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Continuation versus discontinuation of antiplatelet therapy for bleeding and ischaemic events in adults undergoing non-cardiac surgery (Review)

Lewis SR, Pritchard MW, Schofield-Robinson OJ, Alderson P, Smith AF

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[Intervention Review]

Continuation versus discontinuation of antiplatelet therapy for bleeding and ischaemic events in adults undergoing non-cardiac surgery

Sharon R Lewis[1], Michael W Pritchard[1], Oliver J Schofield-Robinson[1], Phil Alderson[2], Andrew F Smith[3]

[1]Lancaster Patient Safety Research Unit, Royal Lancaster Infirmary, Lancaster, UK. [2]National Institute for Health and Care Excellence, Manchester, UK. [3]Department of Anaesthesia, Royal Lancaster Infirmary, Lancaster, UK

Contact address: Sharon R Lewis, Lancaster Patient Safety Research Unit, Royal Lancaster Infirmary, Pointer Court 1, Ashton Road, Lancaster, LA1 4RP, UK. Sharon.Lewis@mbht.nhs.uk, sharonrlewis@googlemail.com.

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ABSTRACT

Background

Antiplatelet agents are recommended for people with myocardial infarction and acute coronary syndromes, transient ischaemic attack or stroke, and for those in whom coronary stents have been inserted. People who take antiplatelet agents are at increased risk of adverse events when undergoing non-cardiac surgery because of these indications. However, taking antiplatelet therapy also introduces risk to the person undergoing surgery because the likelihood of bleeding is increased. Discontinuing antiplatelet therapy before surgery might reduce this risk but subsequently it might make thrombotic problems, such as myocardial infarction, more likely.

Objectives

To compare the effects of continuation versus discontinuation for at least five days of antiplatelet therapy on the occurrence of bleeding and ischaemic events in adults undergoing non-cardiac surgery under general, spinal or regional anaesthesia.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 1), MEDLINE (1946 to January 2018), and Embase (1974 to January 2018). We searched clinical trials registers for ongoing studies, and conducted backward and forward citation searching of relevant articles.

Selection criteria

We included randomized controlled trials of adults who were taking single or dual antiplatelet therapy, for at least two weeks, and were scheduled for elective non-cardiac surgery. Included participants had at least one cardiac risk factor. We planned to include quasi-randomized studies.

We excluded people scheduled for minor surgeries under local anaesthetic or sedation in which bleeding that required transfusion or additional surgery was unlikely. We included studies which compared perioperative continuation of antiplatelet therapy versus discontinuation of antiplatelet therapy or versus substitution of antiplatelet therapy with a placebo for at least five days before surgery.

Data collection and analysis

Two review authors independently assessed studies for inclusion, extracted data, assessed risk of bias and synthesized findings. Our primary outcomes were: all-cause mortality at longest follow-up (up to six months); all-cause mortality (up to 30 days). Secondary

outcomes included: blood loss requiring transfusion of blood products; blood loss requiring further surgical intervention; risk of ischaemic events. We used GRADE to assess the quality of evidence for each outcome

Main results

We included five RCTs with 666 randomized adults. We identified three ongoing studies.

All study participants were scheduled for elective general surgery (including abdominal, urological, orthopaedic and gynaecological surgery) under general, spinal or regional anaesthesia. Studies compared continuation of single or dual antiplatelet therapy (aspirin or clopidogrel) with discontinuation of therapy for at least five days before surgery.

Three studies reported adequate methods of randomization, and two reported methods to conceal allocation. Three studies were placebo-controlled trials and were at low risk of performance bias, and three studies reported adequate methods to blind outcome assessors to group allocation. Attrition was limited in four studies and two studies had reported prospective registration with clinical trial registers and were at low risk of selective outcome reporting bias.

We reported mortality at two time points: the longest follow-up reported by study authors up to six months, and time point reported by study authors up to 30 days. Five studies reported mortality up to six months (of which four studies had a longest follow-up at 30 days, and one study at 90 days) and we found that either continuation or discontinuation of antiplatelet therapy may make little or no difference to mortality up to six months (risk ratio (RR) 1.21, 95% confidence interval (CI) 0.34 to 4.27; 659 participants; low-certainty evidence); the absolute effect is three more deaths per 1000 with continuation of antiplatelets (ranging from eight fewer to 40 more). Combining the four studies with a longest follow-up at 30 days alone showed the same effect estimate, and we found that either continuation or discontinuation of antiplatelet therapy may make little or no difference to mortality at 30 days after surgery (RR 1.21, 95% CI 0.34 to 4.27; 616 participants; low-certainty evidence); the absolute effect is three more deaths per 1000 with continuation of antiplatelets (ranging from nine fewer to 42 more).

We found that either continuation or discontinuation of antiplatelet therapy probably makes little or no difference in incidences of blood loss requiring transfusion (RR 1.37, 95% CI 0.83 to 2.26; 368 participants; absolute effect of 42 more participants per 1000 requiring transfusion in the continuation group, ranging from 19 fewer to 119 more; four studies; moderate-certainty evidence); and may make little or no difference in incidences of blood loss requiring additional surgery (RR 1.54, 95% CI 0.31 to 7.58; 368 participants; absolute effect of six more participants per 1000 requiring additional surgery in the continuation group, ranging from seven fewer to 71 more; four studies; low-certainty evidence). We found that either continuation or discontinuation of antiplatelet therapy may make little or no difference to incidences of ischaemic events (to include peripheral ischaemia, cerebral infarction, and myocardial infarction) within 30 days of surgery (RR 0.67, 95% CI 0.25 to 1.77; 616 participants; absolute effect of 17 fewer participants per 1000 with an ischaemic event in the continuation group, ranging from 39 fewer to 40 more; four studies; low-certainty evidence).

We used the GRADE approach to downgrade evidence for all outcomes owing to limited evidence from few studies. We noted a wide confidence in effect estimates for mortality at the end of follow-up and at 30 days, and for blood loss requiring transfusion which suggested imprecision. We noted visual differences in study results for ischaemic events which suggested inconsistency.

Authors' conclusions

We found low-certainty evidence that either continuation or discontinuation of antiplatelet therapy before non-cardiac surgery may make little or no difference to mortality, bleeding requiring surgical intervention, or ischaemic events. We found moderate-certainty evidence that either continuation or discontinuation of antiplatelet therapy before non-cardiac surgery probably makes little or no difference to bleeding requiring transfusion. Evidence was limited to few studies with few participants, and with few events. The three ongoing studies may alter the conclusions of the review once published and assessed.

PLAIN LANGUAGE SUMMARY

To continue taking or to stop taking antiplatelet drugs for a few days before non-cardiac surgery in adults

Review question

We set out to determine whether continuing to take antiplatelet drugs before non-cardiac surgery that requires general, spinal or regional anaesthesia increases the risk of experiencing serious bleeding, ischaemic event or death in adults, when compared with stopping antiplatelet drugs for at least five days before non-cardiac surgery.

Background

Antiplatelet drugs such as aspirin or clopidogrel reduce the risk of people getting blood clots, and are routinely prescribed for people who have had coronary stents inserted. They are also recommended for people with unstable angina or heart disease, or people who have had a heart attack, heart surgery or a stroke. Taking antiplatelet therapy introduces an increased risk of bleeding, which could lead to problems if a person needs non-cardiac surgery. Stopping usual antiplatelet therapy a few days before surgery might reduce the risk of serious bleeding during surgery. Not taking these antiplatelet drugs could, however, increase the risk of a heart attack, stroke, or death.

Study characteristics

The evidence from randomized controlled trials is current to January 2018. We included five trials with 666 adults in the review. Three studies are ongoing. All participants were taking antiplatelet therapy (aspirin or clopidogrel) at the start of the study. Two studies stopped antiplatelet drugs for at least five days before surgery, and three studies gave participants a placebo instead of antiplatelet therapy during this time.

Key results

We found low-certainty evidence that either continuing or stopping antiplatelet therapy may make little or no difference to the number of people who died up to 30 days or six months after surgery (five studies, 659 participants). We found moderate-certainty evidence that either continuing or stopping antiplatelet therapy probably makes little or no difference to incidences of bleeding serious enough to need a blood transfusion during or immediately after surgery (four studies, 368 participants). We found low-certainty evidence that either continuing or stopping antiplatelet therapy may make little or no difference to bleeding serious enough to need further surgery (four studies, 368 participants), and may make little or no difference to the number of ischaemic events such as stroke or heart attack (four studies, 616 participants).

Quality of the evidence

Some studies had low risk of bias because they had clearly reported their methods for randomizing people to each group, and three studies used a placebo agent so that people did not know whether or not they were continuing their usual antiplatelet therapy. However, we found few studies with few events, with wide variation in results. To continue or stop taking antiplatelet drugs for a few days before non-cardiac surgery might make little or no difference to the number of people who died, who had bleeding that needed further surgery or who had ischaemic events, and it probably makes little or no difference to bleeding that needed a blood transfusion. We found three ongoing studies which will increase certainty in the effect in future updates of the review.

