of change in eGFR/year during the study period • Serious adverse events and adverse events possibly or probably related to study drug, discontinuation of study drug
Starting date	November 2019
Contact information	Leehey D.J Phone: not reported Email: not reported
Notes	• Funding: not reported. • Study status: ongoing

ABI - ankle-brachial index; ACEi - angiotensin-converting enzyme inhibitors; ACS - acute coronary syndrome; AIDS - acquired immune deficiency syndrome; AKI - acute kidney injury; ALT - alanine aminotransferase; ARB - angiotensin receptor blocker; AV - arteriovenous; AVF

- arteriovenous fistula; BARC - Bleeding Academy Research consortium; BP - blood pressure; CAD - coronary artery disease; CKD - chronic kidney disease; CrCl - creatinine clearance; CRP - C-reactive protein; CSA - cyclosporin; CVA - cerebrovascular accident; CYP3A4 - cytochrome P450 3A4; DES - drug-eluting stent; DM - diabetes mellitus; DBP - diastolic BP; DKD - diabetic kidney disease; ECG - electrocardiogram; ESKD - end-stage kidney disease; FBS - fasting blood glucose; (e)GFR - (estimated) glomerular filtration rate; GI - gastrointestinal; HbA1c - haemoglobin A1c; HCT - hematocrit; HD - haemodialysis; HDL - high-density lipoprotein; HIV - human immunodeficiency virus; HRQoL - health-related quality of life; LDL - low-density lipoprotein; MACE - major adverse cardiac events; MDRD - Modification of Diet in Renal Disease; MI - myocardial infarction; NYHA - New York Heart Association; PAD - peripheral artery disease; PCI - percutaneous coronary intervention; PD - peritoneal dialysis; RCT - randomised controlled trial; SBP - systolic BP; SCr - serum creatinine; STEMI - ST-elevation myocardial infarction; TIA - transient ischaemic attack; UACR - urinary albumin/creatinine ratio; ULN - upper limit of normal; UPCR - urinary protein/creatinine ratio; WCC - white cell count

DATA AND ANALYSES

Comparison 1. Antiplatelet agents versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Fatal or nonfatal myocardial infarction	18	15289	Risk Ratio (IV, Random, 95% CI)	0.88 [0.79, 0.99]
1.1.1 CKD	11	11912	Risk Ratio (IV, Random, 95% CI)	0.85 [0.74, 0.99]
1.1.2 HD	6	2929	Risk Ratio (IV, Random, 95% CI)	0.83 [0.49, 1.41]
1.1.3 CKD, dialysis and transplant	1	448	Risk Ratio (IV, Random, 95% CI)	0.99 [0.06, 15.75]
1.2 Fatal or nonfatal stroke	12	10382	Risk Ratio (IV, Random, 95% CI)	1.01 [0.64, 1.59]
1.2.1 CKD	5	7062	Risk Ratio (IV, Random, 95% CI)	1.06 [0.64, 1.74]
1.2.2 HD	6	2872	Risk Ratio (IV, Random, 95% CI)	0.62 [0.15, 2.60]
1.2.3 CKD, dialysis and transplant	1	448	Risk Ratio (IV, Random, 95% CI)	2.97 [0.12, 72.60]
1.3 Death (any cause)	35	18241	Risk Ratio (IV, Random, 95% CI)	0.94 [0.84, 1.06]
1.3.1 CKD	19	13234	Risk Ratio (IV, Random, 95% CI)	0.97 [0.81, 1.16]
1.3.2 HD	14	4523	Risk Ratio (IV, Random, 95% CI)	0.86 [0.72, 1.03]
1.3.3 Transplant	1	36	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.3.4 CKD, dialysis and transplant	1	448	Risk Ratio (IV, Random, 95% CI)	0.99 [0.14, 6.97]
1.4 Haemorrhagic stroke	9	6844	Risk Ratio (IV, Random, 95% CI)	1.22 [0.69, 2.17]
1.4.1 CKD	7	6655	Risk Ratio (IV, Random, 95% CI)	1.22 [0.69, 2.17]
1.4.2 HD	2	189	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.5 Cardiovascular death	21	9606	Risk Ratio (IV, Random, 95% CI)	0.87 [0.65, 1.15]

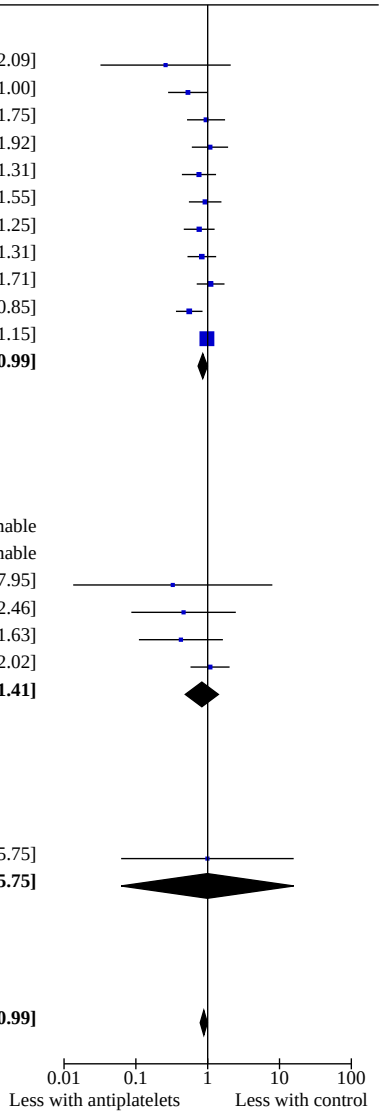
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5.1 CKD	10	6525	Risk Ratio (IV, Random, 95% CI)	0.98 [0.60, 1.59]
1.5.2 HD	9	2597	Risk Ratio (IV, Random, 95% CI)	0.71 [0.47, 1.09]
1.5.3 Transplant	1	36	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.5.4 CKD, dialysis and transplant	1	448	Risk Ratio (IV, Random, 95% CI)	0.99 [0.06, 15.75]
1.6 Fatal bleeding	21	7629	Risk Ratio (IV, Random, 95% CI)	1.39 [0.10, 19.48]
1.6.1 CKD	7	4539	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.6.2 HD	12	2606	Risk Ratio (IV, Random, 95% CI)	1.39 [0.10, 19.48]
1.6.3 Transplant	1	36	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.6.4 CKD, dialysis and transplant	1	448	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.7 Major bleeding	29	16194	Risk Ratio (IV, Random, 95% CI)	1.35 [1.10, 1.65]
1.7.1 CKD	12	11591	Risk Ratio (IV, Random, 95% CI)	1.51 [1.15, 1.98]
1.7.2 HD	15	4119	Risk Ratio (IV, Random, 95% CI)	0.90 [0.53, 1.55]
1.7.3 Transplant	1	36	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.7.4 CKD, dialysis and transplant	1	448	Risk Ratio (IV, Random, 95% CI)	0.66 [0.19, 2.31]
1.8 Minor bleeding	21	13218	Risk Ratio (IV, Random, 95% CI)	1.55 [1.27, 1.90]
1.8.1 CKD	12	11530	Risk Ratio (IV, Random, 95% CI)	1.48 [1.20, 1.83]
1.8.2 HD	8	1240	Risk Ratio (IV, Random, 95% CI)	1.87 [0.65, 5.40]
1.8.3 CKD, dialysis and transplant	1	448	Risk Ratio (IV, Random, 95% CI)	2.81 [1.49, 5.28]
1.9 Kidney failure	11	1722	Risk Ratio (IV, Random, 95% CI)	0.89 [0.70, 1.14]
1.9.1 CKD	8	1247	Risk Ratio (IV, Random, 95% CI)	0.80 [0.59, 1.08]
1.9.2 Transplant	2	100	Risk Ratio (IV, Random, 95% CI)	1.40 [0.73, 2.67]
1.9.3 CKD, dialysis and transplant	1	375	Risk Ratio (IV, Random, 95% CI)	1.17 [0.40, 3.42]
1.10 Doubling of serum creatinine	3	217	Risk Ratio (IV, Random, 95% CI)	0.39 [0.17, 0.86]
1.10.1 CKD	3	217	Risk Ratio (IV, Random, 95% CI)	0.39 [0.17, 0.86]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11 Kidney transplant graft loss	2	91	Risk Ratio (IV, Random, 95% CI)	1.08 [0.58, 2.01]
1.12 Transplant rejection	2	97	Risk Ratio (IV, Random, 95% CI)	0.95 [0.77, 1.19]
1.13 Creatinine clearance	3	90	Mean Difference (IV, Random, 95% CI)	-5.46 [-12.33, 1.41]
1.13.1 CKD	3	90	Mean Difference (IV, Random, 95% CI)	-5.46 [-12.33, 1.41]
1.14 Proteinuria	3	80	Mean Difference (IV, Random, 95% CI)	-0.74 [-1.35, -0.13]
1.14.1 CKD	3	80	Mean Difference (IV, Random, 95% CI)	-0.74 [-1.35, -0.13]
1.15 Dialysis access failure (thrombosis or loss of patency)	17	2847	Risk Ratio (IV, Random, 95% CI)	0.62 [0.50, 0.78]
1.15.1 Fistula	10	1741	Risk Ratio (IV, Random, 95% CI)	0.50 [0.36, 0.69]
1.15.2 Shunt or graft	5	1052	Risk Ratio (IV, Random, 95% CI)	0.80 [0.62, 1.03]
1.15.3 Fistula or graft	1	16	Risk Ratio (IV, Random, 95% CI)	0.50 [0.06, 4.47]
1.15.4 Catheter	1	38	Risk Ratio (IV, Random, 95% CI)	0.44 [0.16, 1.20]
1.16 Early access thrombosis (before 8 weeks)	8	1525	Risk Ratio (IV, Random, 95% CI)	0.52 [0.38, 0.70]
1.17 Loss of primary unassisted patency	2	665	Risk Ratio (IV, Random, 95% CI)	0.95 [0.89, 1.03]
1.18 Failure to attain suitability for dialysis	5	1503	Risk Ratio (IV, Random, 95% CI)	0.63 [0.34, 1.15]
1.19 Need for intervention to attain patency or assist maturation	6	2067	Risk Ratio (IV, Random, 95% CI)	0.87 [0.72, 1.05]
1.20 Hospitalisation (any cause)	3	3535	Risk Ratio (IV, Random, 95% CI)	0.97 [0.87, 1.10]
1.20.1 CKD	1	2009	Risk Ratio (IV, Random, 95% CI)	0.93 [0.72, 1.21]
1.20.2 HD	2	1526	Risk Ratio (IV, Random, 95% CI)	0.96 [0.78, 1.17]
1.21 Cardiovascular hospitalisation	3	3535	Risk Ratio (IV, Random, 95% CI)	0.93 [0.76, 1.14]
1.21.1 CKD	1	2009	Risk Ratio (IV, Random, 95% CI)	0.93 [0.72, 1.21]
1.21.2 HD	2	1526	Risk Ratio (IV, Random, 95% CI)	0.88 [0.58, 1.33]
1.22 Treatment withdrawal	15	2669	Risk Ratio (IV, Random, 95% CI)	0.97 [0.83, 1.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.22.1 CKD	4	202	Risk Ratio (IV, Random, 95% CI)	0.64 [0.27, 1.55]
1.22.2 HD	8	1973	Risk Ratio (IV, Random, 95% CI)	0.99 [0.83, 1.19]
1.22.3 PD	1	10	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.22.4 Transplant	1	36	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.22.5 CKD, dialysis and transplant	1	448	Risk Ratio (IV, Random, 95% CI)	0.95 [0.66, 1.37]

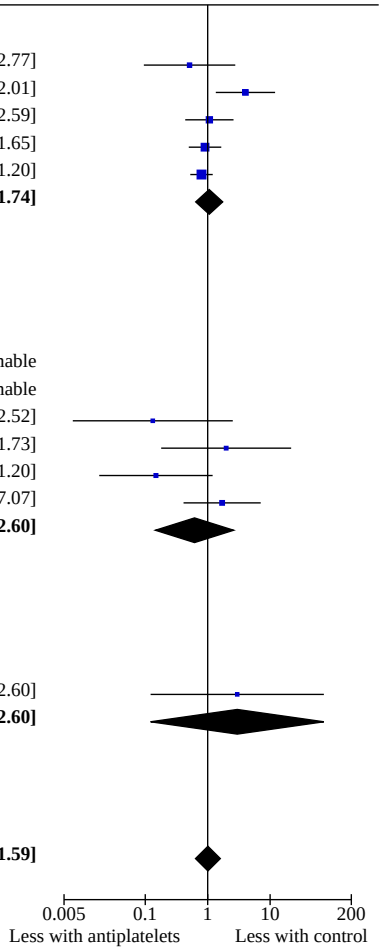
Analysis 1.1. Comparison 1: Antiplatelet agents versus control, Outcome 1: Fatal or nonfatal myocardial infarction

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 CKD						
RAPPORT 1998	1	27	5	35	0.3%	0.26 [0.03 , 2.09]
EPILOG 1997	18	325	17	163	3.3%	0.53 [0.28 , 1.00]
EPISTENT 1998	24	231	15	137	3.6%	0.95 [0.52 , 1.75]
CREDO 2005	21	203	20	208	3.9%	1.08 [0.60 , 1.92]
CHARISMA 2006	22	1006	29	1003	4.4%	0.76 [0.44 , 1.31]
GLOBAL LEADERS 2018	26	428	27	410	4.9%	0.92 [0.55 , 1.55]
EPIC 1994	33	334	24	185	5.4%	0.76 [0.46 , 1.25]
ETDRS 1992	21	79	34	106	6.3%	0.83 [0.52 , 1.31]
IMPACT II 1997	58	547	25	259	6.7%	1.10 [0.70 , 1.71]
HOT 1993	32	1791	59	1828	7.3%	0.55 [0.36 , 0.85]
PURSUIT 1997	256	1430	216	1177	49.2%	0.98 [0.83 , 1.15]
Subtotal (95% CI)		**6401**		**5511**	**95.1%**	**0.85 [0.74 , 0.99]**
Total events:	512		471			
Heterogeneity: Tau² = 0.01; Chi² = 12.00, df = 10 (P = 0.28); I² = 17%						
Test for overall effect: Z = 2.08 (P = 0.04)						
1.1.2 HD						
STOP 1995	0	398	0	413		Not estimable
Ell 1982	0	50	0	57		Not estimable
Creek 1990	0	144	1	141	0.1%	0.33 [0.01 , 7.95]
Kaufman 2003	2	104	4	96	0.5%	0.46 [0.09 , 2.46]
Dember 2005	3	441	7	436	0.7%	0.42 [0.11 , 1.63]
Dixon 2005	19	321	18	328	3.4%	1.08 [0.58 , 2.02]
Subtotal (95% CI)		**1458**		**1471**	**4.7%**	**0.83 [0.49 , 1.41]**
Total events:	24		30			
Heterogeneity: Tau² = 0.00; Chi² = 2.43, df = 3 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.1.3 CKD, dialysis and transplant						
UK-HARP-I 2005	1	225	1	223	0.2%	0.99 [0.06 , 15.75]
Subtotal (95% CI)		**225**		**223**	**0.2%**	**0.99 [0.06 , 15.75]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**8084**		**7205**	**100.0%**	**0.88 [0.79 , 0.99]**
Total events:	537		502			
Heterogeneity: Tau² = 0.00; Chi² = 14.50, df = 15 (P = 0.49); I² = 0%						
Test for overall effect: Z = 2.12 (P = 0.03)						
Test for subgroup differences: Chi² = 0.02, df = 2 (P = 0.99), I² = 0%						



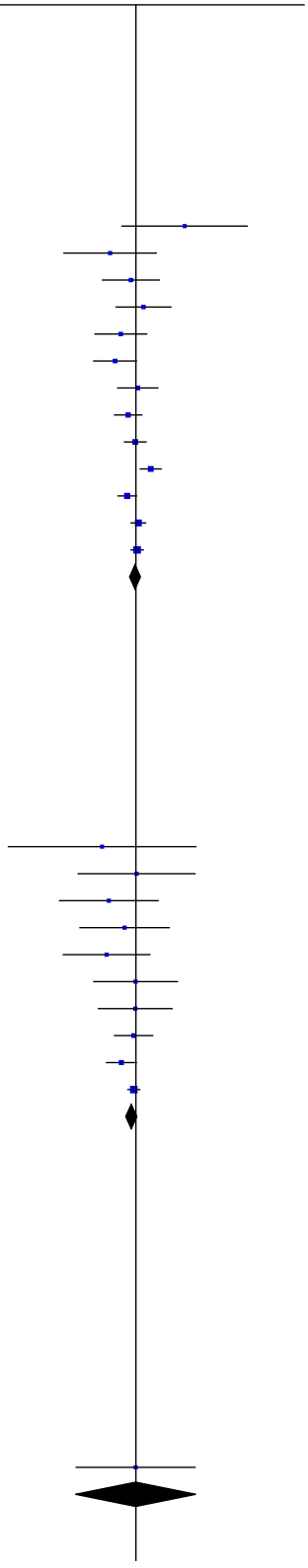
Analysis 1.2. Comparison 1: Antiplatelet agents versus control, Outcome 2: Fatal or nonfatal stroke

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 CKD						
CREDO 2005	2	203	4	208	6.0%	0.51 [0.09 , 2.77]
ETDRS 1992	12	79	4	106	11.5%	4.03 [1.35 , 12.01]
GLOBAL LEADERS 2018	10	428	9	410	14.8%	1.06 [0.44 , 2.59]
CHARISMA 2006	20	1006	22	1003	21.4%	0.91 [0.50 , 1.65]
HOT 1993	39	1791	50	1828	26.6%	0.80 [0.53 , 1.20]
Subtotal (95% CI)		**3507**		**3555**	**80.4%**	**1.06 [0.64 , 1.74]**
Total events:	83		89			
Heterogeneity: Tau² = 0.15; Chi² = 8.00, df = 4 (P = 0.09); I² = 50%						
Test for overall effect: Z = 0.22 (P = 0.83)						
1.2.2 HD						
Ell 1982	0	24	0	26		Not estimable
Creek 1990	0	144	0	141		Not estimable
Kaufman 2003	0	104	3	96	2.2%	0.13 [0.01 , 2.52]
Dember 2005	2	441	1	436	3.3%	1.98 [0.18 , 21.73]
STOP 1995	1	398	7	413	4.2%	0.15 [0.02 , 1.20]
Dixon 2005	5	321	3	328	7.9%	1.70 [0.41 , 7.07]
Subtotal (95% CI)		**1432**		**1440**	**17.6%**	**0.62 [0.15 , 2.60]**
Total events:	8		14			
Heterogeneity: Tau² = 0.98; Chi² = 5.55, df = 3 (P = 0.14); I² = 46%						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.2.3 CKD, dialysis and transplant						
UK-HARP-I 2005	1	225	0	223	1.9%	2.97 [0.12 , 72.60]
Subtotal (95% CI)		**225**		**223**	**1.9%**	**2.97 [0.12 , 72.60]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**5164**		**5218**	**100.0%**	**1.01 [0.64 , 1.59]**
Total events:	92		103			
Heterogeneity: Tau² = 0.16; Chi² = 14.24, df = 9 (P = 0.11); I² = 37%						
Test for overall effect: Z = 0.03 (P = 0.97)						
Test for subgroup differences: Chi² = 0.92, df = 2 (P = 0.63), I² = 0%						



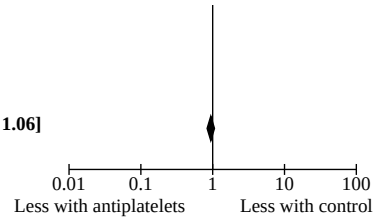
Analysis 1.3. Comparison 1: Antiplatelet agents versus control, Outcome 3: Death (any cause)

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.3.1 CKD						
Donadio 1984	0	25	0	25		Not estimable
Cheng 1998a	0	19	0	12		Not estimable
RESIST 2008	0	50	0	28		Not estimable
Zäuner 1994	0	10	0	8		Not estimable
Khajehdehi 2002	0	57	0	19		Not estimable
Tang 2014	0	43	0	44		Not estimable
CASSIOPEIR 2014	10	600	1	292	0.3%	4.87 [0.63 , 37.84]
RAPPORT 1998	2	27	6	35	0.6%	0.43 [0.09 , 1.97]
EPISTENT 1998	10	231	7	137	1.5%	0.85 [0.33 , 2.17]
CREDO 2005	10	203	8	208	1.6%	1.28 [0.52 , 3.18]
EPILOG 1997	11	325	9	163	1.8%	0.61 [0.26 , 1.45]
IMPACT II 1997	15	547	14	259	2.6%	0.51 [0.25 , 1.04]
EPIC 1994	23	334	12	185	2.8%	1.06 [0.54 , 2.08]
GLOBAL LEADERS 2018	30	428	37	410	5.5%	0.78 [0.49 , 1.23]
Goicoechea 2012	25	46	25	45	7.8%	0.98 [0.67 , 1.42]
CHARISMA 2006	73	1006	45	1003	8.2%	1.62 [1.13 , 2.32]
HOT 1993	62	1791	84	1828	9.7%	0.75 [0.55 , 1.04]
ETDRS 1992	46	79	57	106	13.2%	1.08 [0.84 , 1.40]
PURSUIT 1997	161	1430	127	1176	15.9%	1.04 [0.84 , 1.30]
Subtotal (95% CI)		**7251**		**5983**	**71.6%**	**0.97 [0.81 , 1.16]**
Total events:	478		432			
Heterogeneity: Tau² = 0.03; Chi² = 20.07, df = 12 (P = 0.07); I² = 40%						
Test for overall effect: Z = 0.33 (P = 0.74)						
1.3.2 HD						
Ell 1982	0	24	0	26		Not estimable
Kaegi 1974	0	30	0	32		Not estimable
Abacilar 2015	0	50	0	46		Not estimable
Kobayashi 1980	0	50	0	57		Not estimable
Michie 1977	0	8	1	8	0.1%	0.33 [0.02 , 7.14]
Ghorbani 2009	2	46	2	47	0.4%	1.02 [0.15 , 6.95]
Gröntoft 1998	2	131	5	136	0.5%	0.42 [0.08 , 2.10]
Kaufman 2003	3	104	4	96	0.6%	0.69 [0.16 , 3.01]
Sreedhara 1994	4	83	3	24	0.7%	0.39 [0.09 , 1.61]
Dember 2005	4	441	4	436	0.7%	0.99 [0.25 , 3.93]
Creek 1990	5	144	5	141	0.9%	0.98 [0.29 , 3.31]
STOP 1995	17	398	19	413	3.1%	0.93 [0.49 , 1.76]
Middleton 1992	23	451	37	452	4.8%	0.62 [0.38 , 1.03]
Dixon 2005	105	321	115	328	16.2%	0.93 [0.75 , 1.16]
Subtotal (95% CI)		**2281**		**2242**	**28.1%**	**0.86 [0.72 , 1.03]**
Total events:	165		195			
Heterogeneity: Tau² = 0.00; Chi² = 4.73, df = 9 (P = 0.86); I² = 0%						
Test for overall effect: Z = 1.64 (P = 0.10)						
1.3.3 Transplant						
Quarto Di Palo 1991	0	18	0	18		Not estimable
Subtotal (95% CI)		**18**		**18**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.3.4 CKD, dialysis and transplant						
UK-HARP-I 2005	2	225	2	223	0.4%	0.99 [0.14 , 6.97]
Subtotal (95% CI)		**225**		**223**	**0.4%**	**0.99 [0.14 , 6.97]**
Total events:	2		2			
Heterogeneity: Not applicable						