Summary of findings for the main comparison. Continuation versus discontinuation of antiplatelet therapy for bleeding and ischaemic events in adults undergoing non-cardiac surgery

Continuation versus discontinuation of antiplatelet therapy for bleeding and ischaemic events in adults undergoing non-cardiac surgery

Population: adults undergoing non-cardiac surgery (including abdominal, urological, orthopaedic, and gynaecological surgery)
Setting: hospitals in: Denmark, France, Germany, Sweden, USA
Intervention: continuation of antiplatelet therapy (aspirin, clopidogrel, ticlopidine, or others)
Comparison: discontinuation of antiplatelet therapy; or replacement of antiplatelet therapy with a placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of randomized participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with discontinuation	Risk with continuation				
All-cause mortality (at longest follow-up reported by study authors up to 6 months)	Study population 12 per 1,000	15 per 1,000 (4 to 52)	RR 1.21 (0.34 to 4.27)	659 (5 studies)	⊕⊕⊖⊖ **Low**[1]	4 studies reported longest follow-up at 30 days; 1 study reported longest follow-up at 90 days
All-cause mortality (up to 30 days)	Study population 13 per 1,000	16 per 1,000 (4 to 55)	RR 1.21 (0.34 to 4.27)	616 (4 studies)	⊕⊕⊖⊖ **Low**[1]	4 studies reported mortality at 30 days
Blood loss requiring transfusion of blood products (intraoperatively and postoperatively)	Study population 114 per 1,000	156 per 1,000 (94 to 257)	RR 1.37 (0.83 to 2.26)	368 (4 studies)	⊕⊕⊕⊖ **Moderate**[2]	
Blood loss requiring further surgery (intraoperatively and postoperatively)	Study population 11 per 1,000	17 per 1,000 (3 to 82)	RR 1.54 (0.31 to 7.58)	368 (4 studies)	⊕⊕⊖⊖ **Low**[1]	
Ischaemic events: peripheral thrombosis,	Study population 52 per 1,000	35 per 1,000	RR 0.67 (0.25 to 1.77)	616 (4 studies)	⊕⊕⊖⊖ **Low**[3]	2 studies reported data for major thrombotic events (defined as acute myocardial infarction, severe arrhythmia, cardiac arrest, cardiovascu-

cerebral myocardial infarction (within 30 days of surgery)		(13 to 91)		lar death, stroke, transient ischaemic attack, acute coronary syndrome, peripheral arterial ischaemia, mesenteric arterial ischaemia, deep proximal or distal venous thrombosis, and pulmonary embolism); 1 study reported data for myocardial infarction; and 1 study reported data for cardio-cerebrovascular events (which included acute myocardial infarction, severe arrhythmia, cardiac arrest, cardiovascular death, transient ischaemic attack or stroke)

*__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.

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] We downgraded by 2 levels for imprecision because we noted a wide CI for this effect, and because event data were limited to few studies
[2]We downgraded by 1 level for imprecision because event data were limited to few studies
[3]We downgraded by 1 level for imprecision because event data were limited to few studies and by 1 level for inconsistency because we noted visual differences in results

BACKGROUND

Description of the condition

Platelets play a major role in the pathogenesis of atherosclerotic and thrombotic diseases. Drugs intended to prevent or treat these diseases are widely used. Antiplatelet agents are recommended for people with myocardial infarction and acute coronary syndromes, transient ischaemic attack or stroke, and for those in whom coronary stents have been inserted (NICE 2010). Many people are prescribed two antiplatelet drugs (typically aspirin plus another drug), especially after acute coronary syndromes and coronary artery stenting. In the latter context, these drugs are needed to prevent clots from forming and blocking the stent until normal vascular endothelium grows over the metal of the stent. Stents of different types ('bare metal' or 'drug-eluting') require different durations of treatment; for instance, dual antiplatelet therapy with aspirin and clopidogrel is recommended for at least one month after insertion of a bare metal stent, and for at least 12 months after insertion of a drug-eluting stent (Levine 2016). Interfering with platelet function naturally increases risk of bleeding, but in general this risk is low enough to be acceptable (Sorensen 2009). Anticoagulants such as warfarin are often used to prevent and treat thrombosis, and can also cause bleeding significant enough to warrant pharmacological reversal (Johanson 2015); these are outside the scope of this review.

In the year after stent insertion, about 4% of people will have to undergo non-cardiac surgery (Berger 2010). Such procedures carry increased risk of an adverse outcome, as both myocardial infarction (Hawn 2013; Wijeysundera 2012), and significant bleeding (Singla 2012), are more likely. However, premature discontinuation of dual antiplatelet therapy can be fatal (Korte 2011), in people with coronary stents. On the other hand, dual antiplatelet therapy used for primary prevention of cardiac or cerebrovascular events can be stopped before surgery without major consequences (Oprea 2013).

Description of the intervention

Commonly used antiplatelet agents fall into three pharmacological classes: thromboxane A2 inhibitors (aspirin), thienopyridines (clopidogrel, prasugrel and ticlopidine) and cyclopentyltriazolopyrimidines (ticagrelor).

Aspirin irreversibly inhibits the enzyme cyclo-oxygenase 1, leading to loss of platelet aggregation. This effect persists for the lifespan of the platelet, which is seven to 10 days (Oprea 2013). The remaining drugs act on the P2Y12 receptor on the platelet surface, preventing it from binding with adenosine diphosphate (ADP) and thus inhibiting aggregation (Oprea 2013). Again, for clopidogrel, this effect is irreversible and lasts as long as the platelet itself. Thus it is necessary to discontinue these agents for at least one week to allow their effects to wear off. Ticagrelor, on the other hand, is a reversible antagonist at the ADP receptor, although reversal of its clinical effect might not be straightforward.

How the intervention might work

The person on antiplatelet agents undergoing surgery is therefore at risk for two types of complications: bleeding and thrombosis. Which carries greater risk will depend on the indications for the antiplatelet agent and on the type of surgery proposed; these and other factors can be incorporated into a 'matrix' to help balance the risks for an individual patient (Korte 2011; Rossini 2014). Discontinuing the antiplatelet agent might make thrombotic problems such as myocardial infarction more likely; on the other hand, performing surgery when antiplatelet drugs are still active in the body is likely to increase bleeding. To complicate matters, the haemodynamic instability caused by severe bleeding might in itself lead to myocardial ischaemia and infarction (Devereaux 2016). Some recent studies (Mantz 2011; Oscarsson 2010), have investigated the effects of continuing or discontinuing aspirin during the perioperative period; results demonstrate no difference in the number of bleeding events (Mantz 2011; Oscarsson 2010), but a reduction in the number of major adverse cardiac events when aspirin is continued during the perioperative period (Oscarsson 2010).

Why it is important to do this review

Current recommendations are to usually continue antiplatelet therapy for people with a coronary artery stent (Fleisher 2014; Oprea 2013), and that very low bleeding risk procedures might be undertaken without stopping dual antiplatelet therapy (Keeling 2016). However, very recent evidence suggests that the relationship between continuation of antiplatelet agents and reduced thrombotic complications might not be as simple as one might suppose (Wasowicz 2016). Given this uncertainty and the large numbers of people affected worldwide, a systematic review of available high-quality evidence is necessary. The results of this review might inform clinical guidelines and might have implications for the costs of health care.

OBJECTIVES

To compare the effects of continuation versus discontinuation for at least five days of antiplatelet therapy on the occurrence of bleeding and ischaemic events in adults undergoing non-cardiac surgery under general, spinal or regional anaesthesia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs). We planned to include quasi-randomized studies (e.g. studies in which participants are assigned by alternation, date of birth or medical record number).

Cluster-RCTs were not eligible for inclusion.

Types of participants

We included studies involving adults who were taking antiplatelet therapy for at least two weeks, and were scheduled for elective surgery. Antiplatelet therapy was prescribed as single or dual therapy to include all antiplatelet agents, such as aspirin, clopidogrel, prasugrel, ticlopidine or ticagrelor. Included participants had at least one cardiac risk factor.

We included studies involving people scheduled for surgery under general, spinal or regional anaesthesia. We excluded people scheduled for cardiac surgery, which requires different clinical management (Wong 2016). We excluded people scheduled for minor surgeries (such as dental extraction) under local anaesthetic or sedation.

Types of interventions

We included studies that compared perioperative continuation of antiplatelet agents (i.e. continuation of dual or single agent therapy during the preoperative, intraoperative and postoperative periods) with discontinuation of antiplatelet therapy for five days or longer before surgery.

We included studies that administered a placebo or no treatment during the discontinuation phase. We planned to exclude studies that continued only one agent in a dual therapy, and also those which assessed the effects of other drugs initiated before surgery (Sanders 2013; Zhao 2016; Zou 2016).

Types of outcome measures

We aimed to establish whether risk of bleeding is affected by continuation of antiplatelet therapy. Therefore, we collected data on two measures of bleeding: the number of patients requiring transfusion of any blood product owing to blood loss during or after surgery; and the number of patients requiring additional surgical intervention for blood loss during or after surgery. Both continuation and discontinuation of antiplatelets might increase the risk of ischaemic events, and we collected composite data on ischaemic events. We recorded ischaemic events for a follow-up period of 30 days and recorded the number of deaths at two time points: the longest follow-up time point reported by study authors up to six months, and time points reported by study authors up to 30 days.