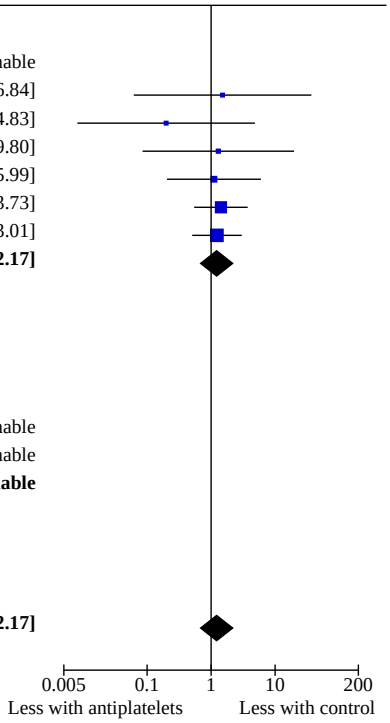
Analysis 1.3. (Continued)

Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**9775**		**8466**	**100.0%**	**0.94 [0.84 , 1.06]**
Total events:	645		629			
Heterogeneity: Tau² = 0.01; Chi² = 26.68, df = 23 (P = 0.27); I² = 14%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi² = 0.90, df = 2 (P = 0.64), I² = 0%						



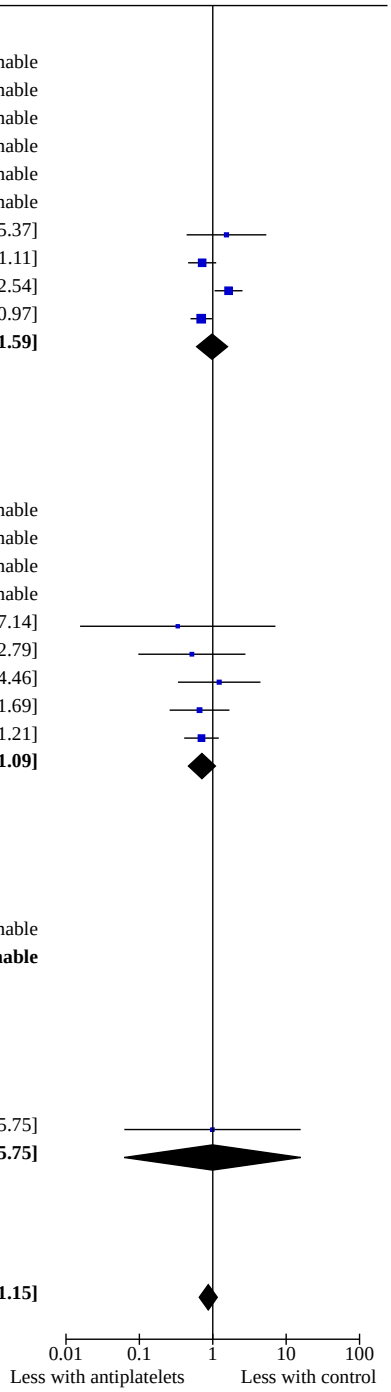
Analysis 1.4. Comparison 1: Antiplatelet agents versus control, Outcome 4: Haemorrhagic stroke

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.4.1 CKD						
PRISM-PLUS 1998	0	300	0	311		Not estimable
EPILOG 1997	1	325	0	163	3.2%	1.51 [0.06 , 36.84]
EPISTENT 1998	0	231	1	137	3.2%	0.20 [0.01 , 4.83]
RAPPORT 1998	1	27	1	35	4.5%	1.30 [0.08 , 19.80]
EPIC 1994	4	334	2	185	11.6%	1.11 [0.20 , 5.99]
CHARISMA 2006	10	1006	7	1003	35.8%	1.42 [0.54 , 3.73]
PURSUIT 1997	12	1425	8	1173	41.7%	1.23 [0.51 , 3.01]
Subtotal (95% CI)		**3648**		**3007**	**100.0%**	**1.22 [0.69 , 2.17]**
Total events:	28		19			
Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 5 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
1.4.2 HD						
Abacilar 2015	0	50	0	46		Not estimable
Ghorbani 2009	0	46	0	47		Not estimable
Subtotal (95% CI)		**96**		**93**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**3744**		**3100**	**100.0%**	**1.22 [0.69 , 2.17]**
Total events:	28		19			
Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 5 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



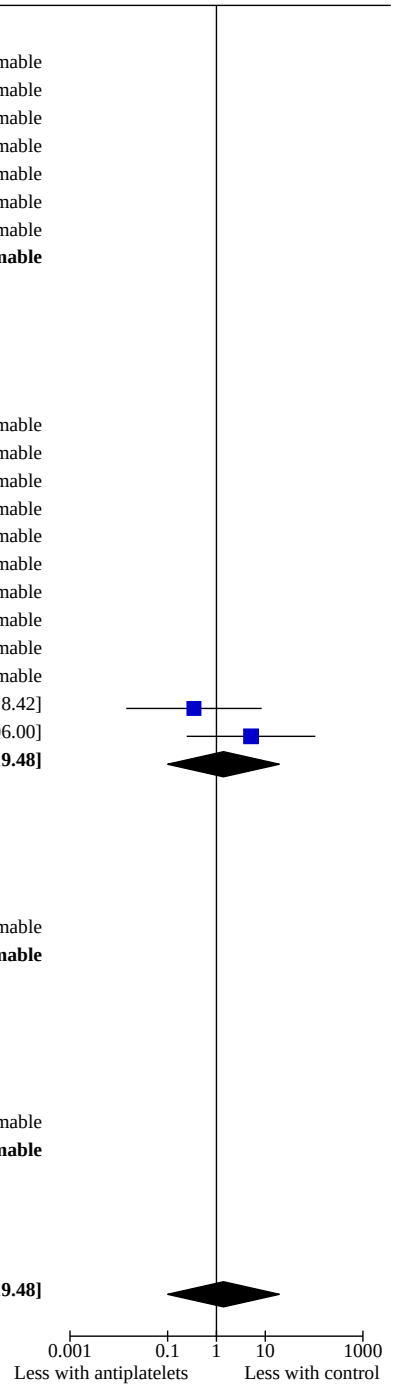
Analysis 1.5. Comparison 1: Antiplatelet agents versus control, Outcome 5: Cardiovascular death

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.5.1 CKD						
Tang 2014	0	43	0	44		Not estimable
RESIST 2008	0	50	0	28		Not estimable
Khajehdehi 2002	0	57	0	19		Not estimable
Cheng 1998a	0	19	0	12		Not estimable
Donadio 1984	0	25	0	25		Not estimable
Zäuner 1994	0	10	0	8		Not estimable
CREDO 2005	6	203	4	208	4.5%	1.54 [0.44 , 5.37]
HOT 1993	33	1791	47	1828	19.6%	0.72 [0.46 , 1.11]
CHARISMA 2006	51	1006	31	1003	19.7%	1.64 [1.06 , 2.54]
ETDRS 1992	32	79	39	67	24.5%	0.70 [0.50 , 0.97]
Subtotal (95% CI)		**3283**		**3242**	**68.3%**	**0.98 [0.60 , 1.59]**
Total events:	122		121			
Heterogeneity: Tau² = 0.16; Chi² = 11.21, df = 3 (P = 0.01); I² = 73%						
Test for overall effect: Z = 0.09 (P = 0.93)						
1.5.2 HD						
Kobayashi 1980	0	50	0	57		Not estimable
Ell 1982	0	24	0	26		Not estimable
Abacilar 2015	0	50	0	46		Not estimable
Kaegi 1974	0	30	0	32		Not estimable
Michie 1977	0	8	1	8	0.8%	0.33 [0.02 , 7.14]
Gröntoft 1998	2	131	4	136	2.6%	0.52 [0.10 , 2.79]
Creek 1990	5	144	4	141	4.2%	1.22 [0.34 , 4.46]
STOP 1995	7	398	11	413	7.3%	0.66 [0.26 , 1.69]
Middleton 1992	21	451	30	452	15.7%	0.70 [0.41 , 1.21]
Subtotal (95% CI)		**1286**		**1311**	**30.7%**	**0.71 [0.47 , 1.09]**
Total events:	35		50			
Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 4 (P = 0.90); I² = 0%						
Test for overall effect: Z = 1.58 (P = 0.11)						
1.5.3 Transplant						
Quarto Di Palo 1991	0	18	0	18		Not estimable
Subtotal (95% CI)		**18**		**18**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.4 CKD, dialysis and transplant						
UK-HARP-I 2005	1	225	1	223	1.0%	0.99 [0.06 , 15.75]
Subtotal (95% CI)		**225**		**223**	**1.0%**	**0.99 [0.06 , 15.75]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**4812**		**4794**	**100.0%**	**0.87 [0.65 , 1.15]**
Total events:	158		172			
Heterogeneity: Tau² = 0.06; Chi² = 13.23, df = 9 (P = 0.15); I² = 32%						
Test for overall effect: Z = 0.98 (P = 0.33)						
Test for subgroup differences: Chi² = 0.96, df = 2 (P = 0.62), I² = 0%						



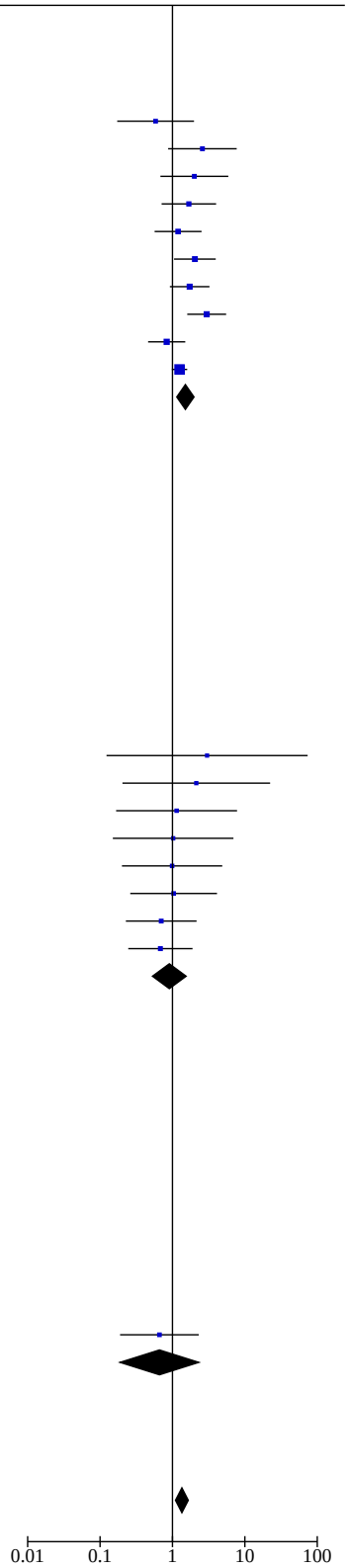
Analysis 1.6. Comparison 1: Antiplatelet agents versus control, Outcome 6: Fatal bleeding

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.6.1 CKD						
Tang 2014	0	43	0	44		Not estimable
RESIST 2008	0	50	0	28		Not estimable
Zäuner 1994	0	10	0	8		Not estimable
Donadio 1984	0	25	0	25		Not estimable
Khajehdehi 2002	0	57	0	19		Not estimable
HOT 1993	0	1791	0	1828		Not estimable
PRISM-PLUS 1998	0	300	0	311		Not estimable
Subtotal (95% CI)		**2276**		**2263**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.6.2 HD						
Michie 1977	0	8	0	8		Not estimable
Kooistra 1994	0	69	0	68		Not estimable
Abacilar 2015	0	50	0	46		Not estimable
Ghorbani 2013	0	32	0	32		Not estimable
Kaufman 2003	0	104	0	96		Not estimable
Ghorbani 2009	0	46	0	47		Not estimable
Dember 2005	0	441	0	436		Not estimable
Kaegi 1974	0	30	0	32		Not estimable
Kobayashi 1980	0	50	0	57		Not estimable
Abdul-Rahman 2007	0	19	0	19		Not estimable
Gröntoft 1998	0	131	1	136	48.2%	0.35 [0.01 , 8.42]
Dixon 2005	2	321	0	328	51.8%	5.11 [0.25 , 106.00]
Subtotal (95% CI)		**1301**		**1305**	**100.0%**	**1.39 [0.10 , 19.48]**
Total events:	2		1			
Heterogeneity: Tau² = 1.10; Chi² = 1.44, df = 1 (P = 0.23); I² = 30%						
Test for overall effect: Z = 0.25 (P = 0.80)						
1.6.3 Transplant						
Quarto Di Palo 1991	0	18	0	18		Not estimable
Subtotal (95% CI)		**18**		**18**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.6.4 CKD, dialysis and transplant						
UK-HARP-I 2005	0	225	0	223		Not estimable
Subtotal (95% CI)		**225**		**223**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**3820**		**3809**	**100.0%**	**1.39 [0.10 , 19.48]**
Total events:	2		1			
Heterogeneity: Tau² = 1.10; Chi² = 1.44, df = 1 (P = 0.23); I² = 30%						
Test for overall effect: Z = 0.25 (P = 0.80)						
Test for subgroup differences: Not applicable						



Analysis 1.7. Comparison 1: Antiplatelet agents versus control, Outcome 7: Major bleeding

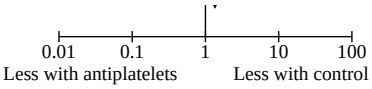
Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.7.1 CKD						
AASER 2017	0	50	0	61		Not estimable
Khajehdehi 2002	0	57	0	19		Not estimable
EPISTENT 1998	5	229	5	134	2.6%	0.59 [0.17 , 1.98]
RAPPORT 1998	8	27	4	35	3.2%	2.59 [0.87 , 7.71]
EPILOG 1997	16	325	4	163	3.3%	2.01 [0.68 , 5.90]
PRISM-PLUS 1998	13	300	8	311	4.9%	1.68 [0.71 , 4.01]
CREDO 2005	14	203	12	208	6.4%	1.20 [0.57 , 2.52]
HOT 1993	26	1791	13	1828	7.9%	2.04 [1.05 , 3.96]
CHARISMA 2006	26	1006	15	1003	8.6%	1.73 [0.92 , 3.24]
EPIC 1994	59	334	11	185	8.8%	2.97 [1.60 , 5.51]
IMPACT II 1997	29	525	16	241	9.5%	0.83 [0.46 , 1.50]
PURSUIT 1997	148	1404	97	1152	28.5%	1.25 [0.98 , 1.60]
Subtotal (95% CI)		**6251**		**5340**	**83.8%**	**1.51 [1.15 , 1.98]**
Total events:	344		185			
Heterogeneity: Tau² = 0.07; Chi² = 15.11, df = 9 (P = 0.09); I² = 40%						
Test for overall effect: Z = 2.94 (P = 0.003)						
1.7.2 HD						
Ell 1982	0	24	0	26		Not estimable
Harter 1979	0	19	0	25		Not estimable
Ghorbani 2013	0	32	0	32		Not estimable
Kamper 1997	0	13	0	14		Not estimable
Ghorbani 2009	0	46	0	47		Not estimable
Abdul-Rahman 2007	0	19	0	19		Not estimable
Michie 1977	0	8	0	8		Not estimable
Middleton 1992	1	451	0	452	0.4%	3.01 [0.12 , 73.61]
Kaegi 1974	2	30	1	32	0.7%	2.13 [0.20 , 22.33]
Kobayashi 1980	2	50	2	57	1.1%	1.14 [0.17 , 7.80]
Andrassy 1974	2	46	2	47	1.1%	1.02 [0.15 , 6.95]
Dember 2005	3	441	3	436	1.6%	0.99 [0.20 , 4.87]
STOP 1995	4	398	4	413	2.1%	1.04 [0.26 , 4.12]
Creek 1990	5	144	7	141	3.1%	0.70 [0.23 , 2.15]
Dixon 2005	6	321	9	328	3.7%	0.68 [0.25 , 1.89]
Subtotal (95% CI)		**2042**		**2077**	**13.7%**	**0.90 [0.53 , 1.55]**
Total events:	25		28			
Heterogeneity: Tau² = 0.00; Chi² = 1.67, df = 7 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						
1.7.3 Transplant						
Quarto Di Palo 1991	0	18	0	18		Not estimable
Subtotal (95% CI)		**18**		**18**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.7.4 CKD, dialysis and transplant						
UK-HARP-I 2005	4	225	6	223	2.5%	0.66 [0.19 , 2.31]
Subtotal (95% CI)		**225**		**223**	**2.5%**	**0.66 [0.19 , 2.31]**
Total events:	4		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
Total (95% CI)		**8536**		**7658**	**100.0%**	**1.35 [1.10 , 1.65]**
Total events:	373		219			
Heterogeneity: Tau² = 0.02; Chi² = 20.38, df = 18 (P = 0.31); I² = 12%						



Analysis 1.7. (Continued)

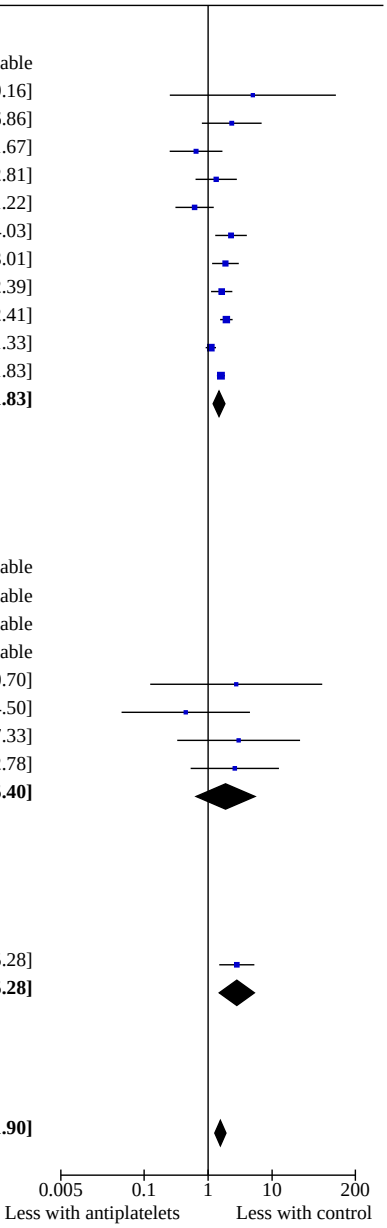
Total events:	373	219

Heterogeneity: Tau² = 0.02; Chi² = 20.38, df = 18 (P = 0.31); I² = 12%
Test for overall effect: Z = 2.89 (P = 0.004)
Test for subgroup differences: Chi² = 4.00, df = 2 (P = 0.14), I² = 50.0%



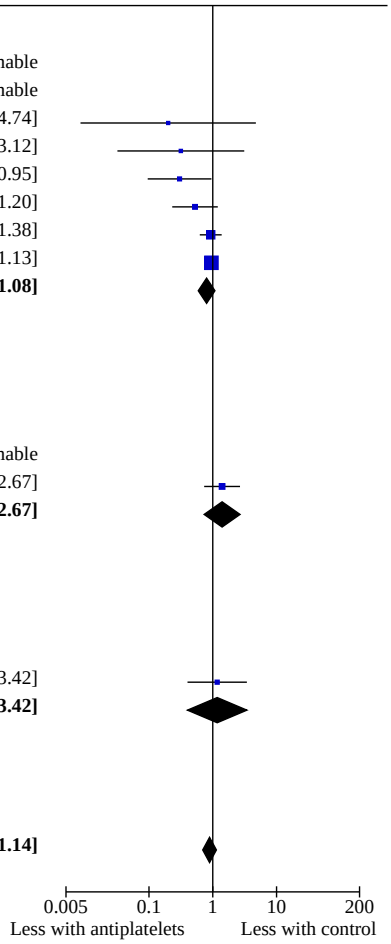
Analysis 1.8. Comparison 1: Antiplatelet agents versus control, Outcome 8: Minor bleeding