Primary outcomes

1. All-cause mortality at longest follow-up (up to six months)
2. All-cause mortality (up to 30 days)

Secondary outcomes

1. Blood loss requiring transfusion of blood products (intraoperatively and postoperatively)
2. Blood loss requiring further surgical intervention (intraoperatively and postoperatively)
3. Risk of ischaemic events: peripheral thrombosis, cerebral infarction, myocardial infarction within 30 days

Search methods for identification of studies

Electronic searches

We identified RCTs through literature searching with systematic and sensitive search strategies as outlined in Chapter 6.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We applied no restrictions to language or publication status.

We searched the following databases for relevant trials.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 1) in the Cochrane Library (searched 2 January 2018)
2. MEDLINE (OvidSP, 1946 to 2 January 2018)
3. Embase (OvidSP, 1974 to 2 January 2018)

We developed a subject-specific search strategy in MEDLINE and used that as the basis for the search strategies in the other listed databases. The search strategy was developed in consultation with the Information Specialist. Search strategies can be found in Appendix 1, Appendix 2, and Appendix 3.

We scanned the following trial registries for ongoing and unpublished trials (24 July 2017).

1. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/AdvSearch.aspx).
2. ClinicalTrials.gov (ClinicalTrials.gov).

Searching other resources

We carried out citation searching of identified included studies in Web of Science (apps.webofknowledge.com), on 3 January 2018 and conducted a search of grey literature through 'Opengrey' (www.opengrey.eu), on 1 August 2017. We carried out backward citation searching of key reviews identified from the searches. We did not need to contact study authors or organizations.

Data collection and analysis

We (Sharon Lewis (SL) and Oliver Schofield-Robinson (OSR)) independently completed all data collection and analysis before comparing results and reaching consensus. We consulted a third review author (Phil Alderson (PA) or Andrew Smith (AS)) to resolve conflicts when necessary.

Selection of studies

We used reference management software to collate the results of searches and to remove duplicates (Endnote). We used Covidence software to screen the results of the search from titles and abstracts, identify potentially relevant studies (Covidence) and consider whether they met the inclusion criteria (see Criteria for considering studies for this review). We included abstracts at this stage. However, we planned to include abstracts in the review only if they contained sufficient information and relevant results that included denominator figures for each intervention/comparison group. We recorded the number of papers retrieved at each stage, and reported this information using a PRISMA flow chart (Liberati 2009). We reported in the review brief details of closely related, but excluded, papers.

Data extraction and management

We used Covidence software to extract data from individual studies (Covidence). A basic template of the data extraction forms is available at www.covidence.org. We adapted the template to include the following information.

1. Methods: the type of study design; setting; dates of study; funding sources.
2. Participants: the number of participants randomized to each group; baseline characteristics; type of surgery; type of antiplatelet therapy and duration of administration.
3. Interventions/comparison: type of control (placebo or no treatment); time of discontinuation of antiplatelet therapy before surgery.
4. Outcomes: all relevant review outcomes measured and reported by study authors.
5. Outcome data: the results of outcome measures.

We considered the applicability of information from individual studies and the generalizability of data to our intended study population (i.e. the potential for indirectness in our review). Had we

identified associated publications from the same study, we planned to create a composite dataset from all eligible publications.

Assessment of risk of bias in included studies

Two review authors (SL and OSR) independently assessed study quality, study limitations and extent of potential bias using the Cochrane 'Risk of bias' tool (Higgins 2011). We considered the following domains.

1. Sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding of participants, personnel and outcome assessors (performance and detection bias).
4. Incomplete outcome data (attrition bias).
5. Selective outcome reporting (reporting bias).
6. Other.

For each domain, we judged whether study authors made sufficient attempts to minimize bias in their study design. We made judgements using one of three measures (high, low or unclear risk of bias). We recorded this information in the 'Risk of bias' tables and presented a summary 'Risk of bias'.

Measures of treatment effect

To calculate risk ratios (RR), we collected dichotomous data for outcomes related to mortality, number of participants requiring transfusion of blood products or additional surgery for blood loss and number of participants having an ischaemic event.

Unit of analysis issues

If we had included multi-arm studies comparing different antiplatelet agents or comparing dual- and single-agent therapies versus a control, we planned to include both comparison groups but split the data for the control group, using a 'halving' method to avoid double-counting, as recommended by *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We collected risk of ischaemic events as composite data. We reported the number of participants who have had at least one ischaemic event and paid attention to how study authors reported this outcome to avoid a unit of analysis issue in which a participant might have experienced more than one different event.

Dealing with missing data

We assessed whether all measured outcomes had been reported by study authors by comparing, when possible, published reports with protocols or clinical trial registration documents that had been prospectively published.

We assessed whether all randomized participants were included in outcome data. We did not need to contact study authors for missing data.

Assessment of heterogeneity

We assessed evidence of inconsistency within our results through consideration of heterogeneity. We assessed clinical heterogeneity by comparing differences in study design, participants, interventions and outcomes in our included studies using the data we collected during data extraction. We assessed statistical heterogeneity by calculating the Chi^2 P value or the I^2 statistic. We judged any heterogeneity above an I^2 statistic of 60% and a Chi^2 P value of 0.05 or less to indicate moderate to substantial statistical heterogeneity (Higgins 2011).

As well as looking at the statistical results, we considered point estimates and overlap of confidence intervals (CIs). If the CIs overlap, the results are more consistent. However, combined studies might show a large consistent effect but with significant heterogeneity. Therefore, we planned to interpret heterogeneity with caution (Guyatt 2011).

Assessment of reporting biases

We attempted to source published protocols for each of our included studies using clinical trial registers. We compared published protocols with published study results to assess the risk of selective reporting bias. Had we identified sufficient studies (i.e. more than 10) (Higgins 2011), we planned to generate a funnel plot to assess risk of publication bias in the review; an asymmetrical funnel plot might indicate publication of only positive results (Egger 1997).

Data synthesis

We completed meta-analysis for outcomes for which we had comparable effect measures from more than one study and when measures of heterogeneity indicated that pooling of results was appropriate. We used Review Manager 5 (Review Manager 2014), to perform meta-analysis.

For each outcome, we calculated risk ratios (RRs) using the summary data presented in each trial report. We used a Mantel-Haenszel effects model, unless events were extremely rare (1 per 1000), in which case we planned to use Peto odds ratios (Higgins 2011). We used a random-effects statistical model to account for the variation in different types of surgical procedures in studies (Borenstein 2010). If evidence suggested moderate statistical or clinical heterogeneity, we planned to investigate this by performing subgroup analyses, as below.

Subgroup analysis and investigation of heterogeneity

We aimed to use subgroup analysis to address potential differences in the population group for which the risk-benefit ratios might differ according to continuation or discontinuation of the drug; whether people were taking a single or dual antiplatelet therapy; and whether they have coronary stents. We also aimed to address whether there is an optimum point at which antiplatelets can be discontinued; people whose therapy has been discontinued earlier than five days might be at increased risk of ischaemic events (Korte 2011).

We planned to perform subgroup analyses as follows.

1. Single antiplatelet treatment versus dual therapy.
2. Coronary stents versus no coronary stents.
3. Discontinuation of antiplatelet agents within five days before surgery versus discontinuation at more than five days before surgery.

Sensitivity analysis

We planned to explore potential effects of decisions made as part of the review process as follows.

1. Excluding all studies that we judged to be at high or unclear risk of selection bias.
2. Using the alternate meta-analytical effects model (fixed-effect).

We compared effect estimates from the above results with effect estimates from the main analysis. We planned to report differences that alter interpretation of the effect. We planned to perform sensitivity analysis on all of our outcomes.

In sensitivity analysis, we used trial sequential analysis on our primary outcomes using software from The Copenhagen Trial Unit (www.ctu.dk/); this alternative meta-analytic method accounted for studies with zero events. See Differences between protocol and review. Also, we assessed decisions made on individual studies as part of the review process.

'Summary of findings' table and GRADE

The GRADE approach incorporates assessment of indirectness, study limitations, inconsistency, publication bias and imprecision. We assessed the certainty of the evidence (high, moderate, low, and very low) using these five GRADE considerations and, if required, downgraded the evidence by one or two levels using assessments at each stage of our analysis (Data collection and analysis; Assessment of risk of bias in included studies; Assessment of heterogeneity; Assessment of reporting biases; Data synthesis). This approach gives an overall measure of how certain we can be that our estimate of effect is correct (Guyatt 2008).

We used the principles of the GRADE system to give an overall assessment of evidence certainty related to each of the following outcomes.

1. All-cause mortality at longest follow-up (up to six months).
2. All-cause mortality at longest follow-up (up to 30 days).
3. Blood loss requiring transfusion of blood products.
4. Blood loss requiring further surgical intervention.
5. Risk of ischaemic events: peripheral thrombosis, cerebral infarction, myocardial infarction within 30 days.

One review author (SL) used GRADEpro software (GRADEpro GDT), to create a 'Summary of findings' table for each comparison (www.guidelinedevelopment.org/). A second author (PA) assessed judgements made and consensus was reached through discussion.

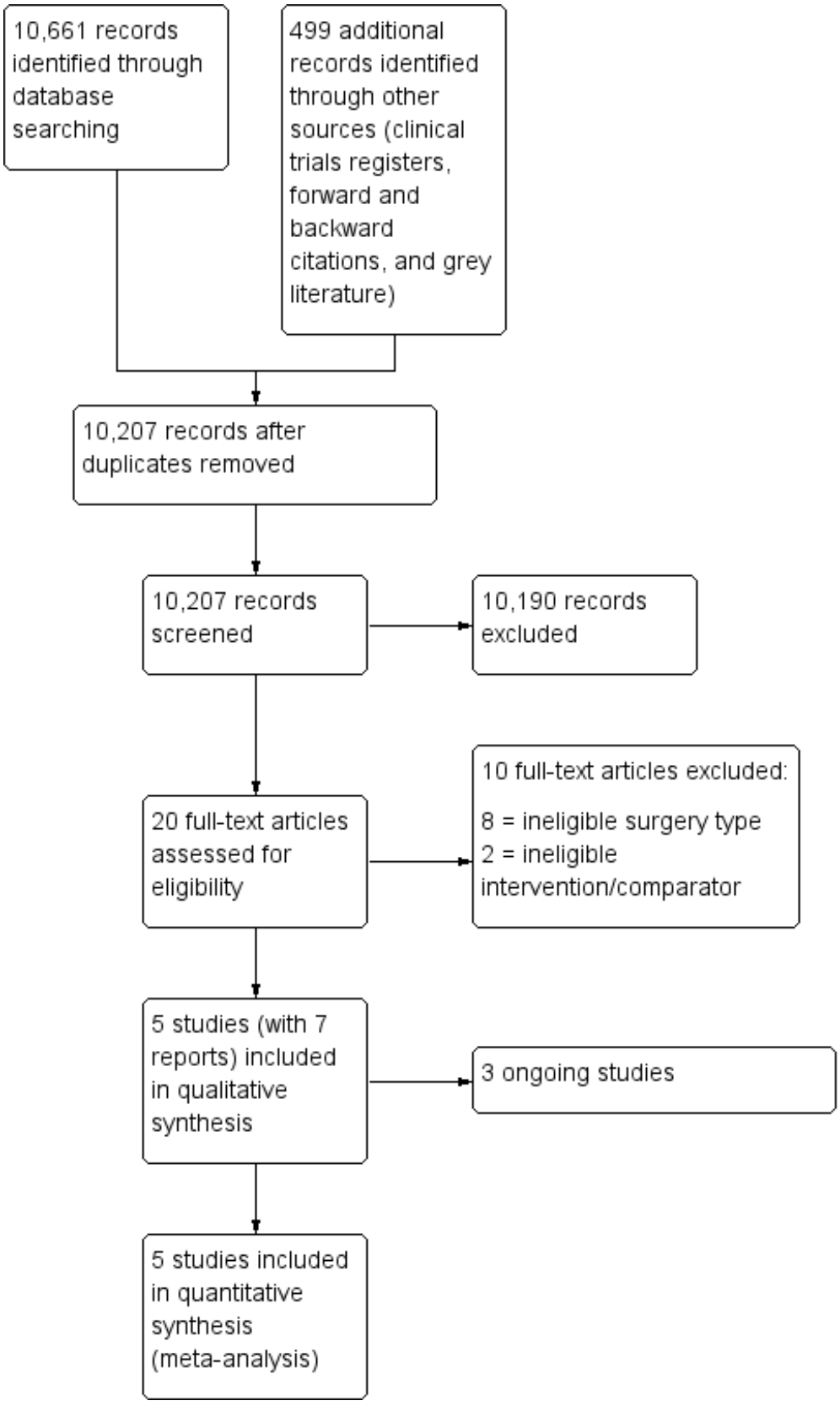
RESULTS

Description of studies

Results of the search

After removing duplicates we screened 10,207 titles and abstracts from database searches, results from clinical trial register searches, grey literature searches, and forward and backward citation searches. We carried out full-text review of 20 articles. We excluded 10 studies. We identified five eligible studies which were randomized controlled trials (RCTs) (two studies had two publications); we found no quasi-randomized studies. We found three ongoing studies. See Figure 1.

Figure 1. Study flow diagram.



Included studies

We included five RCTs with 666 participants (Antolovic 2012; Chu 2016; Mantz 2011; Nielsen 2000; Oscarsson 2010). All studies were parallel design, three were single-centre studies (Antolovic 2012; Chu 2016; Nielsen 2000), and two were multi-centre studies (Mantz 2011; Oscarsson 2010). Two studies had anticipated recruitment of more participants, but stopped early due to recruitment difficulties (Mantz 2011; Oscarsson 2010). In addition, Oscarsson 2010, reported early stopping because of publication during the study period of guidelines about the management of high-risk patients taking aspirin. See Characteristics of included studies tables.

Study population and setting

Participants were adults scheduled for general elective surgery as follows.

1. Inguinal hernia repair, cholecystectomy, colonic/colorectal, laparoscopic (Antolovic 2012).
2. Open inguinal hernia repair, laparoscopic cholecystectomy, laparoscopic or open ventral hernia repair, laparoscopic inguinal repair, Nissen's fundoplication, ostomy closure, open sigmoidectomy and ileostomy (Chu 2016).
3. Orthopaedic, abdominal, urologic, thoracic, oncologic, ears, nose, and throat (ENT) (Mantz 2011).
4. Transurethral prostatectomy (Nielsen 2000) and
5. Abdominal, urologic, orthopaedic, gynaecologic (Oscarsson 2010).

Three studies reported surgery completed under general anaesthesia: in 65.4% participants (Antolovic 2012); in 82% participants (Mantz 2011); and in 22.3% participants (Oscarsson 2010). Surgery was completed using spinal anaesthesia in all participants in Nielsen 2000. One study did not report the type of anaesthesia (Chu 2016).

Three studies reported the number of participants who had coronary stents: 25% participants in Antolovic 2012; 72.1% participants in Chu 2016; and 13.1% participants in Mantz 2011. The studies did not report the length of time since stent insertion. Two studies did not report the number of participants with coronary stents (Nielsen 2000; Oscarsson 2010); one study reported change to study inclusion criteria with a decision to exclude participants with coronary stents in the second year of study (Oscarsson 2010).

Interventions and comparators

In four studies, all participants were on existing antiplatelet therapy (Antolovic 2012; Chu 2016; Mantz 2011; Nielsen 2000), which was: aspirin (100 mg in Antolovic 2012; 150 mg to 300 mg in Nielsen 2000); clopidogrel (75 mg as a single therapy, or in 66.7% participants as dual therapy with aspirin in Chu 2016); and any antiplatelet agent (aspirin, clopidogrel, or ticlopidine and others) in Mantz 2011. In one study, 90% participants were on existing antiplatelet therapy with aspirin (Oscarsson 2010). The studies did not report the length of time that participants had been taking antiplatelet therapy, and we assumed that all participants had been taking antiplatelets for at least two weeks.

Three studies were placebo-controlled trials (Mantz 2011; Nielsen 2000; Oscarsson 2010). These studies substituted existing therapy with placebo or with aspirin (75 mg aspirin in Mantz 2011 and Oscarsson 2010; 150 mg aspirin in Nielsen 2000).

In two studies, participants continued existing antiplatelet therapy at existing dose or discontinued existing antiplatelet therapy without substitution agent during study period (Antolovic 2012; Chu 2016).

Time points for discontinuation of antiplatelet prior to surgery were at: five days before surgery (Antolovic 2012); seven days before surgery (Chu 2016; Oscarsson 2010); and 10 days before surgery (Mantz 2011; Nielsen 2000).

Sources of funding

Four studies reported the sources of funding (Chu 2016; Mantz 2011; Nielsen 2000; Oscarsson 2010). We noted support from pharmaceutical companies in two of these studies (Nielsen 2000; Oscarsson 2010). One study did not report the sources of funding (Antolovic 2012), and the study authors declared no conflict of interest.

Excluded studies

We excluded 10 studies from review of full-text articles (Ardekian 2000; Assia 1998; Danino 2007; Devereaux 2014; Duygu 2010; Eapen 2017; Engheta 2016; Gaspar 1999; Medeiros 2011; Varghese 2015). In one study, interruption of long-term antiplatelet therapy was compared with a substitution agent rather than no agent or a placebo (Danino 2007). One study compared antiplatelets with a placebo, and participants were stratified according to whether they were previously taking antiplatelets; participants who were taking antiplatelets were required to stop treatment for at least three days prior to surgery. We excluded this study because of interruption to treatment (Devereaux 2014). We excluded eight studies because surgery was minor and either under local anaesthetic or sedation (Ardekian 2000; Assia 1998; Duygu 2010; Eapen 2017; Engheta 2016; Gaspar 1999; Medeiros 2011; Varghese 2015). These surgery types were not comparable to other non-cardiac surgical procedures included in the review. We also noted that the risk of bleeding in the studies was limited to use of local haemostatic measures to control bleeding events. See Characteristics of excluded studies.

Awaiting classification

There are no studies awaiting classification.

Ongoing studies

We found three ongoing studies in clinical trials register searches (NCT01806090; NCT02797548; NCT03184805). The studies have an anticipated recruitment of 4616 participants, and compare continuation versus discontinuation of antiplatelet therapy before non-cardiac surgery in adults. See Characteristics of ongoing studies.