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.8.1 CKD						
Khajehdehi 2002	0	57	0	19		Not estimable
Donadio 1984	2	25	0	25	0.4%	5.00 [0.25 , 99.16]
EPISTENT 1998	16	229	4	134	2.9%	2.34 [0.80 , 6.86]
RAPPORT 1998	5	27	10	35	3.6%	0.65 [0.25 , 1.67]
EPILOG 1997	24	325	9	163	5.1%	1.34 [0.64 , 2.81]
CREDO 2005	12	203	20	208	5.7%	0.61 [0.31 , 1.22]
HOT 1993	38	1791	17	1828	7.3%	2.28 [1.29 , 4.03]
EPIC 1994	64	334	19	185	8.8%	1.87 [1.16 , 3.01]
IMPACT II 1997	103	525	29	241	10.7%	1.63 [1.11 , 2.39]
PURSUIT 1997	228	1404	97	1152	14.4%	1.93 [1.54 , 2.41]
PRISM-PLUS 1998	133	300	125	311	15.3%	1.10 [0.92 , 1.33]
CHARISMA 2006	347	1006	218	1003	16.1%	1.59 [1.37 , 1.83]
Subtotal (95% CI)		**6226**		**5304**	**90.2%**	**1.48 [1.20 , 1.83]**
Total events:	972		548			
Heterogeneity: Tau² = 0.06; Chi² = 29.79, df = 10 (P = 0.0009); I² = 66%						
Test for overall effect: Z = 3.64 (P = 0.0003)						
1.8.2 HD						
Michie 1977	0	8	0	8		Not estimable
Kobayashi 1980	0	50	0	57		Not estimable
Kamper 1997	0	13	0	14		Not estimable
Dember 2005	0	441	0	436		Not estimable
Alexopoulos 2011	1	11	0	10	0.4%	2.75 [0.12 , 60.70]
Gröntoft 1985	1	19	2	17	0.7%	0.45 [0.04 , 4.50]
Ghorbani 2013	3	32	1	32	0.8%	3.00 [0.33 , 27.33]
Andrassy 1974	5	45	2	47	1.5%	2.61 [0.53 , 12.78]
Subtotal (95% CI)		**619**		**621**	**3.4%**	**1.87 [0.65 , 5.40]**
Total events:	10		5			
Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 3 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
1.8.3 CKD, dialysis and transplant						
UK-HARP-I 2005	34	225	12	223	6.4%	2.81 [1.49 , 5.28]
Subtotal (95% CI)		**225**		**223**	**6.4%**	**2.81 [1.49 , 5.28]**
Total events:	34		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.20 (P = 0.001)						
Total (95% CI)		**7070**		**6148**	**100.0%**	**1.55 [1.27 , 1.90]**
Total events:	1016		565			
Heterogeneity: Tau² = 0.06; Chi² = 35.63, df = 15 (P = 0.002); I² = 58%						
Test for overall effect: Z = 4.32 (P < 0.0001)						
Test for subgroup differences: Chi² = 3.64, df = 2 (P = 0.16), I² = 45.1%						



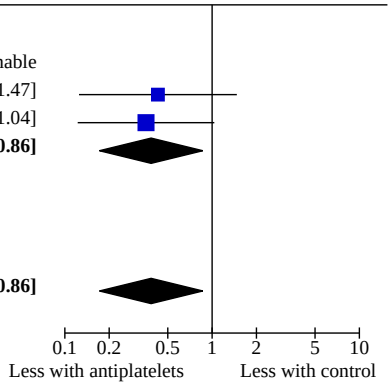
Analysis 1.9. Comparison 1: Antiplatelet agents versus control, Outcome 9: Kidney failure

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.9.1 CKD						
Khajehdehi 2002	0	57	0	19		Not estimable
Zäuner 1994	0	10	0	8		Not estimable
RESIST 2008	0	44	1	26	0.6%	0.20 [0.01 , 4.74]
Cheng 1998a	1	19	2	12	1.1%	0.32 [0.03 , 3.12]
Donadio 1984	3	21	9	19	4.3%	0.30 [0.10 , 0.95]
Goicoechea 2012	7	46	13	45	7.8%	0.53 [0.23 , 1.20]
ETDRS 1992	27	79	39	106	23.4%	0.93 [0.63 , 1.38]
CASSIOPEIR 2014	220	494	113	242	46.3%	0.95 [0.81 , 1.13]
Subtotal (95% CI)		**770**		**477**	**83.5%**	**0.80 [0.59 , 1.08]**
Total events:	258		177			
Heterogeneity: Tau² = 0.04; Chi² = 7.26, df = 5 (P = 0.20); I² = 31%						
Test for overall effect: Z = 1.45 (P = 0.15)						
1.9.2 Transplant						
Quarto Di Palo 1991	0	18	0	18		Not estimable
Schulze 1990	14	32	10	32	11.6%	1.40 [0.73 , 2.67]
Subtotal (95% CI)		**50**		**50**	**11.6%**	**1.40 [0.73 , 2.67]**
Total events:	14		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
1.9.3 CKD, dialysis and transplant						
UK-HARP-I 2005	7	187	6	188	4.8%	1.17 [0.40 , 3.42]
Subtotal (95% CI)		**187**		**188**	**4.8%**	**1.17 [0.40 , 3.42]**
Total events:	7		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
Total (95% CI)		**1007**		**715**	**100.0%**	**0.89 [0.70 , 1.14]**
Total events:	279		193			
Heterogeneity: Tau² = 0.03; Chi² = 9.09, df = 7 (P = 0.25); I² = 23%						
Test for overall effect: Z = 0.92 (P = 0.36)						
Test for subgroup differences: Chi² = 2.61, df = 2 (P = 0.27), I² = 23.5%						



Analysis 1.10. Comparison 1: Antiplatelet agents versus control, Outcome 10: Doubling of serum creatinine

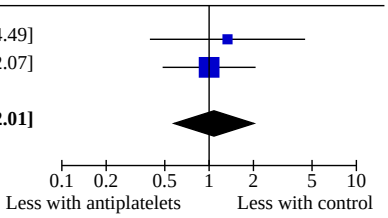
Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.10.1 CKD						
Khajehdehi 2002	0	57	0	19		Not estimable
Donadio 1984	3	25	7	25	42.8%	0.43 [0.12 , 1.47]
Goicoechea 2012	4	46	11	45	57.2%	0.36 [0.12 , 1.04]
Subtotal (95% CI)		**128**		**89**	**100.0%**	**0.39 [0.17 , 0.86]**
Total events:	7		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 2.32 (P = 0.02)						
Total (95% CI)		**128**		**89**	**100.0%**	**0.39 [0.17 , 0.86]**
Total events:	7		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 2.32 (P = 0.02)						
Test for subgroup differences: Not applicable						



Analysis 1.11. Comparison 1: Antiplatelet agents versus control, Outcome 11: Kidney transplant graft loss

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Anderson 1974	5	15	3	12	26.4%	1.33 [0.40 , 4.49]
Schulze 1990	10	32	10	32	73.6%	1.00 [0.48 , 2.07]
Total (95% CI)		**47**		**44**	**100.0%**	**1.08 [0.58 , 2.01]**
Total events:	15		13			

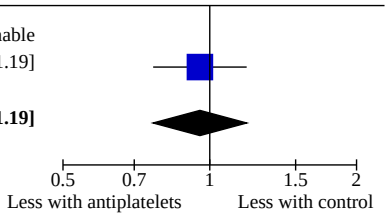
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Antiplatelet agents versus control, Outcome 12: Transplant rejection

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Quarto Di Palo 1991	0	18	0	18		Not estimable
Anderson 1974	27	33	24	28	100.0%	0.95 [0.77 , 1.19]
Total (95% CI)		**51**		**46**	**100.0%**	**0.95 [0.77 , 1.19]**
Total events:	27		24			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable



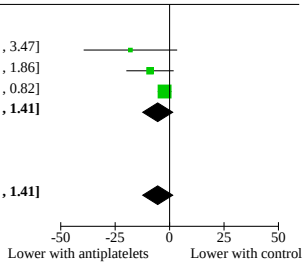
Analysis 1.13. Comparison 1: Antiplatelet agents versus control, Outcome 13: Creatinine clearance

Study or Subgroup	Antiplatelet agent Mean [mL/min]	SD [mL/min]	Total	Placebo/no treatment Mean [mL/min]	SD [mL/min]	Total	Weight	Mean Difference IV, Random, 95% CI [mL/min]
1.13.1 CKD								
Giustina 1998	108	30	15	126	30	15	9.0%	-18.00 [-39.47 , 3.47]
Nyberg 1984	30	13	11	39	13	11	26.1%	-9.00 [-19.86 , 1.86]
Khajehdehi 2002	116.5	5.8	19	118.8	3.8	19	64.9%	-2.30 [-5.42 , 0.82]
Subtotal (95% CI)			**45**			**45**	**100.0%**	**-5.46 [-12.33 , 1.41]**

Heterogeneity: Tau² = 16.40; Chi² = 3.24, df = 2 (P = 0.20); I² = 38%
Test for overall effect: Z = 1.56 (P = 0.12)

Total (95% CI)			**45**			**45**	**100.0%**	**-5.46 [-12.33 , 1.41]**

Heterogeneity: Tau² = 16.40; Chi² = 3.24, df = 2 (P = 0.20); I² = 38%
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Not applicable



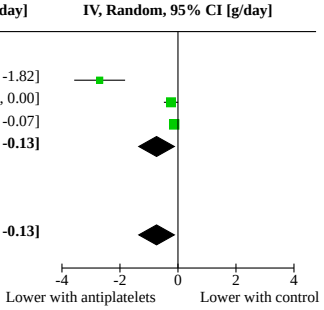
Analysis 1.14. Comparison 1: Antiplatelet agents versus control, Outcome 14: Proteinuria

Study or Subgroup	Antiplatelet agent Mean [g/day]	SD [g/day]	Total	Placebo/no treatment Mean [g/day]	SD [g/day]	Total	Weight	Mean Difference IV, Random, 95% CI [g/day]
1.14.1 CKD								
Zäuner 1994	1.6	0.7	10	4.3	1.1	8	22.0%	-2.70 [-3.58 , -1.82]
Khajehdehi 2002	0.96	0.39	19	1.2	0.38	19	37.8%	-0.24 [-0.48 , 0.00]
Movchan 2001	0.3	0.11	14	0.43	0.04	10	40.1%	-0.13 [-0.19 , -0.07]
Subtotal (95% CI)			**43**			**37**	**100.0%**	**-0.74 [-1.35 , -0.13]**

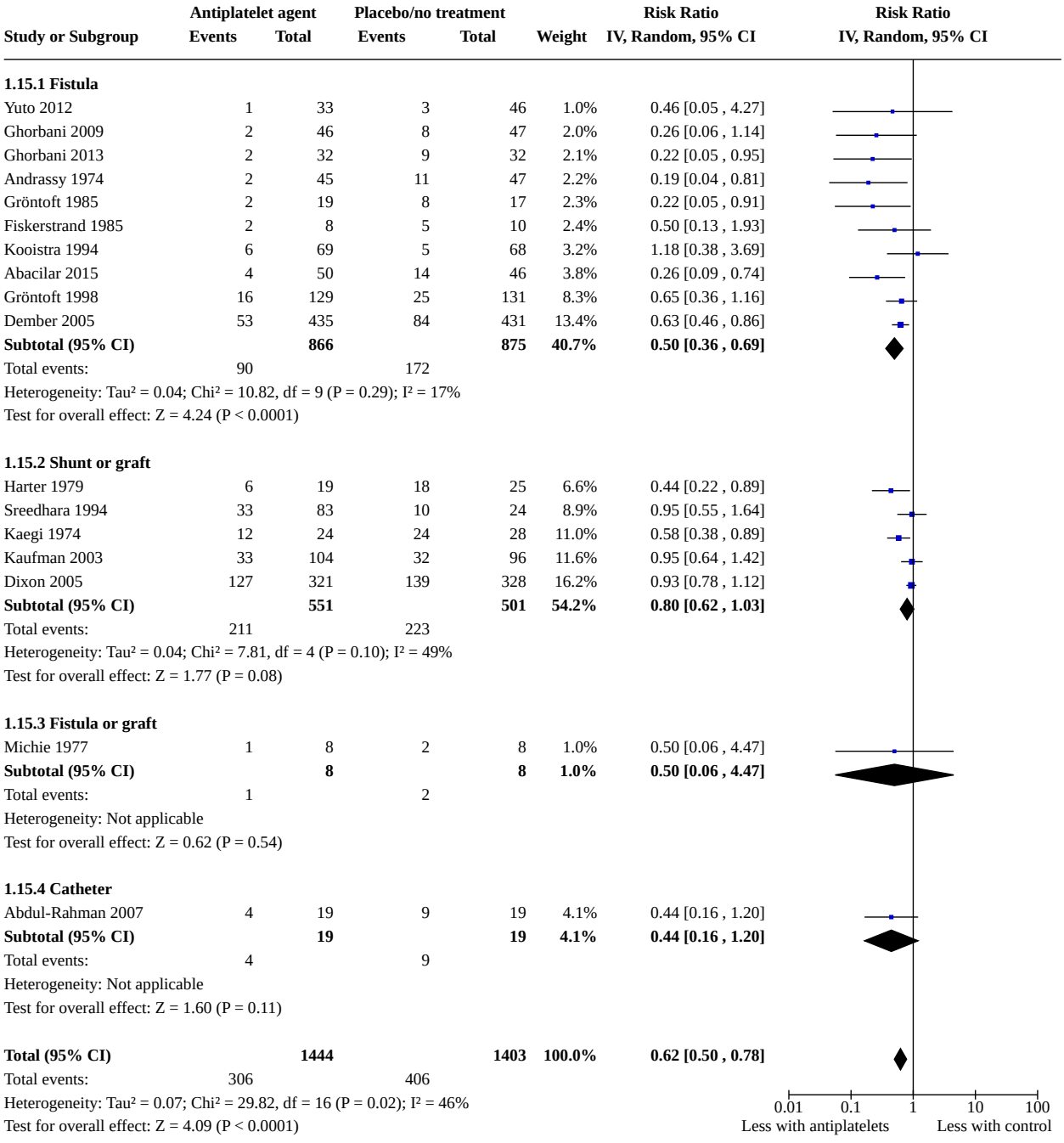
Heterogeneity: Tau² = 0.24; Chi² = 33.38, df = 2 (P < 0.00001); I² = 94%
Test for overall effect: Z = 2.36 (P = 0.02)

Total (95% CI)			**43**			**37**	**100.0%**	**-0.74 [-1.35 , -0.13]**

Heterogeneity: Tau² = 0.24; Chi² = 33.38, df = 2 (P < 0.00001); I² = 94%
Test for overall effect: Z = 2.36 (P = 0.02)
Test for subgroup differences: Not applicable



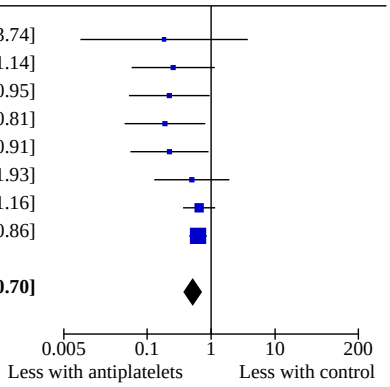
Analysis 1.15. Comparison 1: Antiplatelet agents versus control, Outcome 15: Dialysis access failure (thrombosis or loss of patency)



Analysis 1.16. Comparison 1: Antiplatelet agents versus control, Outcome 16: Early access thrombosis (before 8 weeks)

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Abacilar 2015	0	50	2	46	1.0%	0.18 [0.01 , 3.74]
Ghorbani 2009	2	46	8	47	4.1%	0.26 [0.06 , 1.14]
Ghorbani 2013	2	32	9	32	4.3%	0.22 [0.05 , 0.95]
Andrassy 1974	2	45	11	47	4.3%	0.19 [0.04 , 0.81]
Gröntoft 1985	2	19	8	17	4.6%	0.22 [0.05 , 0.91]
Fiskerstrand 1985	2	8	5	10	4.9%	0.50 [0.13 , 1.93]
Gröntoft 1998	16	129	25	131	22.9%	0.65 [0.36 , 1.16]
Dember 2005	53	435	84	431	53.9%	0.63 [0.46 , 0.86]
Total (95% CI)		**764**		**761**	**100.0%**	**0.52 [0.38 , 0.70]**
Total events:	79		152			

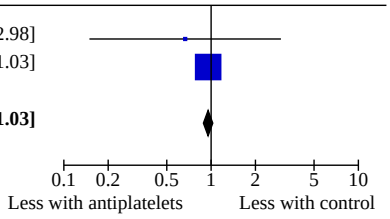
Heterogeneity: Tau² = 0.02; Chi² = 7.62, df = 7 (P = 0.37); I² = 8%
Test for overall effect: Z = 4.25 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1: Antiplatelet agents versus control, Outcome 17: Loss of primary unassisted patency

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Michie 1977	2	8	3	8	0.2%	0.67 [0.15 , 2.98]
Dixon 2005	256	321	274	328	99.8%	0.95 [0.89 , 1.03]
Total (95% CI)		**329**		**336**	**100.0%**	**0.95 [0.89 , 1.03]**
Total events:	258		277			

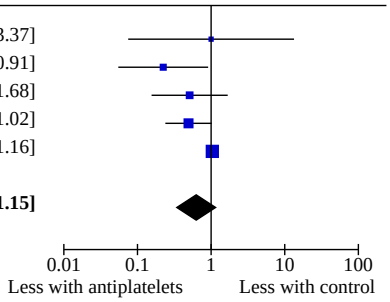
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.27 (P = 0.20)
Test for subgroup differences: Not applicable



Analysis 1.18. Comparison 1: Antiplatelet agents versus control, Outcome 18: Failure to attain suitability for dialysis

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Michie 1977	1	8	1	8	4.8%	1.00 [0.07 , 13.37]
Gröntoft 1985	2	19	8	17	12.8%	0.22 [0.05 , 0.91]
Dixon 2005	4	321	8	328	15.9%	0.51 [0.16 , 1.68]
Harter 1979	6	19	16	25	25.9%	0.49 [0.24 , 1.02]
Dember 2005	238	385	222	373	40.6%	1.04 [0.93 , 1.16]
Total (95% CI)		**752**		**751**	**100.0%**	**0.63 [0.34 , 1.15]**
Total events:	251		255			

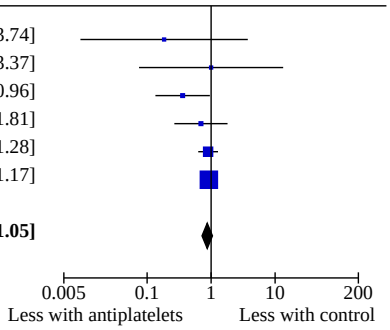
Heterogeneity: Tau² = 0.23; Chi² = 9.66, df = 4 (P = 0.05); I² = 59%
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1: Antiplatelet agents versus control, Outcome 19: Need for intervention to attain patency or assist maturation

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Abacilar 2015	0	50	2	46	0.4%	0.18 [0.01 , 3.74]
Michie 1977	1	8	1	8	0.5%	1.00 [0.07 , 13.37]
Kaegi 1974	4	24	13	28	3.7%	0.36 [0.13 , 0.96]
Dember 2005	7	435	10	431	3.8%	0.69 [0.27 , 1.81]
FAVOURED 2009	44	194	49	194	27.8%	0.90 [0.63 , 1.28]
Dixon 2005	93	321	103	328	63.8%	0.92 [0.73 , 1.17]
Total (95% CI)		**1032**		**1035**	**100.0%**	**0.87 [0.72 , 1.05]**
Total events:	149		178			

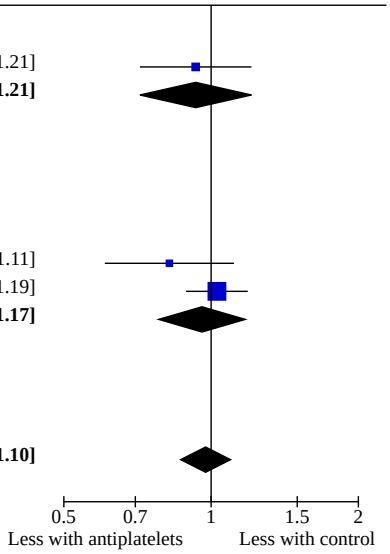
Heterogeneity: Tau² = 0.00; Chi² = 4.66, df = 5 (P = 0.46); I² = 0%
Test for overall effect: Z = 1.46 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1: Antiplatelet agents versus control, Outcome 20: Hospitalisation (any cause)

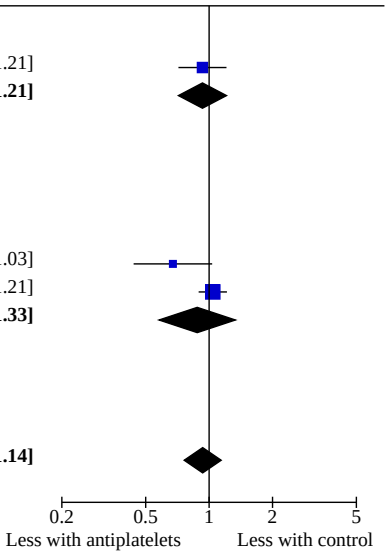
Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.20.1 CKD						
CHARISMA 2006	97	1006	104	1003	20.0%	0.93 [0.72 , 1.21]
Subtotal (95% CI)		**1006**		**1003**	**20.0%**	**0.93 [0.72 , 1.21]**
Total events:	97		104			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
1.20.2 HD						
Dember 2005	64	441	77	436	14.9%	0.82 [0.61 , 1.11]
Dixon 2005	172	321	171	328	65.1%	1.03 [0.89 , 1.19]
Subtotal (95% CI)		**762**		**764**	**80.0%**	**0.96 [0.78 , 1.17]**
Total events:	236		248			
Heterogeneity: Tau² = 0.01; Chi² = 1.69, df = 1 (P = 0.19); I² = 41%						
Test for overall effect: Z = 0.41 (P = 0.68)						
Total (95% CI)		**1768**		**1767**	**100.0%**	**0.97 [0.87 , 1.10]**
Total events:	333		352			

Heterogeneity: Tau² = 0.00; Chi² = 1.85, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%



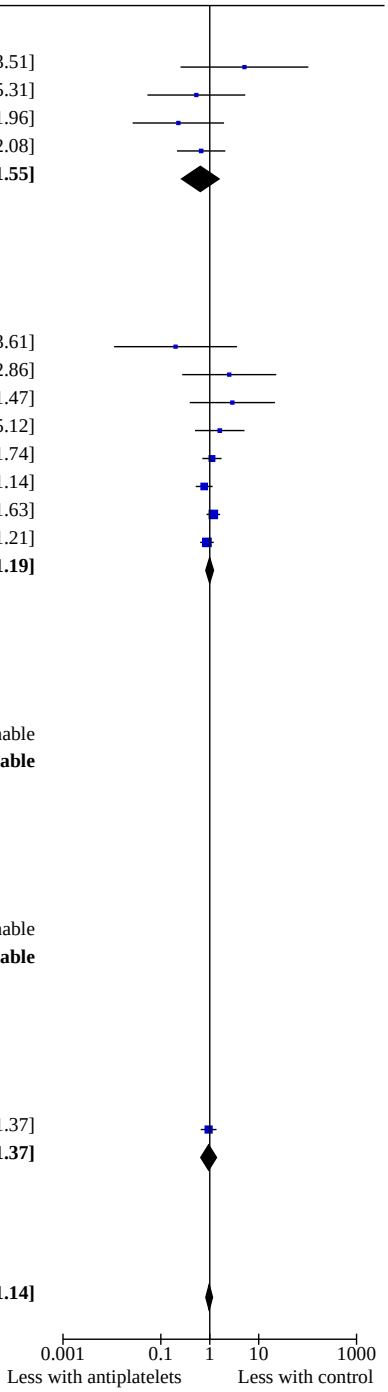
Analysis 1.21. Comparison 1: Antiplatelet agents versus control, Outcome 21: Cardiovascular hospitalisation

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.21.1 CKD						
CHARISMA 2006	97	1006	104	1003	32.5%	0.93 [0.72 , 1.21]
Subtotal (95% CI)		**1006**		**1003**	**32.5%**	**0.93 [0.72 , 1.21]**
Total events:	97		104			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
1.21.2 HD						
Dember 2005	32	441	47	436	16.9%	0.67 [0.44 , 1.03]
Dixon 2005	163	321	160	328	50.6%	1.04 [0.89 , 1.21]
Subtotal (95% CI)		**762**		**764**	**67.5%**	**0.88 [0.58 , 1.33]**
Total events:	195		207			
Heterogeneity: Tau² = 0.07; Chi² = 3.51, df = 1 (P = 0.06); I² = 71%						
Test for overall effect: Z = 0.61 (P = 0.54)						
Total (95% CI)		**1768**		**1767**	**100.0%**	**0.93 [0.76 , 1.14]**
Total events:	292		311			
Heterogeneity: Tau² = 0.01; Chi² = 3.68, df = 2 (P = 0.16); I² = 46%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%						



Analysis 1.22. Comparison 1: Antiplatelet agents versus control, Outcome 22: Treatment withdrawal

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.22.1 CKD						
Tang 2014	2	43	0	44	0.3%	5.11 [0.25 , 103.51]
Giustina 1998	1	16	2	17	0.5%	0.53 [0.05 , 5.31]
Cheng 1998a	1	19	3	13	0.5%	0.23 [0.03 , 1.96]
Donadio 1984	4	25	6	25	1.9%	0.67 [0.21 , 2.08]
Subtotal (95% CI)		**103**		**99**	**3.2%**	**0.64 [0.27 , 1.55]**
Total events:	8		11			
Heterogeneity: Tau² = 0.00; Chi² = 2.75, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.99 (P = 0.32)						
1.22.2 HD						
Michie 1977	0	8	2	8	0.3%	0.20 [0.01 , 3.61]
Fiskerstrand 1985	2	8	1	10	0.5%	2.50 [0.27 , 22.86]
Sreedhara 1994	10	83	1	24	0.6%	2.89 [0.39 , 21.47]
Kaegi 1974	6	30	4	32	1.8%	1.60 [0.50 , 5.12]
Dember 2005	37	441	33	436	12.1%	1.11 [0.71 , 1.74]
Kaufman 2003	30	104	36	96	15.5%	0.77 [0.52 , 1.14]
Dixon 2005	66	321	57	328	24.0%	1.18 [0.86 , 1.63]
Harter 1979	14	19	21	25	24.1%	0.88 [0.64 , 1.21]
Subtotal (95% CI)		**1014**		**959**	**78.9%**	**0.99 [0.83 , 1.19]**
Total events:	165		155			
Heterogeneity: Tau² = 0.00; Chi² = 7.14, df = 7 (P = 0.41); I² = 2%						
Test for overall effect: Z = 0.06 (P = 0.95)						
1.22.3 PD						
Rubin 1982	0	5	0	5		Not estimable
Subtotal (95% CI)		**5**		**5**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.22.4 Transplant						
Quarto Di Palo 1991	0	18	0	18		Not estimable
Subtotal (95% CI)		**18**		**18**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.22.5 CKD, dialysis and transplant						
UK-HARP-I 2005	44	225	46	223	17.9%	0.95 [0.66 , 1.37]
Subtotal (95% CI)		**225**		**223**	**17.9%**	**0.95 [0.66 , 1.37]**
Total events:	44		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
Total (95% CI)		**1365**		**1304**	**100.0%**	**0.97 [0.83 , 1.14]**
Total events:	217		212			
Heterogeneity: Tau² = 0.00; Chi² = 10.83, df = 12 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.72)						
Test for subgroup differences: Chi² = 0.94, df = 2 (P = 0.63), I² = 0%						

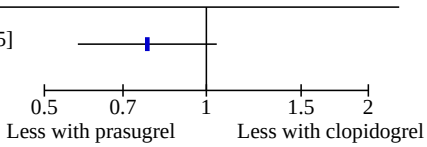


Comparison 2. Prasugrel versus clopidogrel

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Fatal or nonfatal myocardial infarction	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2.2 Death (any cause)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2.3 Cardiovascular death	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2.4 Major bleeding	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2.5 Minor bleeding	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

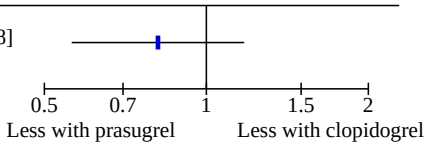
Analysis 2.1. Comparison 2: Prasugrel versus clopidogrel, Outcome 1: Fatal or nonfatal myocardial infarction

Study or Subgroup	Prasugrel Events	Prasugrel Total	Clopidogrel Events	Clopidogrel Total	Risk Ratio IV, Random, 95% CI
TRITON-TIMI 38 2006	67	717	93	773	0.78 [0.58 , 1.05]



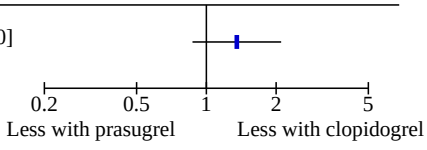
Analysis 2.2. Comparison 2: Prasugrel versus clopidogrel, Outcome 2: Death (any cause)

Study or Subgroup	Prasugrel Events	Prasugrel Total	Clopidogrel Events	Clopidogrel Total	Risk Ratio IV, Random, 95% CI
TRITON-TIMI 38 2006	46	717	61	773	0.81 [0.56 , 1.18]



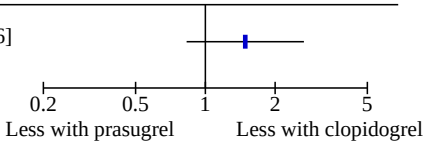
Analysis 2.3. Comparison 2: Prasugrel versus clopidogrel, Outcome 3: Cardiovascular death

Study or Subgroup	Prasugrel Events	Prasugrel Total	Clopidogrel Events	Clopidogrel Total	Risk Ratio IV, Random, 95% CI
TRITON-TIMI 38 2006	42	701	34	768	1.35 [0.87 , 2.10]



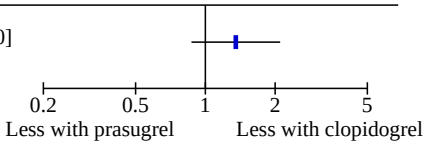
Analysis 2.4. Comparison 2: Prasugrel versus clopidogrel, Outcome 4: Major bleeding

Study or Subgroup	Prasugrel Events	Prasugrel Total	Clopidogrel Events	Clopidogrel Total	Risk Ratio IV, Random, 95% CI
TRITON-TIMI 38 2006	26	707	19	768	1.49 [0.83 , 2.66]



Analysis 2.5. Comparison 2: Prasugrel versus clopidogrel, Outcome 5: Minor bleeding

Study or Subgroup	Prasugrel Events	Prasugrel Total	Clopidogrel Events	Clopidogrel Total	Risk Ratio IV, Random, 95% CI
TRITON-TIMI 38 2006	42	701	34	768	1.35 [0.87 , 2.10]



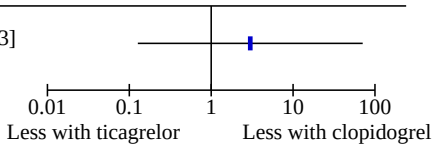
Comparison 3. Ticagrelor versus clopidogrel

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Fatal or nonfatal myocardial infarction	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3.2 Fatal or nonfatal stroke	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3.3 Death (any cause)	3	137	Risk Ratio (IV, Random, 95% CI)	2.00 [0.19, 20.90]
3.3.1 CKD	1	60	Risk Ratio (IV, Random, 95% CI)	2.00 [0.19, 20.90]
3.3.2 HD	2	77	Risk Ratio (IV, Random, 95% CI)	Not estimable
3.4 Cardiovascular death	3	137	Risk Ratio (IV, Random, 95% CI)	5.00 [0.25, 99.95]
3.4.1 CKD	1	60	Risk Ratio (IV, Random, 95% CI)	5.00 [0.25, 99.95]
3.4.2 HD	2	77	Risk Ratio (IV, Random, 95% CI)	Not estimable
3.5 Fatal bleeding	2	77	Risk Ratio (IV, Random, 95% CI)	Not estimable
3.5.1 HD	2	77	Risk Ratio (IV, Random, 95% CI)	Not estimable
3.6 Major bleeding	2	85	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.87]
3.6.1 CKD	1	60	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 7.87]
3.6.2 HD	1	25	Risk Ratio (IV, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.7 Minor bleeding	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3.8 Treatment withdrawal	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

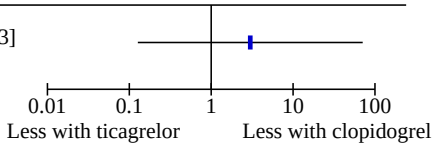
Analysis 3.1. Comparison 3: Ticagrelor versus clopidogrel, Outcome 1: Fatal or nonfatal myocardial infarction

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Clopidrogrel Events	Clopidrogrel Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
OPT-CKD 2018	1	30	0	30	3.00 [0.13 , 70.83]	



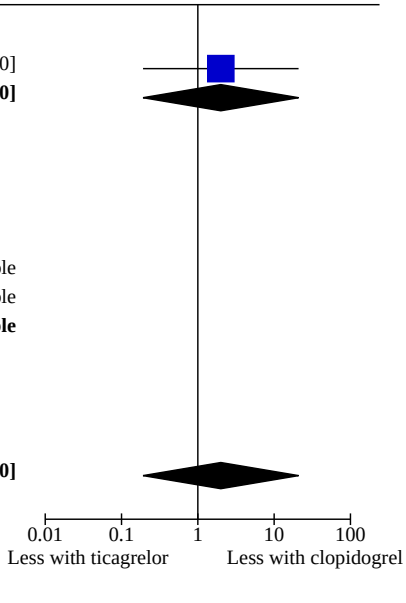
Analysis 3.2. Comparison 3: Ticagrelor versus clopidogrel, Outcome 2: Fatal or nonfatal stroke

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Clopidrogrel Events	Clopidrogrel Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
OPT-CKD 2018	1	30	0	30	3.00 [0.13 , 70.83]	



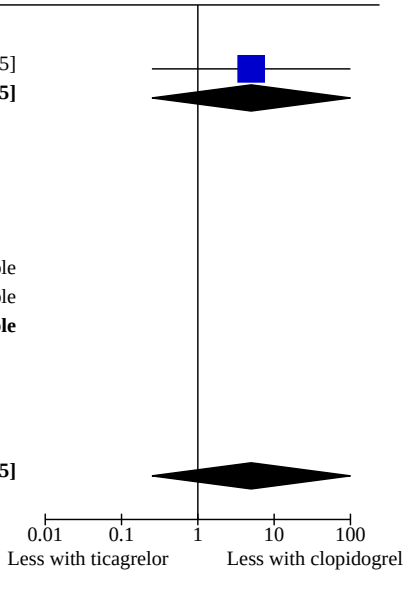
Analysis 3.3. Comparison 3: Ticagrelor versus clopidogrel, Outcome 3: Death (any cause)

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Clopidrogrel Events	Clopidrogrel Total	Weight	Risk Ratio IV, Random, 95% CI
3.3.1 CKD						
OPT-CKD 2018	2	30	1	30	100.0%	2.00 [0.19 , 20.90]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**2.00 [0.19 , 20.90]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
3.3.2 HD						
PIANO-3 2015	0	12	0	13		Not estimable
PIANO-6 2017	0	34	0	18		Not estimable
Subtotal (95% CI)		**46**		**31**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**76**		**61**	**100.0%**	**2.00 [0.19 , 20.90]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
Test for subgroup differences: Not applicable						



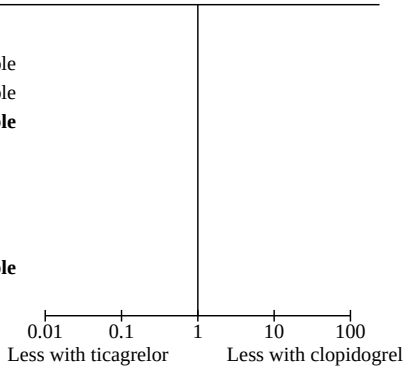
Analysis 3.4. Comparison 3: Ticagrelor versus clopidogrel, Outcome 4: Cardiovascular death

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Clopidrogrel Events	Clopidrogrel Total	Weight	Risk Ratio IV, Random, 95% CI
3.4.1 CKD						
OPT-CKD 2018	2	30	0	30	100.0%	5.00 [0.25 , 99.95]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**5.00 [0.25 , 99.95]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
3.4.2 HD						
PIANO-6 2017	0	34	0	18		Not estimable
PIANO-3 2015	0	12	0	13		Not estimable
Subtotal (95% CI)		**46**		**31**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**76**		**61**	**100.0%**	**5.00 [0.25 , 99.95]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
Test for subgroup differences: Not applicable						



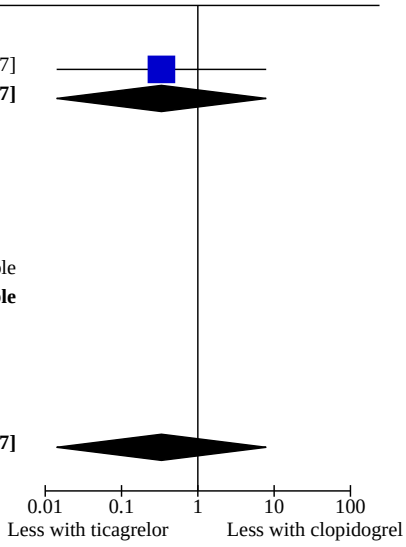
Analysis 3.5. Comparison 3: Ticagrelor versus clopidogrel, Outcome 5: Fatal bleeding

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Clopidrogrel Events	Clopidrogrel Total	Weight	Risk Ratio IV, Random, 95% CI
3.5.1 HD						
PIANO-6 2017	0	34	0	18		Not estimable
PIANO-3 2015	0	12	0	13		Not estimable
Subtotal (95% CI)		**46**		**31**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**46**		**31**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



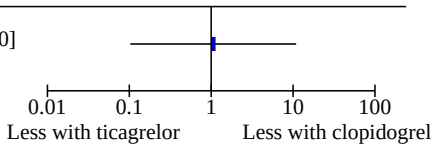
Analysis 3.6. Comparison 3: Ticagrelor versus clopidogrel, Outcome 6: Major bleeding

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Clopidrogrel Events	Clopidrogrel Total	Weight	Risk Ratio IV, Random, 95% CI
3.6.1 CKD						
OPT-CKD 2018	0	30	1	30	100.0%	0.33 [0.01 , 7.87]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**0.33 [0.01 , 7.87]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
3.6.2 HD						
PIANO-3 2015	0	12	0	13		Not estimable
Subtotal (95% CI)		**12**		**13**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**42**		**43**	**100.0%**	**0.33 [0.01 , 7.87]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Not applicable						



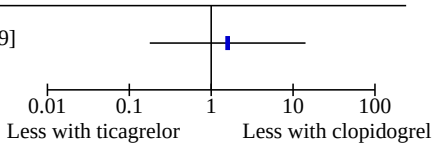
Analysis 3.7. Comparison 3: Ticagrelor versus clopidogrel, Outcome 7: Minor bleeding

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Clopidrogrel Events	Clopidrogrel Total	Risk Ratio IV, Random, 95% CI
PIANO-6 2017	2	34	1	18	1.06 [0.10 , 10.90]



Analysis 3.8. Comparison 3: Ticagrelor versus clopidogrel, Outcome 8: Treatment withdrawal

Study or Subgroup	Ticagrelor Events	Ticagrelor Total	Clopidrogrel Events	Clopidrogrel Total	Risk Ratio IV, Random, 95% CI
PIANO-6 2017	3	34	1	18	1.59 [0.18 , 14.19]

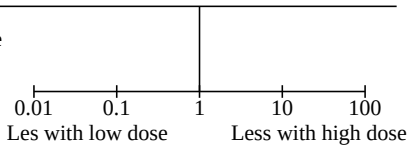


Comparison 4. Clopidogrel (low dose) versus clopidogrel (high dose)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Haemorragic stroke	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4.2 Cardiovascular death	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

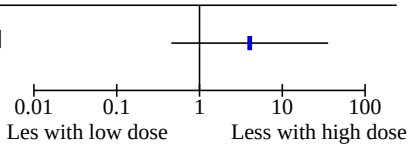
Analysis 4.1. Comparison 4: Clopidogrel (low dose) versus clopidogrel (high dose), Outcome 1: Haemorragic stroke

Study or Subgroup	Low dose Events	Low dose Total	High dose Events	High dose Total	Risk Ratio IV, Random, 95% CI
Liang 2015	0	184	0	186	Not estimable



Analysis 4.2. Comparison 4: Clopidogrel (low dose) versus clopidogrel (high dose), Outcome 2: Cardiovascular death

Study or Subgroup	Low dose Events	Low dose Total	High dose Events	High dose Total	Risk Ratio IV, Random, 95% CI
Liang 2015	4	184	1	186	4.04 [0.46 , 35.83]



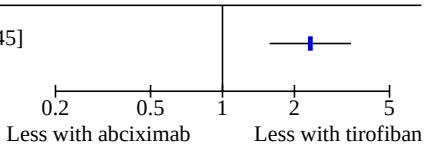
Comparison 5. Abciximab versus tirofiban

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Fatal or nonfatal myocardial infarction	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Death (any cause)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

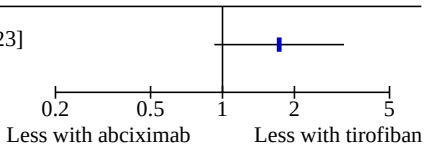
Analysis 5.1. Comparison 5: Abciximab versus tirofiban, Outcome 1: Fatal or nonfatal myocardial infarction

Study or Subgroup	Abciximab Events	Abciximab Total	Tirofiban Events	Tirofiban Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
TARGET 2000	72	388	32	402	2.33 [1.57 , 3.45]	



Analysis 5.2. Comparison 5: Abciximab versus tirofiban, Outcome 2: Death (any cause)

Study or Subgroup	Abciximab Events	Abciximab Total	Tirofiban Events	Tirofiban Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
TARGET 2000	25	388	15	402	1.73 [0.92 , 3.23]	

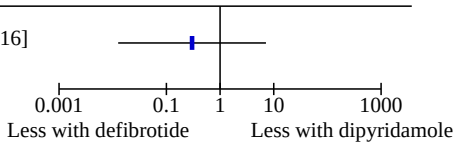


Comparison 6. Defibrotide versus dypiridamole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Death (any cause)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6.2 Cardiovascular death	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6.3 Fatal bleeding	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6.4 Kidney transplant graft loss	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

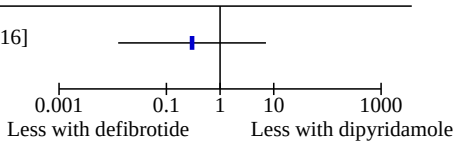
Analysis 6.1. Comparison 6: Defibrotide versus dypiridamole, Outcome 1: Death (any cause)

Study or Subgroup	Defibrotide Events	Defibrotide Total	Dipyridamole Events	Dipyridamole Total	Risk Ratio IV, Random, 95% CI
Frascà 1986	0	40	1	36	0.30 [0.01 , 7.16]



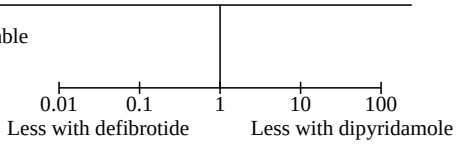
Analysis 6.2. Comparison 6: Defibrotide versus dypiridamole, Outcome 2: Cardiovascular death

Study or Subgroup	Defibrotide Events	Defibrotide Total	Dipyridamole Events	Dipyridamole Total	Risk Ratio IV, Random, 95% CI
Frascà 1986	0	40	1	36	0.30 [0.01 , 7.16]



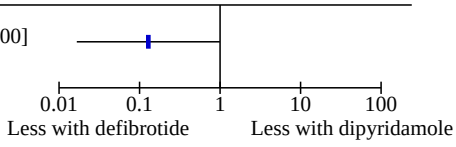
Analysis 6.3. Comparison 6: Defibrotide versus dypiridamole, Outcome 3: Fatal bleeding

Study or Subgroup	Defibrotide Events	Defibrotide Total	Dipyridamole Events	Dipyridamole Total	Risk Ratio IV, Random, 95% CI
Frascà 1986	0	40	0	36	Not estimable



Analysis 6.4. Comparison 6: Defibrotide versus dypiridamole, Outcome 4: Kidney transplant graft loss

Study or Subgroup	Defibrotide Events	Defibrotide Total	Dipyridamole Events	Dipyridamole Total	Risk Ratio IV, Random, 95% CI
Frascà 1986	1	40	7	36	0.13 [0.02 , 1.00]

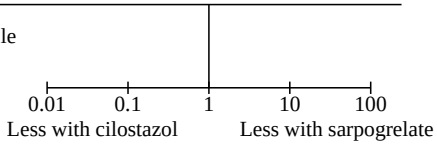


Comparison 7. Cilostazol versus sarpogrelate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Major bleeding	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7: Cilostazol versus sarpogrelate, Outcome 1: Major bleeding

Study or Subgroup	Cilostazol Events	Cilostazol Total	Sarpogrelate Events	Sarpogrelate Total	Risk Ratio IV, Random, 95% CI
Hidaka 2013	0	17	0	18	Not estimable

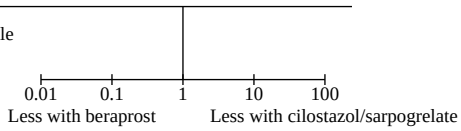


Comparison 8. Beraprost versus cilostazol or sarpogrelate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Fatal or nonfatal myocardial infarction	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8.2 Fatal or nonfatal stroke	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8.3 Death (any cause)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8.4 Cardiovascular death	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8.5 Fatal bleeding	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