Risk of bias in included studies

See Characteristics of included studies tables, and 'Risk of bias' summary and 'Risk of bias' graph (Figure 2; Figure 3).

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

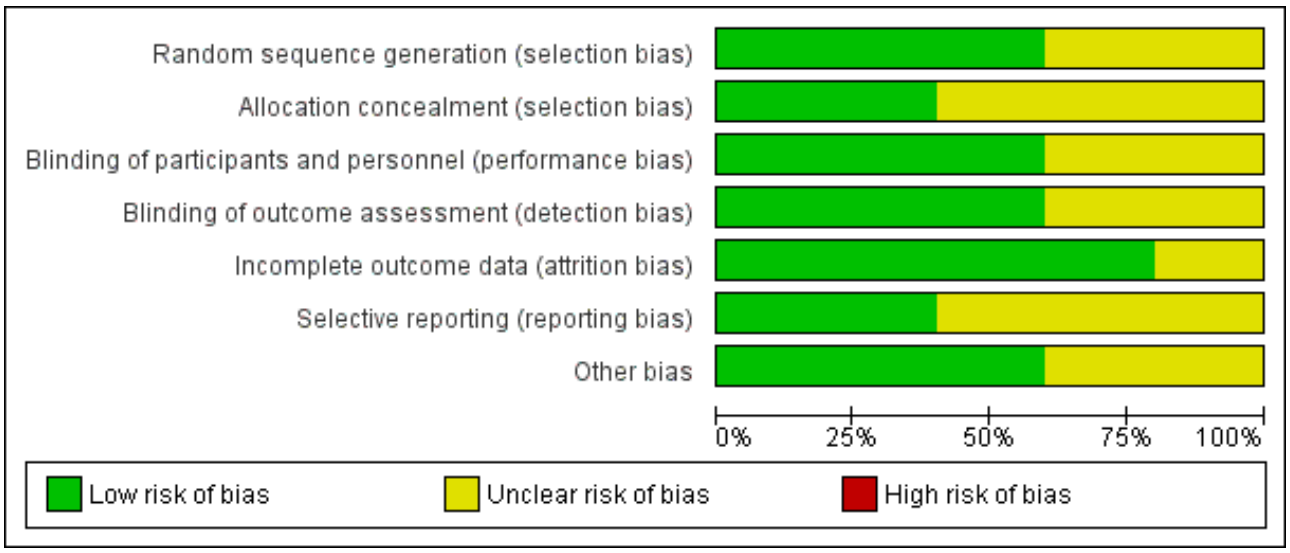
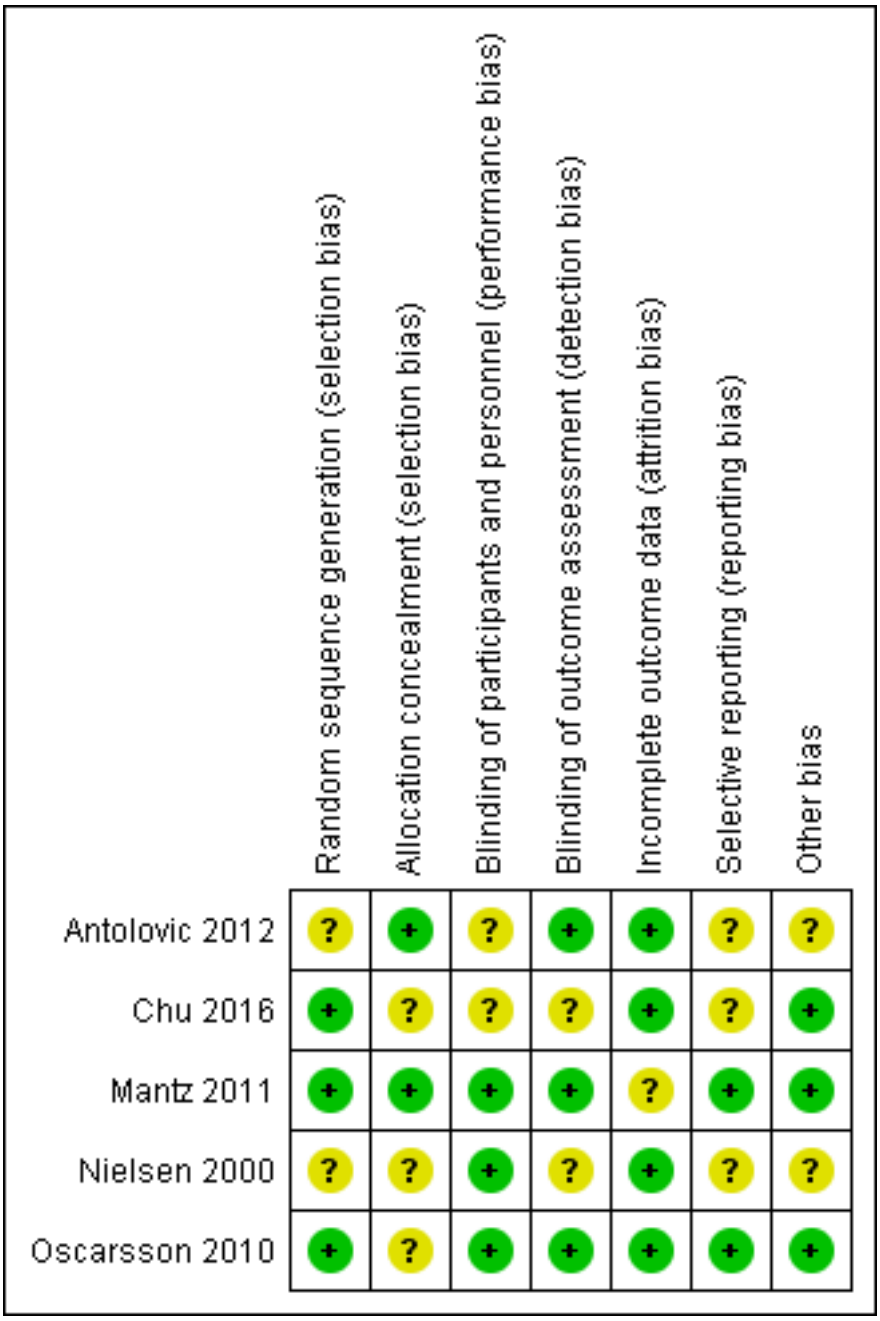


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All included studies were described as randomized, and we judged three of the five studies to have a low risk of bias because they provided sufficient details on the method of randomization (Chu 2016; Mantz 2011; Oscarsson 2010). Two studies reported no details of the method of randomization, and we judged these studies to have an unclear risk of bias (Antolovic 2012; Nielsen 2000).

Two studies reported sufficient detail about methods used to conceal allocation, and we judged these studies to have low risk of bias for allocation concealment (Antolovic 2012; Mantz 2011). The three remaining studies reported no details of allocation concealment, and we judged these studies to have an unclear risk of bias.

Blinding

Three studies were placebo-controlled trials and study authors reported, or we assumed, that participants and personnel were blinded to group allocation. We judged these three studies to have low risk of performance bias (Mantz 2011; Nielsen 2000; Oscarsson 2010). One study reported that participants were not blinded to group allocation (Chu 2016), and one study reported no information about blinding of participants and personnel (Antolovic 2012).We judged these studies to have and unclear risk of performance bias. However, we acknowledge that it is possible

that awareness of group allocation might influence outcome data because some participants might not have adhered to study protocol if requested to discontinue regular antiplatelet therapy.

Three studies reported that outcome assessors were blinded, and we judged these studies to be at low risk of detection bias (Antolovic 2012; Mantz 2011; Oscarsson 2010). The two remaining studies reported insufficient information about blinding of outcome assessors, and we judged these studies to have an unclear risk of bias (Chu 2016; Nielsen 2000).

Incomplete outcome data

Four studies reported no participant losses during the trial or few losses, and we judged these to have low risk of attrition bias (Antolovic 2012; Chu 2016; Nielsen 2000; Oscarsson 2010). One study reported a large number of losses (Mantz 2011), but study authors reported reasons for these losses. We judged this study to have unclear risk of bias because we noted more losses in the continuation group, and we could not be certain of the effect of these losses on the results.

Selective reporting

We found registration with clinical trial registers for two studies, and outcomes were reported according to these documents.We judged these studies to have low risk of selective reporting bias (Mantz 2011; Oscarsson 2010). Two studies reported retrospective clinical trial registration, and it was not feasible to use these documents to assess risk of selective reporting bias (Antolovic 2012; Chu 2016). One study did not report details of a published protocol (Nielsen 2000). We judged these studies to have unclear risk of selective reporting bias.

Other potential sources of bias

One study reported limited baseline characteristics, and details of existing antiplatelet therapies (Nielsen 2000). We noted a difference in ranges of ages between groups in one study (Antolovic 2012). We were unclear whether information that was not reported might have influenced the study results, and we judged these studies to have an unclear of risk of other bias. We noted no other sources of bias in the three remaining studies which we judged to have low risk of bias (Chu 2016; Mantz 2011; Oscarsson 2010).