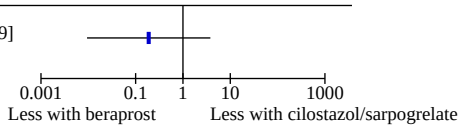
Analysis 8.1. Comparison 8: Beraprost versus cilostazol or sarpogrelate, Outcome 1: Fatal or nonfatal myocardial infarction

Study or Subgroup	Beraprost Events	Beraprost Total	Cilostazol/sarpogrelate Events	Cilostazol/sarpogrelate Total	Risk Ratio IV, Random, 95% CI
J-PADD 2014	0	35	0	33	Not estimable



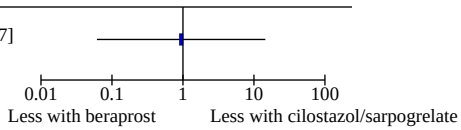
Analysis 8.2. Comparison 8: Beraprost versus cilostazol or sarpogrelate, Outcome 2: Fatal or nonfatal stroke

Study or Subgroup	Beraprost Events	Beraprost Total	Cilostazol/sarpogrelate Events	Cilostazol/sarpogrelate Total	Risk Ratio IV, Random, 95% CI
J-PADD 2014	0	35	2	33	0.19 [0.01 , 3.79]



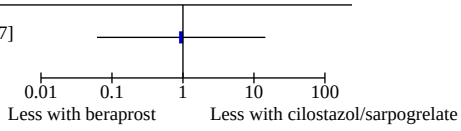
Analysis 8.3. Comparison 8: Beraprost versus cilostazol or sarpogrelate, Outcome 3: Death (any cause)

Study or Subgroup	Beraprost Events	Beraprost Total	Cilostazol/sarpogrelate Events	Cilostazol/sarpogrelate Total	Risk Ratio IV, Random, 95% CI
J-PADD 2014	1	35	1	33	0.94 [0.06 , 14.47]



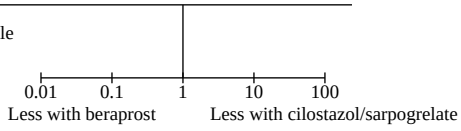
Analysis 8.4. Comparison 8: Beraprost versus cilostazol or sarpogrelate, Outcome 4: Cardiovascular death

Study or Subgroup	Beraprost Events	Beraprost Total	Cilostazol/sarpogrelate Events	Cilostazol/sarpogrelate Total	Risk Ratio IV, Random, 95% CI
J-PADD 2014	1	35	1	33	0.94 [0.06 , 14.47]



Analysis 8.5. Comparison 8: Beraprost versus cilostazol or sarpogrelate, Outcome 5: Fatal bleeding

Study or Subgroup	Beraprost Events	Beraprost Total	Cilostazol/sarpogrelate Events	Cilostazol/sarpogrelate Total	Risk Ratio IV, Random, 95% CI
J-PADD 2014	0	35	0	33	Not estimable



Comparison 9. Primary/secondary prevention for fatal/non fatal myocardial infarction (subgroup analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Secondary prevention	8		Risk Ratio (IV, Random, 95% CI)	Subtotals only
9.1.1 CKD	8	7270	Risk Ratio (IV, Random, 95% CI)	0.93 [0.81, 1.06]

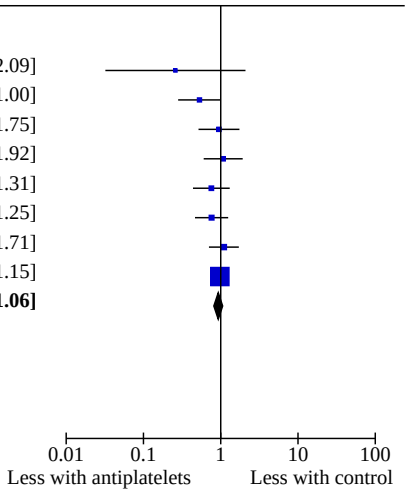
Analysis 9.1. Comparison 9: Primary/secondary prevention for fatal/non fatal myocardial infarction (subgroup analysis), Outcome 1: Secondary prevention

Study or Subgroup	Antiplatelet agent Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
9.1.1 CKD						
RAPPORT 1998	1	27	5	35	0.4%	0.26 [0.03 , 2.09]
EPILOG 1997	18	325	17	163	4.3%	0.53 [0.28 , 1.00]
EPISTENT 1998	24	231	15	137	4.6%	0.95 [0.52 , 1.75]
CREDO 2005	21	203	20	208	5.1%	1.08 [0.60 , 1.92]
CHARISMA 2006	22	1006	29	1003	5.7%	0.76 [0.44 , 1.31]
EPIC 1994	33	334	24	185	7.0%	0.76 [0.46 , 1.25]
IMPACT II 1997	58	547	25	259	8.7%	1.10 [0.70 , 1.71]
PURSUIT 1997	256	1430	216	1177	64.1%	0.98 [0.83 , 1.15]
Subtotal (95% CI)		**4103**		**3167**	**100.0%**	**0.93 [0.81 , 1.06]**
Total events:	433		351			

Heterogeneity: Tau² = 0.00; Chi² = 6.71, df = 7 (P = 0.46); I² = 0%

Test for overall effect: Z = 1.11 (P = 0.27)

Test for subgroup differences: Not applicable



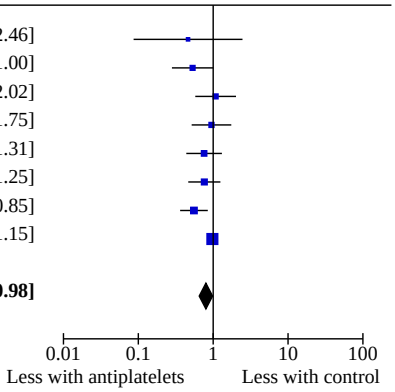
Comparison 10. Sensitivity analysis (adequate allocation concealment)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Fatal or nonfatal myocardial infarction	8	10459	Risk Ratio (IV, Random, 95% CI)	0.80 [0.65, 0.98]
10.2 Death (any cause)	10	11443	Risk Ratio (IV, Random, 95% CI)	1.00 [0.83, 1.22]
10.3 Cardiovascular death	2	5628	Risk Ratio (IV, Random, 95% CI)	1.08 [0.48, 2.44]
10.4 Major bleeding	9	10360	Risk Ratio (IV, Random, 95% CI)	1.53 [1.07, 2.20]

Analysis 10.1. Comparison 10: Sensitivity analysis (adequate allocation concealment), Outcome 1: Fatal or nonfatal myocardial infarction

Study or Subgroup	Antiplatelets Events	Antiplatelets Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Risk Ratio IV, Random, 95% CI
Kaufman 2003	2	104	4	96	1.4%	0.46 [0.09 , 2.46]
EPILOG 1997	18	325	17	163	8.4%	0.53 [0.28 , 1.00]
Dixon 2005	19	321	18	328	8.6%	1.08 [0.58 , 2.02]
EPISTENT 1998	24	231	15	137	9.0%	0.95 [0.52 , 1.75]
CHARISMA 2006	22	1006	29	1003	10.6%	0.76 [0.44 , 1.31]
EPIC 1994	33	334	24	185	12.4%	0.76 [0.46 , 1.25]
HOT 1993	32	1791	59	1828	15.2%	0.55 [0.36 , 0.85]
PURSUIT 1997	256	1430	216	1177	34.4%	0.98 [0.83 , 1.15]
Total (95% CI)		**5542**		**4917**	**100.0%**	**0.80 [0.65 , 0.98]**
Total events:	406		382			

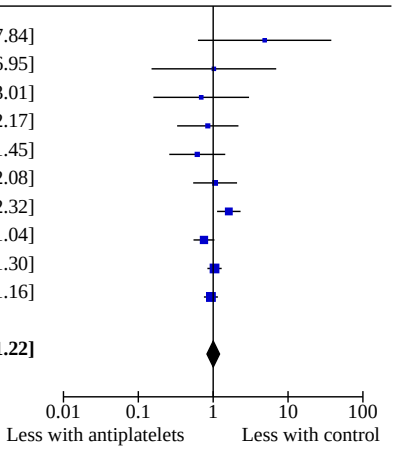
Heterogeneity: Tau² = 0.02; Chi² = 10.14, df = 7 (P = 0.18); I² = 31%
Test for overall effect: Z = 2.15 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 10.2. Comparison 10: Sensitivity analysis (adequate allocation concealment), Outcome 2: Death (any cause)

Study or Subgroup	Antiplatelets Events	Antiplatelets Total	Placebo/no treatment Events	Placebo/no treatment Total	Weight	Risk Ratio IV, Random, 95% CI
CASSIOPEIR 2014	10	600	1	292	0.9%	4.87 [0.63 , 37.84]
Ghorbani 2009	2	46	2	47	1.0%	1.02 [0.15 , 6.95]
Kaufman 2003	3	104	4	96	1.6%	0.69 [0.16 , 3.01]
EPISTENT 1998	10	231	7	137	3.7%	0.85 [0.33 , 2.17]
EPILOG 1997	11	325	9	163	4.4%	0.61 [0.26 , 1.45]
EPIC 1994	23	334	12	185	6.6%	1.06 [0.54 , 2.08]
CHARISMA 2006	73	1006	45	1003	15.7%	1.62 [1.13 , 2.32]
HOT 1993	62	1791	84	1828	17.7%	0.75 [0.55 , 1.04]
PURSUIT 1997	161	1430	127	1176	24.0%	1.04 [0.84 , 1.30]
Dixon 2005	105	321	115	328	24.3%	0.93 [0.75 , 1.16]
Total (95% CI)		**6188**		**5255**	**100.0%**	**1.00 [0.83 , 1.22]**
Total events:	460		406			

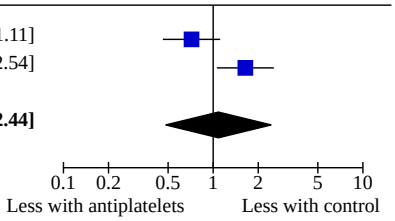
Heterogeneity: Tau² = 0.03; Chi² = 14.25, df = 9 (P = 0.11); I² = 37%
Test for overall effect: Z = 0.03 (P = 0.98)
Test for subgroup differences: Not applicable



Analysis 10.3. Comparison 10: Sensitivity analysis (adequate allocation concealment), Outcome 3: Cardiovascular death

Study or Subgroup	Antiplatelets Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
HOT 1993	33	1791	47	1828	50.0%	0.72 [0.46 , 1.11]
CHARISMA 2006	51	1006	31	1003	50.0%	1.64 [1.06 , 2.54]
Total (95% CI)		**2797**		**2831**	**100.0%**	**1.08 [0.48 , 2.44]**
Total events:	84		78			

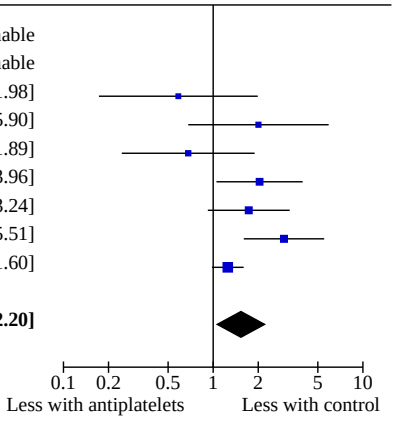
Heterogeneity: Tau² = 0.29; Chi² = 6.83, df = 1 (P = 0.009); I² = 85%
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable



Analysis 10.4. Comparison 10: Sensitivity analysis (adequate allocation concealment), Outcome 4: Major bleeding

Study or Subgroup	Antiplatelets Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Ghorbani 2013	0	32	0	32		Not estimable
Ghorbani 2009	0	46	0	47		Not estimable
EPISTENT 1998	5	229	5	134	6.9%	0.59 [0.17 , 1.98]
EPILOG 1997	16	325	4	163	8.3%	2.01 [0.68 , 5.90]
Dixon 2005	6	321	9	328	9.0%	0.68 [0.25 , 1.89]
HOT 1993	26	1791	13	1828	15.4%	2.04 [1.05 , 3.96]
CHARISMA 2006	26	1006	15	1003	16.2%	1.73 [0.92 , 3.24]
EPIC 1994	59	334	11	185	16.5%	2.97 [1.60 , 5.51]
PURSUIT 1997	148	1404	97	1152	27.6%	1.25 [0.98 , 1.60]
Total (95% CI)		**5488**		**4872**	**100.0%**	**1.53 [1.07 , 2.20]**
Total events:	286		154			

Heterogeneity: Tau² = 0.11; Chi² = 12.43, df = 6 (P = 0.05); I² = 52%
Test for overall effect: Z = 2.30 (P = 0.02)
Test for subgroup differences: Not applicable



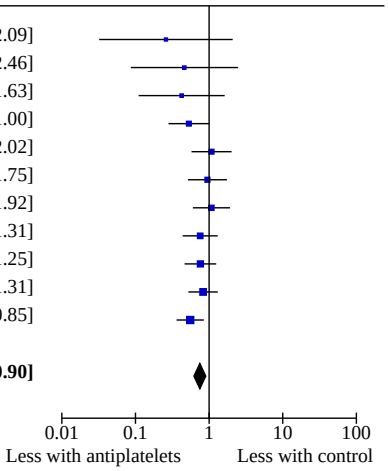
Comparison 11. Sensitivity analysis (low risk of attrition)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Fatal or nonfatal myocardial infarction	11	9387	Risk Ratio (IV, Random, 95% CI)	0.75 [0.62, 0.90]
11.2 Death (any cause)	19	10966	Risk Ratio (IV, Random, 95% CI)	0.99 [0.82, 1.20]
11.3 Cardiovascular death	11	6872	Risk Ratio (IV, Random, 95% CI)	0.94 [0.60, 1.47]
11.4 Major bleeding	17	9549	Risk Ratio (IV, Random, 95% CI)	1.62 [1.19, 2.20]

Analysis 11.1. Comparison 11: Sensitivity analysis (low risk of attrition), Outcome 1: Fatal or nonfatal myocardial infarction

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
RAPPORT 1998	1	27	5	35	0.8%	0.26 [0.03 , 2.09]
Kaufman 2003	2	104	4	96	1.2%	0.46 [0.09 , 2.46]
Dember 2005	3	441	7	436	1.9%	0.42 [0.11 , 1.63]
EPILOG 1997	18	325	17	163	8.4%	0.53 [0.28 , 1.00]
Dixon 2005	19	321	18	328	8.6%	1.08 [0.58 , 2.02]
EPISTENT 1998	24	231	15	137	9.1%	0.95 [0.52 , 1.75]
CREDO 2005	21	203	20	208	10.0%	1.08 [0.60 , 1.92]
CHARISMA 2006	22	1006	29	1003	11.3%	0.76 [0.44 , 1.31]
EPIC 1994	33	334	24	185	13.9%	0.76 [0.46 , 1.25]
ETDRS 1992	21	79	34	106	16.1%	0.83 [0.52 , 1.31]
HOT 1993	32	1791	59	1828	18.7%	0.55 [0.36 , 0.85]
Total (95% CI)		**4862**		**4525**	**100.0%**	**0.75 [0.62 , 0.90]**
Total events:	196		232			

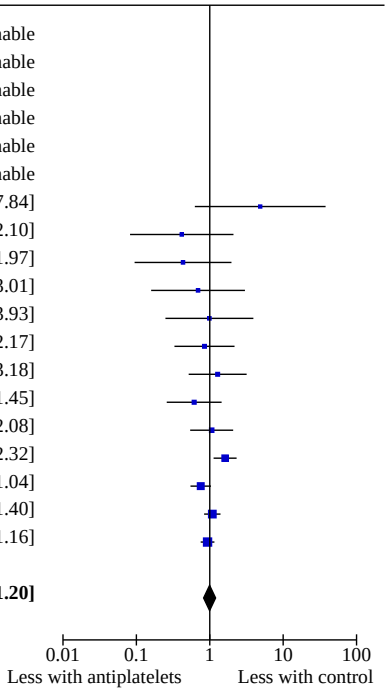
Heterogeneity: Tau² = 0.00; Chi² = 8.63, df = 10 (P = 0.57); I² = 0%
Test for overall effect: Z = 3.09 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 11.2. Comparison 11: Sensitivity analysis (low risk of attrition), Outcome 2: Death (any cause)

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Khajehdehi 2002	0	57	0	19		Not estimable
Zäuner 1994	0	10	0	8		Not estimable
Quarto Di Palo 1991	0	18	0	18		Not estimable
Abacilar 2015	0	50	0	46		Not estimable
Tang 2014	0	43	0	44		Not estimable
Kobayashi 1980	0	50	0	57		Not estimable
CASSIOPEIR 2014	10	600	1	292	0.8%	4.87 [0.63 , 37.84]
Gröntoft 1998	2	131	5	136	1.3%	0.42 [0.08 , 2.10]
RAPPORT 1998	2	27	6	35	1.5%	0.43 [0.09 , 1.97]
Kaufman 2003	3	104	4	96	1.5%	0.69 [0.16 , 3.01]
Dember 2005	4	441	4	436	1.7%	0.99 [0.25 , 3.93]
EPISTENT 1998	10	231	7	137	3.5%	0.85 [0.33 , 2.17]
CREDO 2005	10	203	8	208	3.8%	1.28 [0.52 , 3.18]
EPILOG 1997	11	325	9	163	4.1%	0.61 [0.26 , 1.45]
EPIC 1994	23	334	12	185	6.3%	1.06 [0.54 , 2.08]
CHARISMA 2006	73	1006	45	1003	14.9%	1.62 [1.13 , 2.32]
HOT 1993	62	1791	84	1828	16.8%	0.75 [0.55 , 1.04]
ETDRS 1992	46	79	57	106	20.5%	1.08 [0.84 , 1.40]
Dixon 2005	105	321	115	328	23.2%	0.93 [0.75 , 1.16]
Total (95% CI)		**5821**		**5145**	**100.0%**	**0.99 [0.82 , 1.20]**
Total events:	361		357			

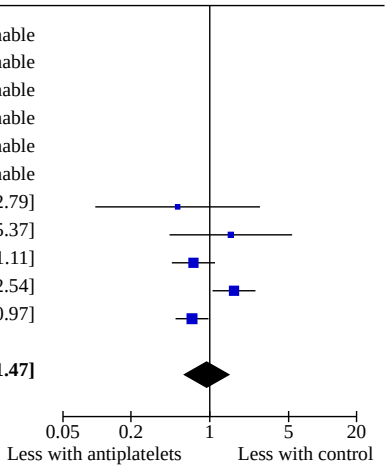
Heterogeneity: Tau² = 0.03; Chi² = 17.06, df = 12 (P = 0.15); I² = 30%
Test for overall effect: Z = 0.06 (P = 0.96)
Test for subgroup differences: Not applicable



Analysis 11.3. Comparison 11: Sensitivity analysis (low risk of attrition), Outcome 3: Cardiovascular death

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Kobayashi 1980	0	50	0	57		Not estimable
Zäuner 1994	0	10	0	8		Not estimable
Tang 2014	0	43	0	44		Not estimable
Quarto Di Palo 1991	0	18	0	18		Not estimable
Khajehdehi 2002	0	57	0	19		Not estimable
Abacilar 2015	0	50	0	46		Not estimable
Gröntoft 1998	2	131	4	136	6.0%	0.52 [0.10 , 2.79]
CREDO 2005	6	203	4	208	9.6%	1.54 [0.44 , 5.37]
HOT 1993	33	1791	47	1828	27.0%	0.72 [0.46 , 1.11]
CHARISMA 2006	51	1006	31	1003	27.1%	1.64 [1.06 , 2.54]
ETDRS 1992	32	79	39	67	30.3%	0.70 [0.50 , 0.97]
Total (95% CI)		**3438**		**3434**	**100.0%**	**0.94 [0.60 , 1.47]**
Total events:	124		125			

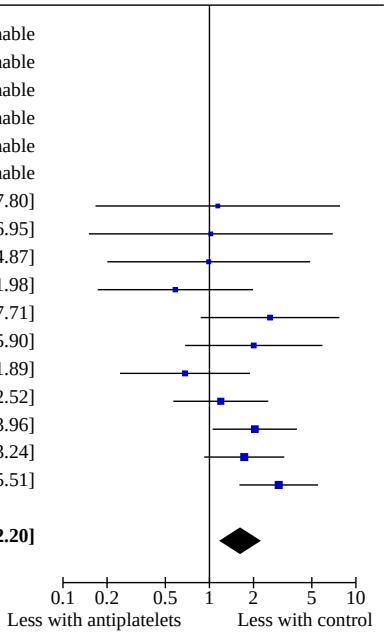
Heterogeneity: Tau² = 0.15; Chi² = 11.62, df = 4 (P = 0.02); I² = 66%
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable



Analysis 11.4. Comparison 11: Sensitivity analysis (low risk of attrition), Outcome 4: Major bleeding

Study or Subgroup	Antiplatelet agent Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Quarto Di Palo 1991	0	18	0	18		Not estimable
Khajehdehi 2002	0	57	0	19		Not estimable
Abdul-Rahman 2007	0	19	0	19		Not estimable
Ghorbani 2013	0	32	0	32		Not estimable
Kamper 1997	0	13	0	14		Not estimable
AASER 2017	0	50	0	61		Not estimable
Kobayashi 1980	2	50	2	57	2.5%	1.14 [0.17 , 7.80]
Andrassy 1974	2	46	2	47	2.5%	1.02 [0.15 , 6.95]
Dember 2005	3	441	3	436	3.5%	0.99 [0.20 , 4.87]
EPISTENT 1998	5	229	5	134	5.7%	0.59 [0.17 , 1.98]
RAPPORT 1998	8	27	4	35	7.0%	2.59 [0.87 , 7.71]
EPILOG 1997	16	325	4	163	7.2%	2.01 [0.68 , 5.90]
Dixon 2005	6	321	9	328	7.9%	0.68 [0.25 , 1.89]
CREDO 2005	14	203	12	208	13.2%	1.20 [0.57 , 2.52]
HOT 1993	26	1791	13	1828	15.9%	2.04 [1.05 , 3.96]
CHARISMA 2006	26	1006	15	1003	17.1%	1.73 [0.92 , 3.24]
EPIC 1994	59	334	11	185	17.6%	2.97 [1.60 , 5.51]
Total (95% CI)		**4962**		**4587**	**100.0%**	**1.62 [1.19 , 2.20]**
Total events:	167		80			

Heterogeneity: Tau² = 0.04; Chi² = 11.82, df = 10 (P = 0.30); I² = 15%
Test for overall effect: Z = 3.07 (P = 0.002)
Test for subgroup differences: Not applicable



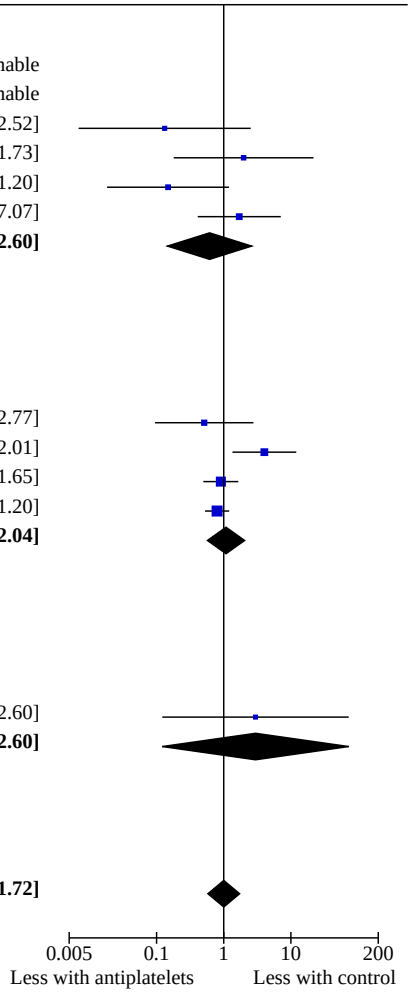
Comparison 12. Stroke (subgroup analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Stage of CKD	11	9544	Risk Ratio (IV, Random, 95% CI)	1.00 [0.58, 1.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1.1 HD	6	2872	Risk Ratio (IV, Random, 95% CI)	0.62 [0.15, 2.60]
12.1.2 CKD	4	6224	Risk Ratio (IV, Random, 95% CI)	1.08 [0.57, 2.04]
12.1.3 Predialysis, dialysis and transplant	1	448	Risk Ratio (IV, Random, 95% CI)	2.97 [0.12, 72.60]
12.2 Diabetes	6	4368	Risk Ratio (IV, Random, 95% CI)	1.49 [0.68, 3.25]
12.2.1 Less than 50% diabetic patients	3	1525	Risk Ratio (IV, Random, 95% CI)	0.96 [0.15, 6.03]
12.2.2 At least 50% diabetic patients	3	2843	Risk Ratio (IV, Random, 95% CI)	1.70 [0.64, 4.49]
12.3 Sex	7	7987	Risk Ratio (IV, Random, 95% CI)	1.19 [0.68, 2.07]
12.3.1 Less than 50% males	2	4268	Risk Ratio (IV, Random, 95% CI)	0.85 [0.56, 1.28]
12.3.2 At least 50% males	5	3719	Risk Ratio (IV, Random, 95% CI)	1.44 [0.53, 3.95]
12.4 Duration of intervention	11	9544	Risk Ratio (IV, Random, 95% CI)	1.00 [0.58, 1.72]
12.4.1 Less than 6 months	3	1212	Risk Ratio (IV, Random, 95% CI)	1.98 [0.18, 21.73]
12.4.2 Between 6 and 12 months	4	1870	Risk Ratio (IV, Random, 95% CI)	0.37 [0.12, 1.12]
12.4.3 More than 12 months	4	6462	Risk Ratio (IV, Random, 95% CI)	1.24 [0.67, 2.32]

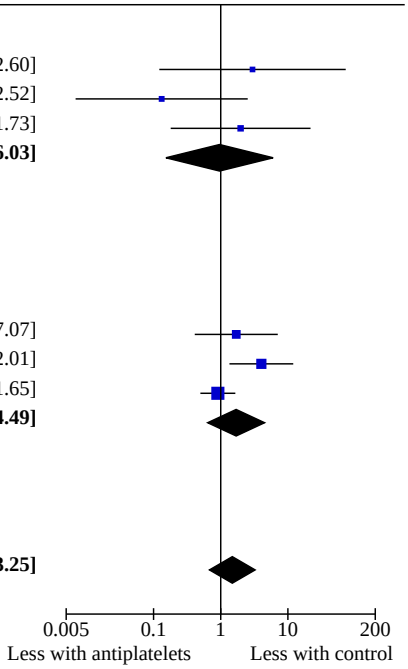
Analysis 12.1. Comparison 12: Stroke (subgroup analysis), Outcome 1: Stage of CKD

Study or Subgroup	Antiplatelet agent Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
12.1.1 HD						
Ell 1982	0	24	0	26		Not estimable
Creek 1990	0	144	0	141		Not estimable
Kaufman 2003	0	104	3	96	3.1%	0.13 [0.01 , 2.52]
Dember 2005	2	441	1	436	4.5%	1.98 [0.18 , 21.73]
STOP 1995	1	398	7	413	5.6%	0.15 [0.02 , 1.20]
Dixon 2005	5	321	3	328	10.2%	1.70 [0.41 , 7.07]
Subtotal (95% CI)		**1432**		**1440**	**23.3%**	**0.62 [0.15 , 2.60]**
Total events:	8		14			
Heterogeneity: Tau² = 0.98; Chi² = 5.55, df = 3 (P = 0.14); I² = 46%						
Test for overall effect: Z = 0.66 (P = 0.51)						
12.1.2 CKD						
CREDO 2005	2	203	4	208	7.9%	0.51 [0.09 , 2.77]
ETDRS 1992	12	79	4	106	14.2%	4.03 [1.35 , 12.01]
CHARISMA 2006	20	1006	22	1003	23.8%	0.91 [0.50 , 1.65]
HOT 1993	39	1791	50	1828	28.1%	0.80 [0.53 , 1.20]
Subtotal (95% CI)		**3079**		**3145**	**74.0%**	**1.08 [0.57 , 2.04]**
Total events:	73		80			
Heterogeneity: Tau² = 0.23; Chi² = 7.93, df = 3 (P = 0.05); I² = 62%						
Test for overall effect: Z = 0.24 (P = 0.81)						
12.1.3 Predialysis, dialysis and transplant						
UK-HARP-I 2005	1	225	0	223	2.7%	2.97 [0.12 , 72.60]
Subtotal (95% CI)		**225**		**223**	**2.7%**	**2.97 [0.12 , 72.60]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**4736**		**4808**	**100.0%**	**1.00 [0.58 , 1.72]**
Total events:	82		94			
Heterogeneity: Tau² = 0.23; Chi² = 14.15, df = 8 (P = 0.08); I² = 43%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Chi² = 0.94, df = 2 (P = 0.63), I² = 0%						



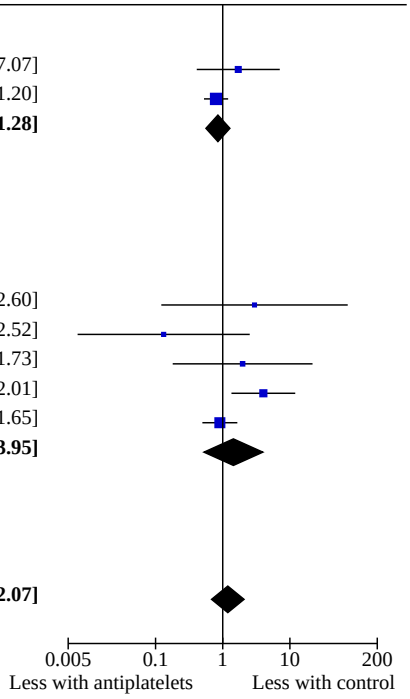
Analysis 12.2. Comparison 12: Stroke (subgroup analysis), Outcome 2: Diabetes

Study or Subgroup	Antiplatelet agent Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
12.2.1 Less than 50% diabetic patients						
UK-HARP-I 2005	1	225	0	223	5.3%	2.97 [0.12 , 72.60]
Kaufman 2003	0	104	3	96	6.1%	0.13 [0.01 , 2.52]
Dember 2005	2	441	1	436	8.7%	1.98 [0.18 , 21.73]
Subtotal (95% CI)		**770**		**755**	**20.1%**	**0.96 [0.15 , 6.03]**
Total events:	3		4			
Heterogeneity: Tau² = 0.59; Chi² = 2.57, df = 2 (P = 0.28); I² = 22%						
Test for overall effect: Z = 0.04 (P = 0.97)						
12.2.2 At least 50% diabetic patients						
Dixon 2005	5	321	3	328	18.4%	1.70 [0.41 , 7.07]
ETDRS 1992	12	79	4	106	24.5%	4.03 [1.35 , 12.01]
CHARISMA 2006	20	1006	22	1003	36.9%	0.91 [0.50 , 1.65]
Subtotal (95% CI)		**1406**		**1437**	**79.9%**	**1.70 [0.64 , 4.49]**
Total events:	37		29			
Heterogeneity: Tau² = 0.47; Chi² = 5.63, df = 2 (P = 0.06); I² = 64%						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**2176**		**2192**	**100.0%**	**1.49 [0.68 , 3.25]**
Total events:	40		33			
Heterogeneity: Tau² = 0.34; Chi² = 8.32, df = 5 (P = 0.14); I² = 40%						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%						

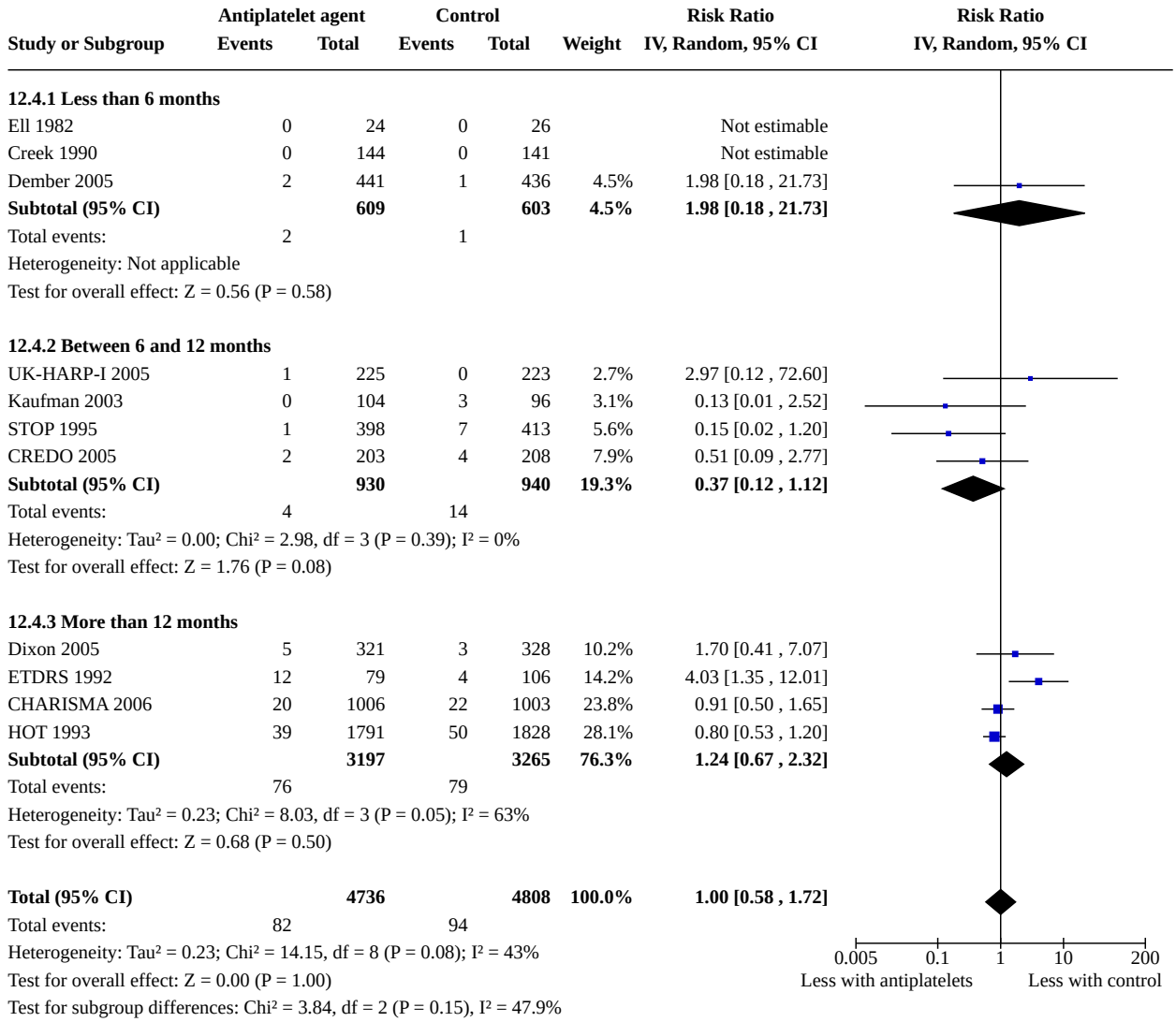


Analysis 12.3. Comparison 12: Stroke (subgroup analysis), Outcome 3: Sex

Study or Subgroup	Antiplatelet agent Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
12.3.1 Less than 50% males						
Dixon 2005	5	321	3	328	11.2%	1.70 [0.41 , 7.07]
HOT 1993	39	1791	50	1828	33.9%	0.80 [0.53 , 1.20]
Subtotal (95% CI)		**2112**		**2156**	**45.1%**	**0.85 [0.56 , 1.28]**
Total events:	44		53			
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 1 (P = 0.31); I² = 1%						
Test for overall effect: Z = 0.79 (P = 0.43)						
12.3.2 At least 50% males						
UK-HARP-I 2005	1	225	0	223	2.8%	2.97 [0.12 , 72.60]
Kaufman 2003	0	104	3	96	3.3%	0.13 [0.01 , 2.52]
Dember 2005	2	441	1	436	4.8%	1.98 [0.18 , 21.73]
ETDRS 1992	12	79	4	106	16.0%	4.03 [1.35 , 12.01]
CHARISMA 2006	20	1006	22	1003	28.1%	0.91 [0.50 , 1.65]
Subtotal (95% CI)		**1855**		**1864**	**54.9%**	**1.44 [0.53 , 3.95]**
Total events:	35		30			
Heterogeneity: Tau² = 0.57; Chi² = 8.15, df = 4 (P = 0.09); I² = 51%						
Test for overall effect: Z = 0.71 (P = 0.48)						
Total (95% CI)		**3967**		**4020**	**100.0%**	**1.19 [0.68 , 2.07]**
Total events:	79		83			
Heterogeneity: Tau² = 0.19; Chi² = 10.59, df = 6 (P = 0.10); I² = 43%						
Test for overall effect: Z = 0.61 (P = 0.54)						
Test for subgroup differences: Chi² = 0.91, df = 1 (P = 0.34), I² = 0%						



Analysis 12.4. Comparison 12: Stroke (subgroup analysis), Outcome 4: Duration of intervention



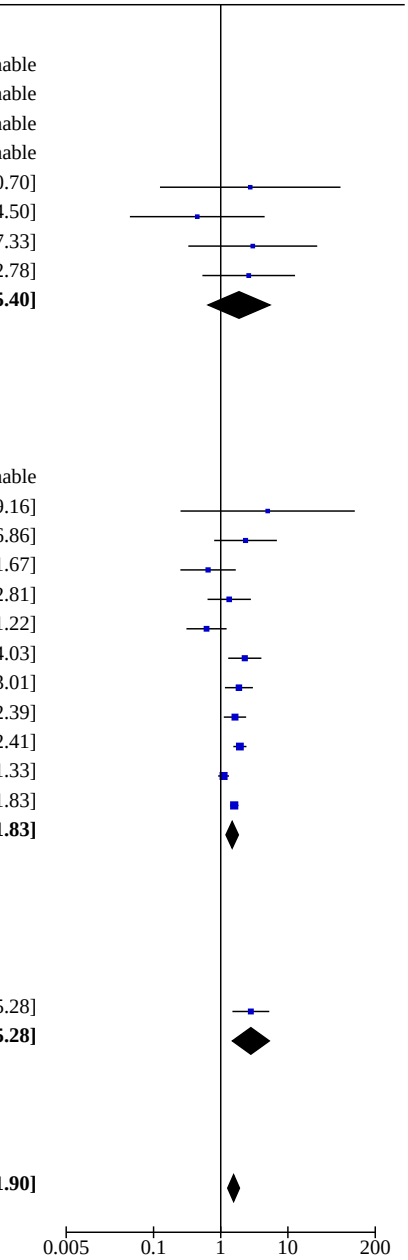
Comparison 13. Minor bleeding (subgroup analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Stage of CKD	21	13218	Risk Ratio (IV, Random, 95% CI)	1.55 [1.27, 1.90]
13.1.1 HD	8	1240	Risk Ratio (IV, Random, 95% CI)	1.87 [0.65, 5.40]
13.1.2 CKD	12	11530	Risk Ratio (IV, Random, 95% CI)	1.48 [1.20, 1.83]
13.1.3 Predialysis, dialysis and transplant	1	448	Risk Ratio (IV, Random, 95% CI)	2.81 [1.49, 5.28]
13.2 Diabetes	5	3431	Risk Ratio (IV, Random, 95% CI)	1.87 [1.24, 2.83]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2.1 Less than 50% diabetic patients	3	1346	Risk Ratio (IV, Random, 95% CI)	2.81 [1.51, 5.21]
13.2.2 At least 50% diabetic patients	2	2085	Risk Ratio (IV, Random, 95% CI)	1.59 [1.37, 1.83]
13.3 Sex	11	7377	Risk Ratio (IV, Random, 95% CI)	1.80 [1.29, 2.51]
13.3.1 Less than 50% males	3	3802	Risk Ratio (IV, Random, 95% CI)	2.28 [1.29, 4.03]
13.3.2 At least 50% males	8	3575	Risk Ratio (IV, Random, 95% CI)	1.71 [1.12, 2.60]
13.4 Duration of intervention	21	13218	Risk Ratio (IV, Random, 95% CI)	1.55 [1.27, 1.90]
13.4.1 Less than 6 months	9	1316	Risk Ratio (IV, Random, 95% CI)	1.87 [0.65, 5.40]
13.4.2 Between 6 and 12 months	10	6274	Risk Ratio (IV, Random, 95% CI)	1.47 [1.11, 1.96]
13.4.3 More than 12 months	2	5628	Risk Ratio (IV, Random, 95% CI)	1.71 [1.28, 2.27]

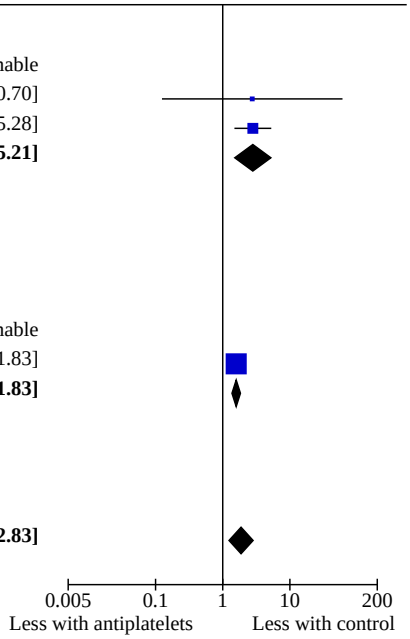
Analysis 13.1. Comparison 13: Minor bleeding (subgroup analysis), Outcome 1: Stage of CKD

Study or Subgroup	Antiplatelet agent Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
13.1.1 HD						
Michie 1977	0	8	0	8		Not estimable
Kamper 1997	0	13	0	14		Not estimable
Dember 2005	0	441	0	436		Not estimable
Kobayashi 1980	0	50	0	57		Not estimable
Alexopoulos 2011	1	11	0	10	0.4%	2.75 [0.12 , 60.70]
Gröntoft 1985	1	19	2	17	0.7%	0.45 [0.04 , 4.50]
Ghorbani 2013	3	32	1	32	0.8%	3.00 [0.33 , 27.33]
Andrassy 1974	5	45	2	47	1.5%	2.61 [0.53 , 12.78]
Subtotal (95% CI)		**619**		**621**	**3.4%**	**1.87 [0.65 , 5.40]**
Total events:	10		5			
Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 3 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
13.1.2 CKD						
Khajehdehi 2002	0	57	0	19		Not estimable
Donadio 1984	2	25	0	25	0.4%	5.00 [0.25 , 99.16]
EPISTENT 1998	16	229	4	134	2.9%	2.34 [0.80 , 6.86]
RAPPORT 1998	5	27	10	35	3.6%	0.65 [0.25 , 1.67]
EPILOG 1997	24	325	9	163	5.1%	1.34 [0.64 , 2.81]
CREDO 2005	12	203	20	208	5.7%	0.61 [0.31 , 1.22]
HOT 1993	38	1791	17	1828	7.3%	2.28 [1.29 , 4.03]
EPIC 1994	64	334	19	185	8.8%	1.87 [1.16 , 3.01]
IMPACT II 1997	103	525	29	241	10.7%	1.63 [1.11 , 2.39]
PURSUIT 1997	228	1404	97	1152	14.4%	1.93 [1.54 , 2.41]
PRISM-PLUS 1998	133	300	125	311	15.3%	1.10 [0.92 , 1.33]
CHARISMA 2006	347	1006	218	1003	16.1%	1.59 [1.37 , 1.83]
Subtotal (95% CI)		**6226**		**5304**	**90.2%**	**1.48 [1.20 , 1.83]**
Total events:	972		548			
Heterogeneity: Tau² = 0.06; Chi² = 29.79, df = 10 (P = 0.0009); I² = 66%						
Test for overall effect: Z = 3.64 (P = 0.0003)						
13.1.3 Predialysis, dialysis and transplant						
UK-HARP-I 2005	34	225	12	223	6.4%	2.81 [1.49 , 5.28]
Subtotal (95% CI)		**225**		**223**	**6.4%**	**2.81 [1.49 , 5.28]**
Total events:	34		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.20 (P = 0.001)						
Total (95% CI)		**7070**		**6148**	**100.0%**	**1.55 [1.27 , 1.90]**
Total events:	1016		565			
Heterogeneity: Tau² = 0.06; Chi² = 35.63, df = 15 (P = 0.002); I² = 58%						
Test for overall effect: Z = 4.32 (P < 0.0001)						
Test for subgroup differences: Chi² = 3.64, df = 2 (P = 0.16), I² = 45.1%						