Effects of interventions

See: **Summary of findings for the main comparison** Continuation versus discontinuation of antiplatelet therapy for bleeding and ischaemic events in adults undergoing non-cardiac surgery

Primary outcomes

1. All-cause mortality at longest follow-up (up to six months)

All five studies reported mortality (Antolovic 2012; Chu 2016; Mantz 2011; Nielsen 2000; Oscarsson 2010). Longest follow-up time points for data were 30 days after surgery in four studies (Antolovic 2012; Mantz 2011; Nielsen 2000; Oscarsson 2010), and at 90 days in one study (Chu 2016).

We noted no evidence of a difference in deaths according to whether participants continued or discontinued antiplatelet therapy (risk ratio (RR) 1.21, 95% confidence interval (CI) 0.34 to 4.27; 659 participants; Analysis 1.1).

We used the GRADE approach to downgrade the evidence to low quality. We downgraded by two levels for imprecision because we noted a wide CI for this effect and because event data were limited to only three of the five studies. See Summary of findings for the main comparison.

2. All-cause mortality (up to 30 days)

Four studies reported mortality at 30 days (Antolovic 2012; Mantz 2011; Nielsen 2000; Oscarsson 2010).

We noted no evidence of a difference in deaths according to whether participants continued or discontinued antiplatelet therapy (RR 1.21, 95% CI 0.34 to 4.27; 616 participants; Analysis 1.2).

We used the GRADE approach to downgrade the evidence to low quality. We downgraded by two levels for imprecision because we noted a wide CI for this effect and because event data were limited to only three of the four studies. See Summary of findings for the main comparison.

Secondary outcomes

1. Blood loss requiring transfusion of blood products (intraoperatively and postoperatively)

Four studies reported blood loss requiring transfusion (Antolovic 2012; Chu 2016; Nielsen 2000; Oscarsson 2010). We interpreted data in Nielsen 2000, from a graph in the published report. One study reported major bleeding events but did not define major bleeding by need for transfusion or surgery and we could not include these data in the analysis (Mantz 2011). We noted no difference between groups in these data and have reported the results separately in Table 1. Bleeding was not monitored in any of these trials (Wikkelsø 2016).

We noted no evidence of a difference in the number of participants requiring blood transfusions according to whether participants continued or discontinued antiplatelets (RR 1.37, 95% CI 0.83 to 2.26; 368 participants; Analysis 1.3).

We used the GRADE approach to downgrade the evidence to moderate quality. We downgraded by one level for imprecision because event data were limited to only three of four studies. See Summary of findings for the main comparison.

2. Blood loss requiring further surgical intervention (intraoperatively and postoperatively)

Four studies reported blood loss requiring surgical intervention (Antolovic 2012; Chu 2016; Nielsen 2000; Oscarsson 2010). One study reported major bleeding events but did not define major bleeding by need for transfusion or surgery, and we could not include these data in analysis (Mantz 2011). We noted no difference between groups in these data and have reported it separately in Table 1.

We noted no difference in number of participants with blood loss requiring surgical interventions (RR 1.54, 95% CI 0.31 to 7.58; 368 participants; Analysis 1.4).

We used the GRADE approach to downgrade the evidence to low quality. We downgraded by two levels for imprecision because event data were limited to only three of four studies and because we noted a wide CI for this effect. See Summary of findings for the main comparison.

3. Risk of ischaemic events: peripheral thrombosis, cerebral infarction, myocardial infarction within 30 days

Four studies reported ischaemic events (Antolovic 2012; Mantz 2011; Nielsen 2000; Oscarsson 2010). We reported data collected for major thrombotic events (defined as acute myocardial infarction, severe arrhythmia, cardiac arrest, cardiovascular death, severe pulmonary embolism, transient ischaemic attack, or stroke in Antolovic 2012; and defined as stroke, transient ischaemic attack, acute coronary syndrome, peripheral arterial ischaemia, mesenteric arterial ischaemia, deep proximal and distal venous thrombosis, and pulmonary embolism in Mantz 2011); for myocardial infarction in Nielsen 2000; and for cardio-cerebrovascular events (which included acute myocardial infarction, severe arrhythmia, cardiac arrest, cardiovascular death, transient ischaemic attack or stroke) in Oscarsson 2010.

We noted no evidence of a difference in number of participants with an ischaemic event (RR 0.67, 95% CI 0.25 to 1.77; 616 participants; Analysis 1.5).

We used the GRADE approach to downgrade the evidence to low quality. We downgraded by one level for imprecision because event data were limited to only three of four studies. We downgraded by one level for inconsistency because we noted visual differences in results. See Summary of findings for the main comparison.

Subgroup analysis

We did not conduct subgroup analysis because we included insufficient studies for each outcome to justify meaningful subgroup analysis (Higgins 2011).

Sensitivity analysis

We completed the following sensitivity analyses which were specified in the protocol.

1. **Studies at high or unclear risk of selection bias.** We judged only one study to have low risk of selection bias in both domains (sequence generation and allocation concealment), and sensitivity analysis was not feasible.
2. **Meta-analytical effects model**. We assessed whether using a fixed-effect model would alter effect estimates for our outcomes. We found no difference in interpretation of effect estimates depending on meta-analytical effects model for each of our outcomes.

We completed the following sensitivity analyses which were performed as posthoc decisions (see Differences between protocol and review).

1. **Assessment of the primary outcomes using trial sequential analysis.** We used a conventional test boundary and a random-effects model (DerSimonian-Laird method) to perform trial sequential analysis using software from The Copenhagen Trial Unit (www.ctu.dk/) with continuity corrected for studies with zero events. We found no difference in interpretation of the result for all-cause mortality at the end of follow-up (up to six months), and all-cause mortality (up to 30 days) when analysis accounted for studies with zero events (RR 1.17, 95% CI 0.37 to 3.67).
2. **Decisions made during the review process**. We included one study in which 10% of participants were not on antiplatelet therapy before the start of the study (Oscarsson 2010). In sensitivity analysis, we excluded this study. We noted no difference to interpretation of effect estimates for each outcome. In one study, we interpreted data for the number of participants with a bleeding event requiring transfusion from a graph (Nielsen 2000). In sensitivity analysis, we excluded this study for this outcome and noted no difference to interpretation of the effect estimate.

DISCUSSION

Summary of main results

We included five studies comparing continuation of antiplatelet therapy with discontinuation of antiplatelet before non-cardiac surgery. The five studies included 666 adults. We found three ongoing studies.

We found no evidence of a difference in mortality up to six months, and up to 30 days, after surgery, and no evidence of a difference in bleeding requiring further surgery or in ischaemic events. We used the GRADE approach to downgrade evidence for these outcomes to low certainty. We found no evidence of a difference in bleeding requiring transfusion, and we used the GRADE approach to downgrade evidence to moderate certainty.

Overall completeness and applicability of evidence

We included studies of adults who were taking antiplatelet drugs and were scheduled for a variety of different surgical procedures. The study authors did not report the length of time that the participants had been on antiplatelet therapy. Three studies reported the number of people who had a coronary stent, and this was balanced between the groups. However, the length of time since insertion of stent was not reported by study authors. We noted that the number of people with coronary stents differed between these three studies.

Evidence was limited to five studies. Because data were limited, we did not conduct subgroup analysis to explore whether potential differences between studies (e.g. whether participants were on single or dual therapy, had coronary stents, or discontinuation of therapy was before or after five days) could influence the results.

Quality of the evidence

Three studies reported adequate methods of randomization, and two reported methods to conceal allocation. Three studies were placebo-controlled trials and were at low risk of performance bias, and three studies reported adequate methods to blind outcome assessors to group allocation. Attrition was limited in four studies and two studies had reported prospective registration with clinical trial registers and were at low risk of selective outcome reporting bias.

We used the GRADE approach to downgrade evidence for this review. We noted limited available data for each outcome, a wide confidence interval in evidence for mortality and for blood loss requiring further surgery, and visual differences noted between studies for ischaemic events; we used these reasons to downgrade evidence to low certainty, or moderate certainty.

Potential biases in the review process

We conducted a thorough search and used two review authors to assess study eligibility, to extract data, and to assess risk of bias in included studies, and believe that we reduced potential bias in the review process by using two review authors. However, we did not contact study authors to clarify missing information (such as length of follow-up, funding sources, or missing information for 'Risk of bias' assessments), and judgements made in the review were based only on information in published reports.

We included one study in which some participants were not on antiplatelets before the start of the trial (Oscarsson 2010). We carried out sensitivity analysis and results were unaffected if this study was excluded from analysis; we believed that including this study did not introduce bias to the results.

We made a post-hoc decision to exclude studies in which people were scheduled for minor surgeries under local anaesthetic or sedation. These type of surgeries would introduce considerable clinically heterogeneity in the review, and are unlikely to lead to major bleeding requiring transfusion or additional surgery. For this review, eight of the 10 excluded studies were studies of minor surgeries under local anaesthetic or sedation (dental extraction, cataract surgery, removal of skin tumour). These studies did not measure outcome data or provide useful information for this review and, therefore, exclusion of these studies did not influence effect estimates for this review. See Differences between protocol and review.