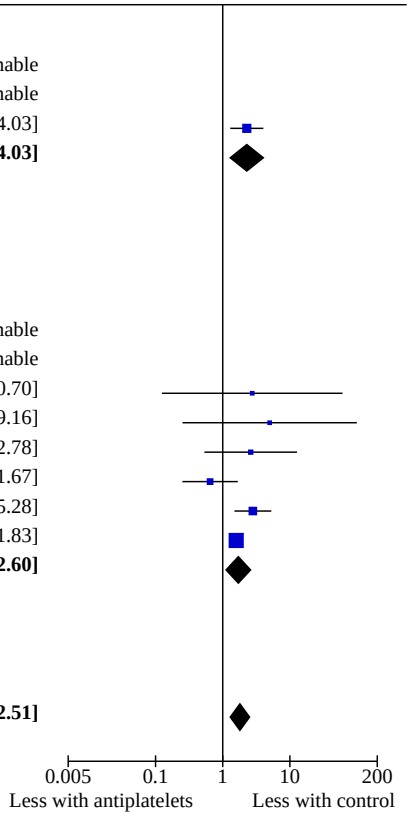
Analysis 13.2. Comparison 13: Minor bleeding (subgroup analysis), Outcome 2: Diabetes

Study or Subgroup	Antiplatelet agent Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
13.2.1 Less than 50% diabetic patients						
Dember 2005	0	441	0	436		Not estimable
Alexopoulos 2011	1	11	0	10	1.7%	2.75 [0.12 , 60.70]
UK-HARP-I 2005	34	225	12	223	27.5%	2.81 [1.49 , 5.28]
Subtotal (95% CI)		**677**		**669**	**29.3%**	**2.81 [1.51 , 5.21]**
Total events:	35		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 3.27 (P = 0.001)						
13.2.2 At least 50% diabetic patients						
Khajehdehi 2002	0	57	0	19		Not estimable
CHARISMA 2006	347	1006	218	1003	70.7%	1.59 [1.37 , 1.83]
Subtotal (95% CI)		**1063**		**1022**	**70.7%**	**1.59 [1.37 , 1.83]**
Total events:	347		218			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.24 (P < 0.00001)						
Total (95% CI)		**1740**		**1691**	**100.0%**	**1.87 [1.24 , 2.83]**
Total events:	382		230			
Heterogeneity: Tau² = 0.06; Chi² = 3.09, df = 2 (P = 0.21); I² = 35%						
Test for overall effect: Z = 2.99 (P = 0.003)						
Test for subgroup differences: Chi² = 3.09, df = 1 (P = 0.08), I² = 67.6%						



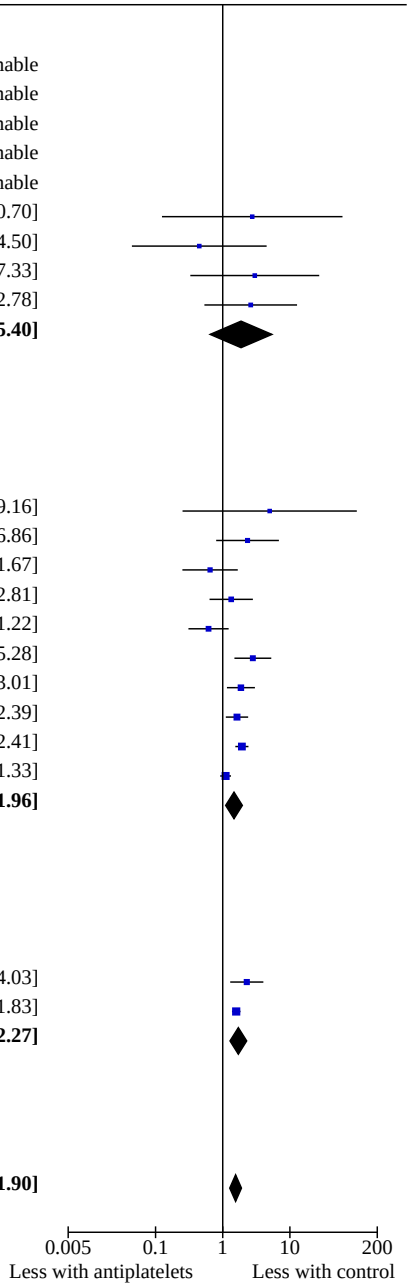
Analysis 13.3. Comparison 13: Minor bleeding (subgroup analysis), Outcome 3: Sex

Study or Subgroup	Antiplatelet agent Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
13.3.1 Less than 50% males						
Khajehdehi 2002	0	57	0	19		Not estimable
Kobayashi 1980	0	50	0	57		Not estimable
HOT 1993	38	1791	17	1828	20.3%	2.28 [1.29 , 4.03]
Subtotal (95% CI)		**1898**		**1904**	**20.3%**	**2.28 [1.29 , 4.03]**
Total events:	38		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.85 (P = 0.004)						
13.3.2 At least 50% males						
Michie 1977	0	8	0	8		Not estimable
Dember 2005	0	441	0	436		Not estimable
Alexopoulos 2011	1	11	0	10	1.1%	2.75 [0.12 , 60.70]
Donadio 1984	2	25	0	25	1.2%	5.00 [0.25 , 99.16]
Andrassy 1974	5	45	2	47	4.0%	2.61 [0.53 , 12.78]
RAPPORT 1998	5	27	10	35	9.8%	0.65 [0.25 , 1.67]
UK-HARP-I 2005	34	225	12	223	17.8%	2.81 [1.49 , 5.28]
CHARISMA 2006	347	1006	218	1003	45.8%	1.59 [1.37 , 1.83]
Subtotal (95% CI)		**1788**		**1787**	**79.7%**	**1.71 [1.12 , 2.60]**
Total events:	394		242			
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 7.57$, df = 5 (P = 0.18); $I^2 = 34\%$						
Test for overall effect: Z = 2.50 (P = 0.01)						
Total (95% CI)		**3686**		**3691**	**100.0%**	**1.80 [1.29 , 2.51]**
Total events:	432		259			
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 8.93$, df = 6 (P = 0.18); $I^2 = 33\%$						
Test for overall effect: Z = 3.48 (P = 0.0005)						
Test for subgroup differences: $Chi^2 = 0.65$, df = 1 (P = 0.42), $I^2 = 0\%$						



Analysis 13.4. Comparison 13: Minor bleeding (subgroup analysis), Outcome 4: Duration of intervention

Study or Subgroup	Antiplatelet agent Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
13.4.1 Less than 6 months						
Kamper 1997	0	13	0	14		Not estimable
Khajehdehi 2002	0	57	0	19		Not estimable
Kobayashi 1980	0	50	0	57		Not estimable
Dember 2005	0	441	0	436		Not estimable
Michie 1977	0	8	0	8		Not estimable
Alexopoulos 2011	1	11	0	10	0.4%	2.75 [0.12 , 60.70]
Gröntoft 1985	1	19	2	17	0.7%	0.45 [0.04 , 4.50]
Ghorbani 2013	3	32	1	32	0.8%	3.00 [0.33 , 27.33]
Andrassy 1974	5	45	2	47	1.5%	2.61 [0.53 , 12.78]
Subtotal (95% CI)		**676**		**640**	**3.4%**	**1.87 [0.65 , 5.40]**
Total events:	10		5			
Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 3 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
13.4.2 Between 6 and 12 months						
Donadio 1984	2	25	0	25	0.4%	5.00 [0.25 , 99.16]
EPISTENT 1998	16	229	4	134	2.9%	2.34 [0.80 , 6.86]
RAPPORT 1998	5	27	10	35	3.6%	0.65 [0.25 , 1.67]
EPILOG 1997	24	325	9	163	5.1%	1.34 [0.64 , 2.81]
CREDO 2005	12	203	20	208	5.7%	0.61 [0.31 , 1.22]
UK-HARP-I 2005	34	225	12	223	6.4%	2.81 [1.49 , 5.28]
EPIC 1994	64	334	19	185	8.8%	1.87 [1.16 , 3.01]
IMPACT II 1997	103	525	29	241	10.7%	1.63 [1.11 , 2.39]
PURSUIT 1997	228	1404	97	1152	14.4%	1.93 [1.54 , 2.41]
PRISM-PLUS 1998	133	300	125	311	15.3%	1.10 [0.92 , 1.33]
Subtotal (95% CI)		**3597**		**2677**	**73.3%**	**1.47 [1.11 , 1.96]**
Total events:	621		325			
Heterogeneity: Tau² = 0.11; Chi² = 30.31, df = 9 (P = 0.0004); I² = 70%						
Test for overall effect: Z = 2.65 (P = 0.008)						
13.4.3 More than 12 months						
HOT 1993	38	1791	17	1828	7.3%	2.28 [1.29 , 4.03]
CHARISMA 2006	347	1006	218	1003	16.1%	1.59 [1.37 , 1.83]
Subtotal (95% CI)		**2797**		**2831**	**23.4%**	**1.71 [1.28 , 2.27]**
Total events:	385		235			
Heterogeneity: Tau² = 0.02; Chi² = 1.47, df = 1 (P = 0.23); I² = 32%						
Test for overall effect: Z = 3.67 (P = 0.0002)						
Total (95% CI)		**7070**		**6148**	**100.0%**	**1.55 [1.27 , 1.90]**
Total events:	1016		565			
Heterogeneity: Tau² = 0.06; Chi² = 35.63, df = 15 (P = 0.002); I² = 58%						
Test for overall effect: Z = 4.32 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.61, df = 2 (P = 0.74), I² = 0%						



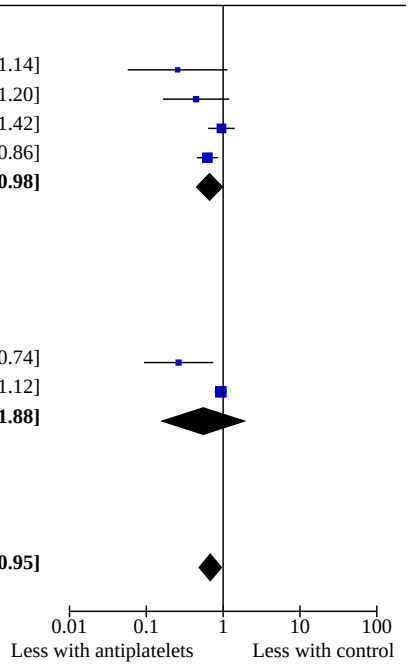
Comparison 14. Dialysis access failure (subgroup analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Diabetes	6	1942	Risk Ratio (IV, Random, 95% CI)	0.68 [0.49, 0.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1.1 Less than 50% diabetic patients	4	1197	Risk Ratio (IV, Random, 95% CI)	0.67 [0.45, 0.98]
14.1.2 At least 50% diabetic patients	2	745	Risk Ratio (IV, Random, 95% CI)	0.55 [0.16, 1.88]
14.2 Sex	12	2513	Risk Ratio (IV, Random, 95% CI)	0.65 [0.51, 0.82]
14.2.1 Less than 50% males	4	838	Risk Ratio (IV, Random, 95% CI)	0.75 [0.52, 1.09]
14.2.2 At least 50% males	8	1675	Risk Ratio (IV, Random, 95% CI)	0.60 [0.45, 0.79]
14.3 Duration of intervention	17	2847	Risk Ratio (IV, Random, 95% CI)	0.62 [0.50, 0.78]
14.3.1 Less than 6 months	11	1705	Risk Ratio (IV, Random, 95% CI)	0.55 [0.44, 0.70]
14.3.2 Between 6 and 12 months	4	386	Risk Ratio (IV, Random, 95% CI)	0.59 [0.37, 0.96]
14.3.3 More than 12 months	2	756	Risk Ratio (IV, Random, 95% CI)	0.94 [0.79, 1.11]

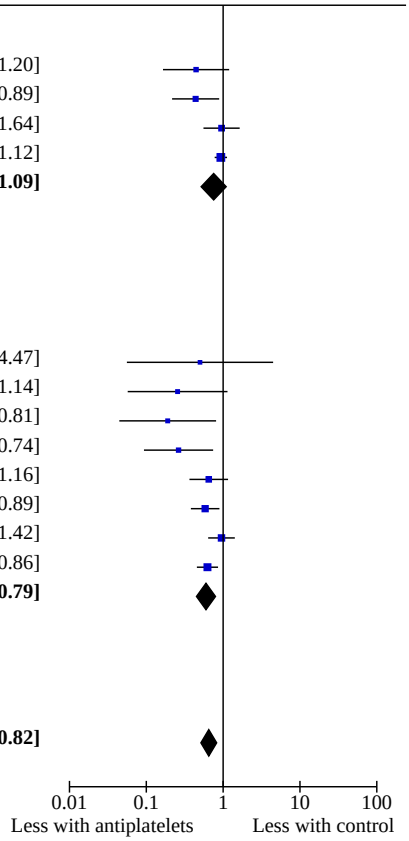
Analysis 14.1. Comparison 14: Dialysis access failure (subgroup analysis), Outcome 1: Diabetes

Study or Subgroup	Antiplatelet agent Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
14.1.1 Less than 50% diabetic patients						
Ghorbani 2009	2	46	8	47	4.3%	0.26 [0.06 , 1.14]
Abdul-Rahman 2007	4	19	9	19	8.4%	0.44 [0.16 , 1.20]
Kaufman 2003	33	104	32	96	22.8%	0.95 [0.64 , 1.42]
Dember 2005	53	435	84	431	26.0%	0.63 [0.46 , 0.86]
Subtotal (95% CI)		**604**		**593**	**61.4%**	**0.67 [0.45 , 0.98]**
Total events:	92		133			
Heterogeneity: Tau² = 0.06; Chi² = 5.31, df = 3 (P = 0.15); I² = 44%						
Test for overall effect: Z = 2.07 (P = 0.04)						
14.1.2 At least 50% diabetic patients						
Abacilar 2015	4	50	14	46	7.8%	0.26 [0.09 , 0.74]
Dixon 2005	127	321	139	328	30.8%	0.93 [0.78 , 1.12]
Subtotal (95% CI)		**371**		**374**	**38.6%**	**0.55 [0.16 , 1.88]**
Total events:	131		153			
Heterogeneity: Tau² = 0.66; Chi² = 5.57, df = 1 (P = 0.02); I² = 82%						
Test for overall effect: Z = 0.95 (P = 0.34)						
Total (95% CI)		**975**		**967**	**100.0%**	**0.68 [0.49 , 0.95]**
Total events:	223		286			
Heterogeneity: Tau² = 0.08; Chi² = 13.67, df = 5 (P = 0.02); I² = 63%						
Test for overall effect: Z = 2.28 (P = 0.02)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.77), I² = 0%						

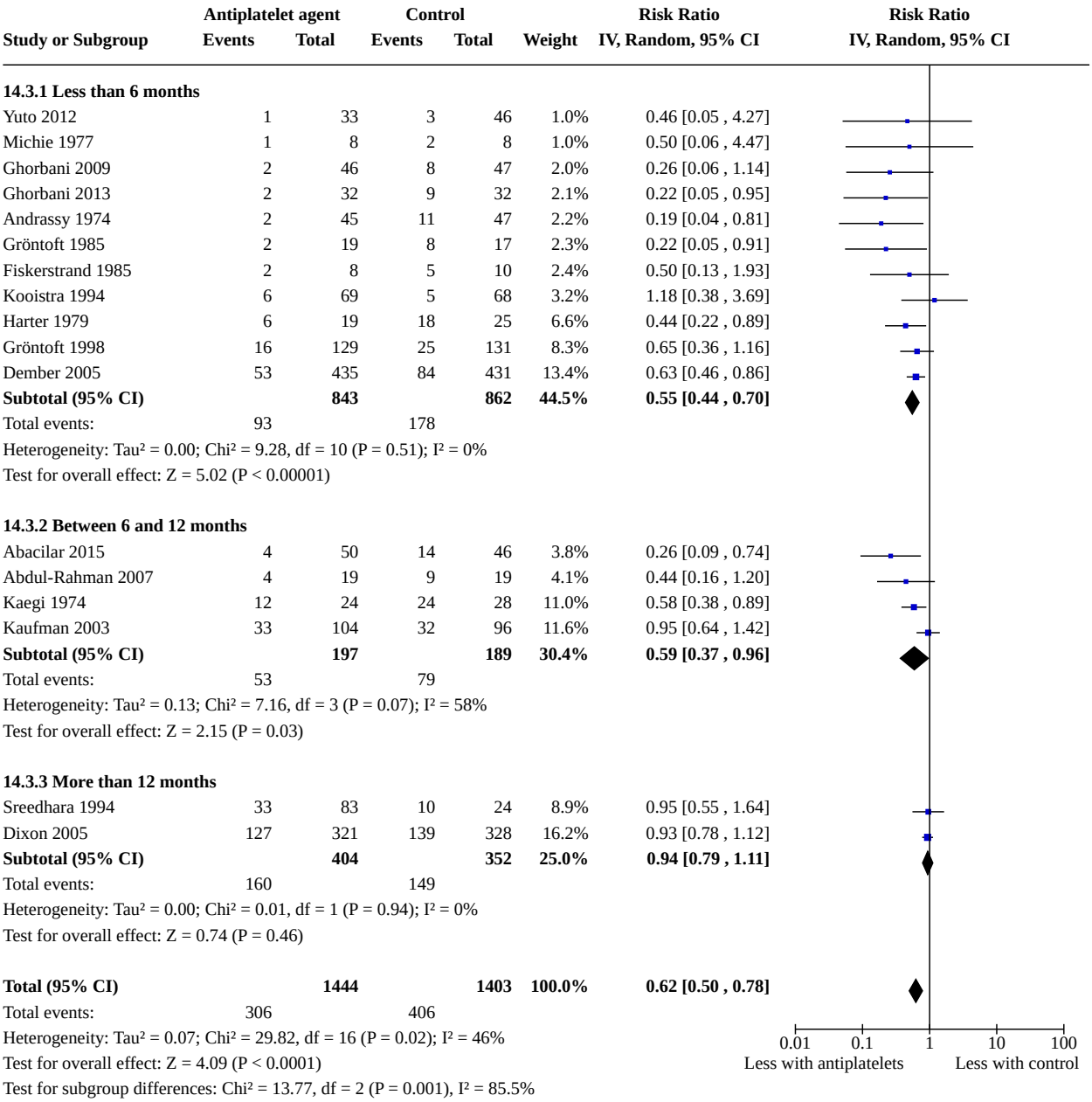


Analysis 14.2. Comparison 14: Dialysis access failure (subgroup analysis), Outcome 2: Sex

Study or Subgroup	Antiplatelet agent Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
14.2.1 Less than 50% males						
Abdul-Rahman 2007	4	19	9	19	4.4%	0.44 [0.16 , 1.20]
Harter 1979	6	19	18	25	7.3%	0.44 [0.22 , 0.89]
Sreedhara 1994	33	83	10	24	9.9%	0.95 [0.55 , 1.64]
Dixon 2005	127	321	139	328	18.6%	0.93 [0.78 , 1.12]
Subtotal (95% CI)		**442**		**396**	**40.2%**	**0.75 [0.52 , 1.09]**
Total events:	170		176			
Heterogeneity: Tau² = 0.07; Chi² = 6.04, df = 3 (P = 0.11); I² = 50%						
Test for overall effect: Z = 1.49 (P = 0.14)						
14.2.2 At least 50% males						
Michie 1977	1	8	2	8	1.1%	0.50 [0.06 , 4.47]
Ghorbani 2009	2	46	8	47	2.2%	0.26 [0.06 , 1.14]
Andrassy 1974	2	45	11	47	2.3%	0.19 [0.04 , 0.81]
Abacilar 2015	4	50	14	46	4.1%	0.26 [0.09 , 0.74]
Gröntoft 1998	16	129	25	131	9.3%	0.65 [0.36 , 1.16]
Kaegi 1974	12	24	24	28	12.4%	0.58 [0.38 , 0.89]
Kaufman 2003	33	104	32	96	13.1%	0.95 [0.64 , 1.42]
Dember 2005	53	435	84	431	15.2%	0.63 [0.46 , 0.86]
Subtotal (95% CI)		**841**		**834**	**59.8%**	**0.60 [0.45 , 0.79]**
Total events:	123		200			
Heterogeneity: Tau² = 0.05; Chi² = 11.03, df = 7 (P = 0.14); I² = 37%						
Test for overall effect: Z = 3.55 (P = 0.0004)						
Total (95% CI)		**1283**		**1230**	**100.0%**	**0.65 [0.51 , 0.82]**
Total events:	293		376			
Heterogeneity: Tau² = 0.07; Chi² = 23.03, df = 11 (P = 0.02); I² = 52%						
Test for overall effect: Z = 3.58 (P = 0.0003)						
Test for subgroup differences: Chi² = 0.92, df = 1 (P = 0.34), I² = 0%						



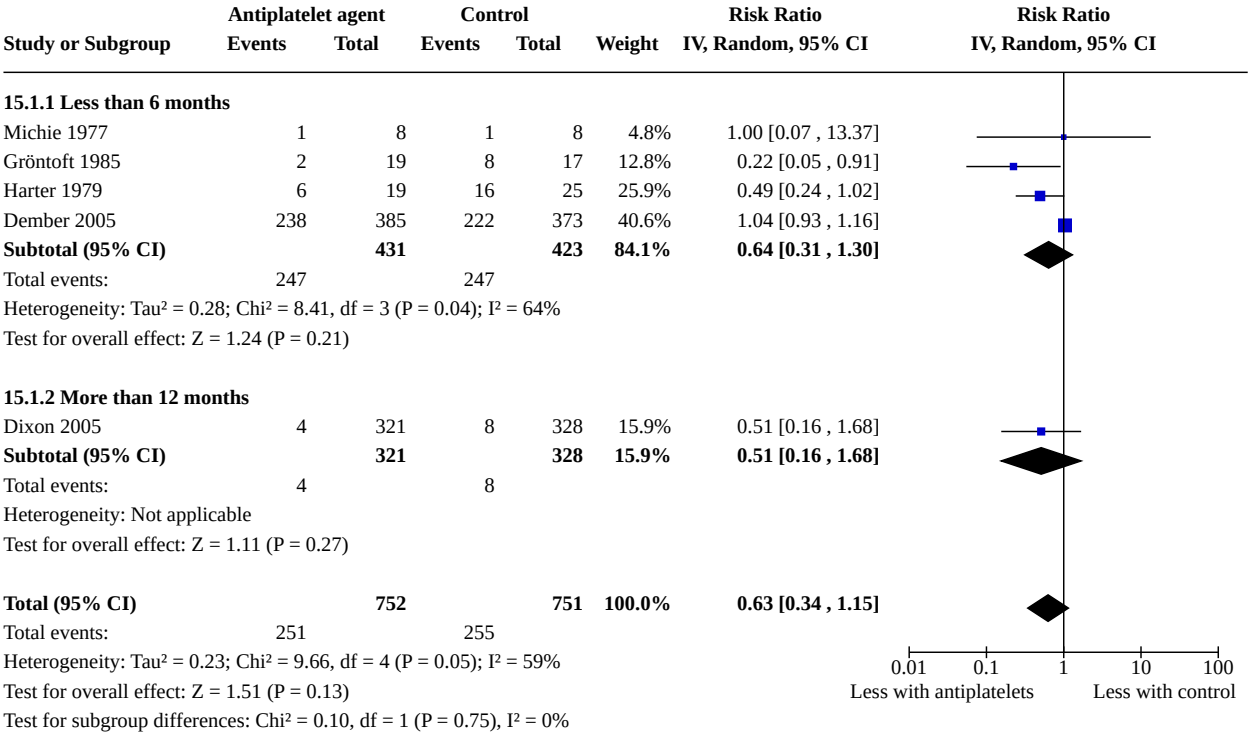
Analysis 14.3. Comparison 14: Dialysis access failure (subgroup analysis), Outcome 3: Duration of intervention



Comparison 15. Failure to attain suitability for dialysis (subgroup analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Duration of intervention	5	1503	Risk Ratio (IV, Random, 95% CI)	0.63 [0.34, 1.15]
15.1.1 Less than 6 months	4	854	Risk Ratio (IV, Random, 95% CI)	0.64 [0.31, 1.30]
15.1.2 More than 12 months	1	649	Risk Ratio (IV, Random, 95% CI)	0.51 [0.16, 1.68]

Analysis 15.1. Comparison 15: Failure to attain suitability for dialysis (subgroup analysis), Outcome 1: Duration of intervention



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Phosphodiesterase Inhibitors] explode all trees 2. MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees 3. ((antiplatelet next agent*) or (anti-platelet next agent*)):ti,ab,kw 4. ((antiplatelet next therap*) or (anti-platelet next therap*)):ti,ab,kw 5. (platelet next aggregation next inhibit*):ti,ab,kw 6. (phosphodiesterase next inhibit*):ti,ab,kw 7. (thrombocyte next aggregation next inhibit*):ti,ab,kw 8. ((antithrombocytic next agent*) or (anti-thrombocytic next agent*)):ti,ab,kw 9. ((antithrombocytic next therap*) or (anti-thrombocytic next therap*)):ti,ab,kw 10.alprostadil:ti,ab,kw 11.aspirin:ti,ab,kw 12.acetylsalicylic acid:ti,ab,kw 13.((adenosine next reuptake next inhibit*) or (adenosine re-uptake next inhibit*)):ti,ab,kw 14.(adenosine next diphosphate next receptor next inhibit*):ti,ab,kw 15.dipyridamole:ti,ab,kw 16.disintegrins:ti,ab,kw

(Continued)

17.dilazep next dihydrochloride:ti,ab,kw
18.epoprostenol:ti,ab,kw
19.iloprost:ti,ab,kw
20.ketanserin:ti,ab,kw
21.milrinone:ti,ab,kw
22.pentoxifylline:ti,ab,kw
23."S-nitrosoglutathione":ti,ab,kw
24."S-nitrosothiols":ti,ab,kw
25.trapidil:ti,ab,kw
26.ticlopidine:ti,ab,kw
27.clopidogrel:ti,ab,kw
28.(sulfinpyrazone or sulphinpyrazone):ti,ab,kw
29.cilostazol:ti,ab,kw
30.(P2Y12 near/2 antagonis*):ti,ab,kw
31.prasugrel:ti,ab,kw
32.ticagrelor:ti,ab,kw
33.cangrelor:ti,ab,kw
34.elinogrel:ti,ab,kw
35."glycoprotein IIB/IIIA inhibitors":ti,ab,kw
36.abciximab:ti,ab,kw
37.eptifibatide:ti,ab,kw
38.tirofiban:ti,ab,kw
39.defibrotide:ti,ab,kw
40.picotamide:ti,ab,kw
41.beraprost:ti,ab,kw
42.ticlid:ti,ab,kw
43.aggrenox:ti,ab,kw
44.ditazole:ti,ab,kw
45.ditazole:ti,ab,kw
46.vorapaxar
47.{OR #1-#46}
48.dialysis:ti,ab,kw
49.(haemodialysis or haemodialysis):ti,ab,kw
50.(hemofiltration or haemofiltration):ti,ab,kw
51.(hemodiafiltration or haemodiafiltration):ti,ab,kw
52.(PD or CAPD or CCPD or APD):ti,ab,kw
53.(renal next (insufficiency or impairment)):ti,ab,kw
54.(kidney next failure):ti,ab,kw
55.(kidney next disease*):ti,ab,kw
56.ur*emi*:ti,ab,kw
57.((chronic next kidney) or (chronic next renal)):ti,ab,kw
58.(CKF or CKD or CRF or CRD):ti,ab,kw
59.(predialysis or pre-dialysis):ti,ab,kw
60.((end-stage next renal) or (end-stage next kidney) or (endstage next renal) or (endstage next kidney)):ti,ab,kw
61.(ESKD or ESRD or ESKF or ESRF):ti,ab,kw
62.(renal next replacement next therapy):ti,ab,kw
63.((kidney next transplant*) or (renal next transplant*) or (kidney next *graft*) or (renal next *graft*)):ti,ab,kw
64.{OR #48-#63}
65.#47 and #64

(Continued)

MEDLINE

1. exp Platelet Aggregation Inhibitors/
2. exp Phosphodiesterase Inhibitors/
3. Adenosine Diphosphate/ai [Antagonists & Inhibitors]
4. Platelet Glycoprotein GPIIb-IIIa Complex/ai [Antagonists & Inhibitors]
5. Sulfinpyrazone/
6. (antiplatelet agents$ or anti-platelet agent$).tw.
7. (antiplatelet therap$ or anti-platelet therap$).tw.
8. platelet aggregation inhibit$.tw.
9. phosphodiesterase inhibit$.tw.
10. thrombocyte aggregation inhibit$.tw.
11. (antithrombocytic agent$ or anti-thrombocytic agent$).tw.
12. (antithrombocytic therap$ or anti-thrombocytic therap$).tw.
13. alprostadil.tw.
14. aspirin.tw.
15. acetylsalicylic acid.tw.
16. (adenosine reuptake inhibit$ or adenosine re-uptake inhibit$).tw.
17. adenosine diphosphate receptor inhibit$.tw.
18. dipyridamole.tw.
19. disintegrins.tw.
20. epoprostenol.tw.
21. iloprost.tw.
22. ketanserin.tw.
23. milrinone.tw.
24. pentoxifylline.tw.
25. S-nitrosoglutathione.tw.
26. S-nitrosothioles.tw.
27. trapidil.tw.
28. ticlopidine.tw.
29. clopidogrel.tw.
30. (sulfinpyrazone or sulphinpyrazone).tw.
31. cilostazol.tw.
32. (P2Y12 adj2 antagonis$).tw.
33. prasugrel.tw.
34. ticagrelor.tw.
35. cangrelor.tw.
36. elinogrel.tw.
37. "glycoprotein IIB/IIIA inhibitors".tw.
38. abciximab.tw.
39. eptifibatide.tw.
40. tirofiban.tw.
41. defibrotide.tw.
42. picotamide.tw.
43. beraprost.tw.
44. ticlid.tw.
45. aggrenox.tw.
46. ditazole.tw.
47. or/1-46
48. exp Renal Dialysis/
49. (haemodialysis or haemodialysis).tw.
50. (hemofiltration or haemofiltration).tw.
51. (hemodiafiltration or haemodiafiltration).tw.

(Continued)

	52.dialysis.tw. 53.(PD or CAPD or CCPD or APD).tw. 54.Renal Insufficiency/ 55.Kidney Failure/ 56.exp Renal Insufficiency, Chronic/ 57.Kidney Diseases/ 58.Uremia/ 59.(end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 60.(ESRF or ESKF or ESRD or ESKD).tw. 61.(chronic kidney or chronic renal).tw. 62.(CKF or CKD or CRF or CRD).tw. 63.(predialysis or pre-dialysis).tw. 64.ur?emi$.tw. 65.or/48-64 66.and/47,65
EMBASE	1. exp Antithrombocytic Agent/ 2. exp Phosphodiesterase Inhibitor/ 3. Defibrotide/ 4. thromboxane synthase inhibitor/ 5. platelet aggregation inhibit$.tw. 6. (antiplatelet agents$ or anti-platelet agent$).tw. 7. (antiplatelet therap$ or anti-platelet therap$).tw. 8. thrombocyte aggregation inhibit$.tw. 9. (antithrombocytic agent$ or anti-thrombocytic agent$).tw. 10.(antithrombocytic therap$ or anti-thrombocytic therap$).tw. 11.adenosine diphosphate receptor inhibit$.tw. 12.(phosphodiesterase adj2 inhibit$).tw. 13.(adenosine reuptake inhibit$ or adenosine re-uptake inhibit$).tw. 14.(thromboxane synthetase inhibitor* or thromboxane synthase inhibitor*).tw. 15.aspirin.tw. 16.acetylsalicylic acid.tw. 17.dipyridamole.tw. 18.dilazep dihydrochloride.tw. 19.disintegrins.tw. 20.epoprostenol.tw. 21.iloprost.tw. 22.ketanserin.tw. 23.milrinone.tw. 24.pentoxifylline.tw. 25.S-nitrosoglutathione.tw. 26.S-nitrosothioles.tw. 27.trapidil.tw. 28.ticlopidine.tw. 29.clopidogrel.tw. 30.(sulfinpyrazone or sulphinpyrazone).tw. 31.cilostazol.tw. 32.(P2Y12 adj2 antagonis$).tw. 33.prasugrel.tw. 34.ticagrelor.tw. 35.cangrelor.tw. 36.elinogrel.tw.

(Continued)

37."glycoprotein IIB/IIIA inhibit$".tw.
38.abciximab.tw.
39.eptifibatide.tw.
40.tirofiban.tw.
41.defibrotide.tw.
42.picotamide.tw.
43.beraprost.tw.
44.ticlid.tw.
45.aggrenox.tw.
46.ditazole.tw.
47.sarpogrelate.tw.
48.alprostadil.tw.
49.vorapaxar.tw.
50.or/1-49
51.exp Renal Replacement Therapy/
52.(haemodialysis or haemodialysis).tw.
53.(hemofiltration or haemofiltration).tw.
54.(hemodiafiltration or haemodiafiltration).tw.
55.dialysis.tw.
56.(PD or CAPD or CCPD or APD).tw.
57.Kidney Disease/
58.Chronic Kidney Disease/
59.Kidney Failure/
60.Chronic Kidney Failure/
61.mild renal impairment/
62.stage 1 kidney disease/
63.moderate renal impairment/
64.severe renal impairment/
65.severe renal impairment/
66.renal replacement therapy-dependent renal disease/
67.Uremia/
68.(chronic kidney or chronic renal).tw.
69.(CKF or CKD or CRF or CRD).tw.
70.(end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
71.(ESRF or ESKF or ESRD or ESKD).tw.
72.(predialysis or pre-dialysis).tw.
73.ur?emi$.tw
74.exp Kidney Transplantation/
75.((kidney or renal) adj (transplant* or graft* or allograft*)).tw.
76.or/51-75
77.and/50,76

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria

(Continued)

Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with

(Continued)

	substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

FEEDBACK

Feedback concerning conclusions, 9 May 2013

Summary

Dear Editor,

Thank you for a much needed review addressing the gaps in literature regarding the risks and benefits of antiplatelets in the chronic kidney disease (CKD) population. We thought the literature search was very thorough and well done. However, we came up with a few questions upon reading this review and felt that the stated conclusion "antiplatelets reduce myocardial infarction...including those with early stages of CKD who do not have clinically-evident occlusive cardiovascular disease" may not be accurately reflected by the presented data.

Looking at the first primary outcome - fatal and non-fatal myocardial infarction (MI), it was unclear whether the population studied was addressing primary prevention, secondary prevention or acute treatment of MI as the included populations had different cardiovascular histories. Of the two studies that were given the most weight in the analysis (HOT Study 2010 and PURSUIT Study 1998), one investigated primary prevention of MI using ASA versus placebo, while the other investigated acute treatment of MI using eptifibatide + ASA + heparin compared to ASA + heparin. In the non-CKD population, efficacy of antiplatelets is dependent on the indication (i.e. primary or secondary prophylaxis or treatment). Different antiplatelets also have different places in therapy.

We therefore feel that it may be inappropriate to pool these trials together as they were investigating different populations.

In this same analysis, there were also multiple interventions such as single antiplatelets versus placebo (HOT study 2010, Ell study 1982, Creek 1990, Dember 2008, STOP study 1995, UK-HARP-I study 2005, ETDRS 1992), dual antiplatelets versus placebo (Kaufman 2003), as well as dual antiplatelets versus single antiplatelet agents (CREDO study 2008, CHARISMA study 2009, EPILOG study 1997, EPIC study 1994, EPISTENT study 1998, Dixon study 2009, RAPPORT study 1998, PURSUIT study 1998, and IMPACT II 1997). With both placebo and antiplatelet in the "control" arms of one meta-analysis, comparison groups and treatment groups are not clearly delineated from one another. As this was unclear, readers may be misled into believing that the effect is driven purely from antiplatelet compared to placebo, when this is not the case. Even pooling the data on the seven placebo-controlled trials may be inappropriate as they were studied in different patient

populations and indications (e.g. primary prevention, non-cardiovascular outcomes). Similarly, the "treatment arms" of the meta-analysis contained one or more antiplatelet agents, which may have biased the result towards the treatment arm over single agent or placebo "control". This can also make it difficult to isolate the beneficial agent in the dual antiplatelet studies. Due to the differences in treatment arms and patient populations, we feel it would valuable to investigate the outcomes of these factors in separate analyses.

It should also be mentioned that the patients included in this review were derived as subgroups from larger studies with different baseline cardiovascular risk factors (e.g. diabetes, coronary artery disease, hypertension, etc). As a result, one cannot conclude that patients with only CKD, and no additional cardiovascular risk factors, would benefit from antiplatelet use to decrease cardiovascular outcomes such as fatal and non-fatal MIs. Dixon 2009 and Dember 2008 were two studies enrolling haemodialysis patients with a primary outcome of AV graft patency or thrombosis; fatal and non-fatal MIs were only reported as an adverse effect and could have been under-reported in the study.

We commend the authors for assessing bias in the included trials and for performing a sensitivity analysis to explore the impact of the bias. We feel that with the relatively high percentage of unclear or high risk of biases that exist in the trials, it would have been beneficial for the authors to report on the results of their sensitivity analyses to clarify the role of the bias and to substantiate the reported results.

We feel that the author's conclusion "antiplatelet agents reduce myocardial infarction" may be too broad of a conclusion to be drawn based on the analysis that was performed looking at fatal and non-fatal MI. As well, their specific reference to "patients with early stages of CKD who do not have a clinically-evident occlusive cardiovascular disease" suggests this effect is shown in the CKD

population when using antiplatelets for primary prevention; however, this aspect was not separated out in their analysis. We feel that the pooling of studies with varying patient populations and treatments is not appropriate in helping clinicians determine whether antiplatelets provide any benefit for MI in patients with CKD. While we did not explore the other identified primary outcomes in this review, we wonder if similar concerns exist for not only the efficacy but also the safety outcomes. We would appreciate an investigation into single antiplatelet therapy versus placebo for various cardiovascular indications. We hope the authors will provide clarification and address these concerns in their future updates.

We look forward to hearing your response to our comments.

Sincerely,

Gloria Su, BSc. Pharm
Wan-Yun Polinna Tsai, BSc. Pharm
Megan Harbin, BSc. Pharm
Asal Taheri, BSc. Pharm
Aaron M Tejani, BSc. Pharm, PharmD

Reply

Thanks for the constructive comments.

1. Primary versus secondary prevention versus acute treatment

We combined treatment estimates for all available studies comparing antiplatelet therapy (with or without standard therapy) versus placebo/no treatment (with or without standard therapy alone) to examine treatment effects, which is a standard starting point for meta-analyses. For the outcome of fatal or nonfatal myocardial infarction, there was little or no heterogeneity in the treatment effects observed in all the available trials, suggesting that treatment estimates could be appropriately summarised into a single effect size.

While not necessary in the absence of significant heterogeneity, we explored for pre-specified trial-level variables that might have modified the treatment estimates that we observed. We specifically wished to know whether treatment effects differed for patients with existing cardiovascular disease compared to those without cardiovascular disease but this was not feasible due to as we found insufficient numbers of studies that were clearly primary prevention or secondary prevention studies. However, the lack of heterogeneity in the overall summary estimate suggests that antiplatelet agents have similar effects irrespective of the presence or absence of cardiovascular disease.

2. Multiple interventions:

Unlike the relative lack of primary versus secondary prevention trials, there was sufficient studies to explore any differences in treatment effects based on the class of antiplatelet used. While there were numerous different strategies for antiplatelet treatment in contributing trials, all the treatment interventions could be characterised by an antiplatelet agent in addition to standard care versus no treatment/placebo in addition to standard care. We have called this antiplatelet therapy versus control to acknowledge the heterogeneity of the intervention strategies used (rather than antiplatelet treatment versus placebo).

We used stratified analyses according to overall class of antiplatelet drug where possible but there was lack of power from available studies to understand fully all the various treatment effects for each individual antiplatelet regimen. An individual patient meta-analysis would be needed to give a more fine-grained understanding of the different interventions and their combinations in the CKD population.

3. Deriving patients from subgroups of larger studies:

Patients with CKD were evaluated in *post-hoc* analyses of larger trials in broader populations. These included trials in populations with acute coronary syndromes requiring percutaneous coronary artery procedures, patients with hypertension and those with diabetes mellitus. Trials of treatment tended to use different interventions (glycoprotein IIb/IIIa inhibitors with or without clopidogrel) whereas trials of primary or secondary prevention did not use these agents, preventing useful stratified analyses for either class of agent or cardiovascular prevention in these trials. We have concluded that the lack of *a priori* assessment of glycoprotein IIb/IIIa inhibitors in people with CKD is an important limitation of the current evidence.

4. Potential under-reporting of clinical outcomes

We agree that many trials were not designed to evaluate mortality and cardiovascular outcomes and that these events were reported in an *ad hoc* fashion (not prespecified) which may have underestimated their frequency. We include evaluation of this aspect of trials when considering whether they are at risk of bias due to selective reporting of expected outcomes.

5. Risks of bias

We did not specify risk of bias items as sources of heterogeneity we would explore in stratified analyses. In further updates of this review and if deemed appropriate and feasible, we will explore attrition bias and allocation concealment as potential sources of heterogeneity in subgroup or sensitivity analyses.

6. Conclusions

In conclusion, we thank Dr Su and others for constructive comments to this review. We agree that the review cannot provide high quality information about antiplatelet agents as primary prevention for cardiovascular disease in people with CKD. We acknowledge the limitations of studies in which adults with CKD were studied *post hoc* and which are heterogeneous for presence of cardiovascular disease and antiplatelet agent studied. We agree that clinical events may be under-reported in available studies and will explore in future versions of this review the effects of risk of bias on the estimated treatment effects of antiplatelet treatment in CKD.

Contributors

Suetonia Palmer

Giovanni Strippoli

WHAT'S NEW

Date	Event	Description
18 December 2021	New citation required but conclusions have not changed	New studies have not altered the previous conclusions
18 December 2021	New search has been performed	New studies incorporated

HISTORY

Protocol first published: Issue 11, 2010
Review first published: Issue 2, 2013

Date	Event	Description
5 November 2019	Amended	Search strategies updated
24 November 2014	Amended	Feedback and reply incorporated
11 March 2013	New citation required but conclusions have not changed	Minor amendment to abstract

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: MR, SP
2. Study selection: NP, VS, MR, SP
3. Extract data from studies: NP, VS, MR, SP
4. Enter data into RevMan: NP, VS, MR, SP
5. Carry out the analysis: NP, VS, MR, SP
6. Interpret the analysis: NP, VS, MR, SP, JC, VP, SZ, AW, MJ, GFMS
7. Draft the final review: NP, VS, MR, SP, JC, VP, SZ, AW, MJ, GFMS
8. Disagreement resolution: GFMS
9. Update the review: NP, SP, GFMS

DECLARATIONS OF INTEREST

- Patrizia Natale has declared they have no conflict of interest
- Suetonia C Palmer has declared they have no conflict of interest
- Valeria M Saglimbene has declared they have no conflict of interest
- Marinella Ruospo has declared they have no conflict of interest
- Mona Razavian has declared they have no conflict of interest
- Jonathan C Craig has declared they have no conflict of interest
- Meg J Jardine is supported by a Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship; is responsible for research projects that have received unrestricted funding from Gambro, Baxter, CSL, Amgen, Eli Lilly, and MSD; has served on advisory boards sponsored by Akebia, Astra Zeneca, Baxter, Boehringer Ingelheim, Merck and Vifor; serves on Steering Committee for trials sponsored by Janssen and CSL; spoken at scientific meetings sponsored by Janssen, Amgen, Roche and Vifor; with any consultancy, honoraria or travel support paid to her institution
- Angela C Webster has declared they have no conflict of interest
- Giovanni FM Strippoli has declared they have no conflict of interest

Editorial contributions

- Sign-off Editor (final editorial decision): Dr Elisabeth Hodson

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We included studies of antiplatelet agents of fewer than two months follow-up, even if they did not provide outcome data for vascular access outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

*Platelet Aggregation Inhibitors [adverse effects]; Proteinuria; Renal Dialysis; *Renal Insufficiency, Chronic [complications] [therapy]

MeSH check words

Humans