Agreements and disagreements with other studies or reviews

We found no systematic reviews that considered only randomized controlled trials (RCTs) for non-cardiac surgery. One review recommended discontinuation of clopidogrel for at least five days before surgery, but this judgement was based on limited evidence from observational studies of non-cardiac surgery, and evidence from studies of cardiac surgery (Au 2012). Another review concluded no evidence of excessive bleeding from continuation of aspirin using limited evidence from both RCTs and observational studies (Sahebally 2014). Burger 2005 noted an increase in the risk of bleeding complications with aspirin use but without an increase in the severity of the bleeding event; this review included both RCTs and observation studies. We excluded one large RCT from this review because participants taking aspirin were required to stop at least three days before surgery, and was not comparable with other studies in this review (Devereaux 2014). We noted that this large study of non-cardiac surgery similarly found little or no difference in all-cause mortality at 30 days or in ischaemic events. Devereaux 2014 found an increased risk of major bleeding in participants who were taking aspirin in the perioperative period.

AUTHORS' CONCLUSIONS

Implications for practice

We found low-certainty evidence that either continuation or discontinuation of antiplatelet therapy before non-cardiac surgery may make little or no difference to mortality, bleeding requiring surgical intervention, or ischaemic events. We found moderate-certainty evidence that either continuation or discontinuation of antiplatelet therapy before non-cardiac surgery probably makes little or no difference to bleeding requiring transfusion. Evidence was limited to few studies with few participants, and with few events. The three ongoing studies may alter the conclusions of the review once published and assessed.

Implications for research

Additional randomized controlled trials (RCTs) of antiplatelet therapy management in adults undergoing non-cardiac surgery are required to add certainty to the review outcomes. We found three ongoing studies with an anticipated large sample size. These studies will increase certainty in the effect in future updates.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Antolovic 2012

Methods	RCT, single-centre, parallel study
Participants	**Total number of randomized participants:** 52 **Inclusion criteria** 1. > 18 years of age, treated with low-dose acetylsalicylic acid on a long-term medication basis, a low- or intermediate-risk patient according to cardiological evaluation and scheduled for elective cholecystectomy, inguinal hernia repair or colonic/colorectal surgery **Exclusion criteria** 1. Perioperative continuation of usual acetylsalicylic acid intake was imperative due to medical indication (e.g. shortly after coronary stent implantation, interfering haematologic disorders etc.) 2. Cardiologically evaluated as high-risk patients 3. Concomitant treatment with coumarin-type anticoagulation or clopidogrel 4. Emergency procedures 5. Simultaneous participation in another study 6. Mental condition rendering the participant incapable of understanding the nature, scope, and consequences of the trial **Type of surgery** 1. Elective general and abdominal surgery (inguinal hernia repair, cholecystectomy, colonic/colorectal, laparoscopic) **Baseline characteristics** **Continuation group** 1. Age, mean; median (range): 66.3; 68.5 (22 to 84) years 2. Gender, M/F: 23/3 3. BMI, mean (SD): 26.59 (± 4.12) kg/m^2 4. ASA score, n: ASA II:10; ASA III:15; ASA IV: 1 5. Type of anaesthesia, n: GA: 18; SPA: 4; GA + epidural: 3; LA + SPA: 1 6. Participants who had coronary stent, n: bare-metal stent: 7; drug-eluting stent: 1 7. Type of antiplatelet therapy prior to study: aspirin - 25 participants 100 mg daily; 1 participant 50 mg daily 8. Duration of antiplatelet therapy prior to study: study authors report "long-term" basis **Discontinuation group**

Antolovic 2012 *(Continued)*

1. Age, mean; median (range): 68.5; 67.0 (54 to 88) years
2. Gender, M/F: 18/8
3. BMI, mean (SD): 27.36 (± 5.06) kg/m^2
4. ASA score: ASA II: 8; ASA III: 17; ASA IV: 1
5. Type of anaesthesia, n: GA: 16; SPA: 3; GA + epidural: 7; LA + SPA: 0
6. Participants who had coronary stent, n: bare-metal stent: 4; drug-eluting stent: 1
7. Type of antiplatelet therapy prior to study: aspirin - dose not reported
8. Duration of antiplatelet therapy prior to study: study authors report "long-term" basis

Overall

1. Reasons antiplatelet therapy, n: primary prevention: 19; history of cardiovascular events, secondary prevention: 31; graft protection after traumatic aortic rupture repair: 2

Country: Germany

Setting: hospital

Interventions	**Continuation group** 1. Number of randomized participants = 26; 0 losses; 26 analysed participants 2. Details: participants continued on usual prescribed antiplatelet dose (25 participants = 100 mg a day, 1 participant = 50 mg) during whole study period **Discontinuation group** 1. Number of randomized participants = 26; 0 losses; 26 analysed participants 2. Details: participants discontinued antiplatelet medication 5 days prior to surgery. Study period for 5 days postoperatively. No placebo treatment
Outcomes	1. Incidence of perioperative bleeding episodes and clinically apparent thromboembolic events, acute myocardial infarction, severe arrhythmia, cardiac arrest, cardiovascular death, severe pulmonary embolism, TIA, stroke, within 30 days after surgery 2. Duration of surgical interventions 3. Intraoperative blood loss 4. Transfusion requirements 5. Length of postoperative blood loss 6. Length of postoperative hospital stay 7. Necessity for re-admission 8. Medical and surgical morbidity within 30 days after surgery
Notes	**Funding/declarations of interest:** funding not reported. Study authors declare no conflicts of interest **Study dates:** January 2009 to January 2010

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized, but no additional details provided in the published study report
Allocation concealment (selection bias)	Low risk	Allocation was concealed in opaque, sequentially numbered envelopes supplied by external trial centre
Blinding of participants and personnel (performance bias)	Unclear risk	Participants are not blinded which might influence adherence to study protocol for participants in the discontinuation group. Study authors do not state if personnel were aware of group allocation

Antolovic 2012 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent observers performed data collection
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent losses
Selective reporting (reporting bias)	Unclear risk	Retrospective clinical trial registration ISRCTN45810007. Not feasible to assess risk of selective outcome reporting bias
Other bias	Unclear risk	Baseline characteristics well reported. We noted that mean age of participants was similar between groups, but age ranges showed that the youngest participant in the intervention group was considerably younger than in the control group

Chu 2016

Methods	RCT, single-centre, parallel study
Participants	**Total number of randomized participants:** 48 **Inclusion criteria** 1. Patients > 18 years of age, receiving clopidogrel 75 mg daily at the time of evaluation, and a non-emergent procedure indication **Exclusion criteria** 1. Use of any non aspirin, non clopidogrel antiplatelet agents (i.e. prasugrel, ticagrelor, cilostazol) 2. Emergent nature of surgery 3. Pregnancy 4. History of bleeding disorders unrelated to medication 5. Inability to obtain medical clearance from the anaesthesiologist, cardiologist, or surgeon **Type of surgery** 1. Open inguinal hernia repair 2. Laparoscopic cholecystectomy 3. Laparoscopic and open ventral hernia repair 4. Laparoscopic inguinal repair 5. Nissen's fundoplication 6. Ostomy closure 7. Open sigmoidectomy and ileostomy **Baseline characteristics** **Continuation group** 1. Age, mean: 67.9 years 2. ASA score: ASA II: 1; ASA > II: 21 3. Participants who had coronary stent, n: 13 4. Type of antiplatelet therapy prior to study: all participants on 75 mg clopidogrel, 18 participants also taking aspirin 5. Reasons for antiplatelet therapy, n: coronary stent 13, CVA 2, other (not specified) 7

Chu 2016 *(Continued)*

	6. Duration of antiplatelet therapy prior to study: not reported **Discontinuation group** 1. Age, mean: 67.9 years 2. ASA score: ASA 2: 4; ASA > 2: 17 3. Participants who had coronary stent, n: 18 4. Type of antiplatelet therapy prior to study: all participants on 75 mg clopidogrel, 14 participants also taking aspirin 5. Reasons of antiplatelet therapy, n: coronary stent 18, CVA 1, other (not specified) 2 6. Duration of antiplatelet therapy prior to study: not reported **Country:** USA **Setting:** hospital
Interventions	**Continuation group** 1. Number of randomized participants = 25; 3 losses (received different procedure); 22 analysed participants 2. Details: participant continued to take 75 mg clopidogrel, discontinued aspirin 7 days prior to surgery if taking as part of DAPT **Discontinuation group** 1. Number of randomized participants = 23; 2 losses (1 had surgery postponed, 1 received different procedure); 21 analysed participants 2. Details: participant discontinued clopidogrel, and discontinued aspirin if taking as part of DAPT
Outcomes	1. Perioperative bleeding requiring intraoperative or postoperative transfusion of blood products 2. Bleeding-related readmission 3. Re-operation 4. Mortality within 90 days of surgery 5. Perioperative myocardial infarction or CVAs within 90 days of surgery 6. Length of hospital stay
Notes	**Funding/declarations of interest:** grant from Doris Duke Foundation **Study dates:** January 2011 to May 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of computerized software for randomization method
Allocation concealment (selection bias)	Unclear risk	No details describing allocation concealment were provided in the published study report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel were not blinded to group allocation and we did not know whether this would influence performance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details describing blinding of outcome assessment were provided in the published study report

Chu 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses, explained by study authors
Selective reporting (reporting bias)	Unclear risk	Retrospective clinical trial registration NCT01960296. Not feasible to make judgement on risk of selective reporting bias
Other bias	Low risk	No other sources of bias identified

Mantz 2011

Methods	RCT, multi-centre, parallel study
Participants	**Total number of randomized participants:** 291 **Inclusion criteria** 1. ≥ 18 years of age, receiving anti-platelet therapy (aspirin, clopidogrel, ticlopidine, or dipyridamole) for secondary prevention of coronary artery disease, stroke, TIA, or peripheral vascular ischaemic disease, and undergoing elective intermediate- or high-risk elective non-cardiac surgery (i.e. surgery planned for > 2 hours in duration and associated with significant volume changes) **Exclusion criteria** 1. Undergoing emergency surgery 2. Undergoing surgeries involving carotid endarterectomy and coronary bypass grafting, opthamological surgery of the posterior chamber, and intracranial neurosurgery, superficial surgery, and colonoscopy 3. Pregnancy 4. A recent (< 30 days before randomization) major cardiac event (i.e. unstable angina, myocardial infarction, or coronary revascularization) 5. Presence of a drug-eluting stent 6. Active bleeding 7. Absolute contraindications to aspirin or anti-coagulants 8. Haemorrhagic (thrombotic) risk linked to maintenance/interruption, respectively, was considered unacceptable from the attending anaesthetist, cardiologist, or surgeon's perspective **Types of surgery** 1. All types of elective procedures were considered (orthopaedic, abdominal, urologic, thoracic, oncologic, ENT) **Baseline characteristics** **Continuation group** 1. Age, mean (SD): 70 (± 10) years 2. Gender, M/F: 115/30 3. Weight, mean (SD): 77 (± 14) kg 4. Severity of illness: no details 5. Type of anaesthesia, n: GA: 95 6. Type of surgery, n: orthopaedic: 78; abdominal: 25; urologic: 24; other: 19. Note: numbers are as reported by study authors (total is for 146, not 145) 7. Reason for having antiplatelet therapy: secondary prevention of coronary artery disease, stroke, TIA, or peripheral vascular ischaemic disease, and undergoing elective intermediate- or high-risk elective non-cardiac surgery 8. Participants with coronary stent, n: 21

Mantz 2011 *(Continued)*

	9. Type of antiplatelet therapy prior to study, n: aspirin: 104; clopidogrel: 48; ticlopidine (+ others): 2 (doses not reported) 10. Duration of antiplatelet therapy prior to study: not reported **Discontinuation group** 1. Age, mean (SD): 69 (± 10) years 2. Gender, M/F: 107/39 3. Weight, mean (SD): 77.2 (± 16) kg 4. Severity of illness: no details 5. Type of anaesthesia, n: GA: 105 6. Type of surgery, n: orthopaedic: 74; abdominal: 35; urologic: 21; other: 16 7. Reason for having antiplatelet therapy: secondary prevention of coronary artery disease, stroke, TIA, or peripheral vascular ischaemic disease, and undergoing elective intermediate- or high-risk elective non-cardiac surgery 8. Participants with coronary stent, n: 17 9. Type of antiplatelet therapy prior to study, n: aspirin: 107; clopidogrel: 41; ticlopidine (+ others): 5 (doses not reported) 10. Duration of antiplatelet therapy prior to study: not reported **Country:** France **Setting:** hospital
Interventions	**Continuation group** 1. Number of randomized participants = 145; losses = 35; number of analysed participants = 145 (used ITT) 2. Details: existing antiplatelet therapy discontinued 10 days prior to study and switched to aspirin 75 mg which was continued up to morning of surgery. Participants resumed initial anti-platelet therapy after surgery as soon as medical staff felt it was clinically appropriate **Discontinuation group** 1. Number of randomized participants = 146; losses = 26; number of analysed participants = 146 (used ITT) 2. Details: existing antiplatelet therapy discontinued 10 days prior to study and switched to a placebo. Participants resumed initial anti-platelet therapy after surgery as soon as medical staff felt it was clinically appropriate
Outcomes	1. Death 2. Major thrombotic events (stroke, TIA, acute coronary syndrome, peripheral arterial ischaemia, mesenteric arterial ischaemia, deep proximal and distal venous thrombosis based on clinical symptoms, and pulmonary embolism), measured from time of randomization until 30 days 3. Major bleeding events (cerebral haemorrhage documented by CT scan, bleeding requiring an intervention (i.e. surgical reoperation, endovascular embolization or an endoscopic intervention), or bleeding requiring 3 units of red blood cells), measured from time of randomization until 30 days
Notes	**Funding/declarations of interest:** grant from French Ministry of Health and sponsored by the Department of Clinical Research and Development, Assistance Publique des Hôpitaux de Paris **Study dates:** June 2005 to September 2007. **Note** 1. Trial stopped early due to difficulties recruiting participants
Risk of bias	

Mantz 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of a computer-generated randomization system
Allocation concealment (selection bias)	Low risk	Allocation maintained through use of a centralized system, accessed by telephone
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled trial. Investigators, patients, and healthcare providers were not aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators collecting outcome data were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Use of ITT analysis, but high number of losses with more losses in the continuation group; losses explained by study authors
Selective reporting (reporting bias)	Low risk	Clinical trial registration NCT00190307. Registered shortly after start of recruitment. Outcomes reported according to registration documents
Other bias	Low risk	No other sources of bias identified

Nielsen 2000

Methods	RCT, single-centre, parallel study
Participants	**Total number of randomized participants:** 55 **Inclusion criteria** 1. Male patients on low-dose acetylsalicylic acid therapy (150 mg to 300 mg) with obstructive symptoms, and clinical and laboratory evidence suggestive of benign or malignant prostatic enlargement **Exclusion criteria** 1. Undergoing treatment with anticoagulants, and other NSAIDs 2. Recent (within 6 months) myocardial infarction 3. Unstable angina 4. Stroke 5. Transient cerebral ischaemia 6. History of bleeding diathesis 7. Serum creatinine > 200 mmol/L 8. Arterial hypertension with blood pressure > 220/120 mmHg **Type of surgery** 1. TURP **Baseline characteristics** **Continuation group** 1. Age, median (IQR): 70 (66 to 74) years

Nielsen 2000 *(Continued)*

2. Gender: all male participants
3. BMI, mean (SD): not reported
4. Severity of illness: not reported
5. Type of anaesthesia, n: SPA: all participants
6. Participants with coronary stent, n: not reported
7. Reason for having antiplatelet therapy: not reported
8. Type of antiplatelet therapy prior to study: 150 mg to 300 mg aspirin
9. Duration of antiplatelet therapy prior to study: not reported

Discontinuation group

1. Age, median (IQR): 69 (65 to 76) years
2. Gender: all male participants
3. BMI, mean (SD): not reported
4. Severity of illness score: not reported
5. Type of anaesthesia, n: SPA: all participants
6. Participants with coronary stent, n: not reported
7. Reason for having antiplatelet therapy: not reported
8. Type of antiplatelet therapy prior to study: 150 to 300 mg aspirin
9. Duration of antiplatelet therapy prior to study: not reported

Country: Denmark

Setting: hospital

Interventions	**Continuation group** 1. Number of analysed participants = 26 (study authors report 2 losses after randomization but do not report total number of randomized participants in each group) 2. Details: usual dose of aspirin was discontinued 10 days before surgery and participant given 150 mg aspirin. Participants resumed usual dose after catheter removal **Discontinuation group** 1. Number of analysed participants = 27 (study authors report 2 losses after randomization but do not report total number of randomized participants in each group) 2. Details: usual antiplatelet therapy discontinued 10 days prior to study and participant given placebo. Participants resumed usual antiplatelet therapy after catheter removal
Outcomes	1. Intra-operative and postoperative blood loss 2. Transfusion requirements 3. Re-operation due to blood loss 4. Myocardial infarction 5. Mortality 6. Secondary haemorrhage 7. Length of hospital stay 8. Median time to catheter removal 9. Histology
Notes	**Funding/declarations of interest:** Leo Pharmaceutical Products, Ballerup, Denmark. Donated medication **Study dates:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Nielsen 2000 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Stated as randomized but no additional details describing random sequence generation were provided in the published study report
Allocation concealment (selection bias)	Unclear risk	Allocation list was kept at the pharmaceutical company which provided the drugs. No additional details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind and placebo was used to blind the participants. We assumed that personnel were also blinded to group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details describing blinding of outcome assessment were provided in the published study report
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two losses from each group. Study authors do not report to which group these participants belonged. However, few losses and unlikely to influence outcome data
Selective reporting (reporting bias)	Unclear risk	Clinical trial registration or prospectively published protocol not reported. Not feasible to assess risk of selective reporting bias
Other bias	Unclear risk	Study is supported by pharmaceutical company. Study authors do not report level of involvement in trial design and management by the company. Baseline characteristics not reported

Oscarsson 2010

Methods	RCT, multi-centre, parallel study
Participants	**Total number of randomized participants:** 220 **Inclusion criteria** 1. Undergoing elective, high- or intermediate-risk non-cardiac surgery. Having one of the following cardiac risk factors: ischaemic heart disease (angina pectoris or previous myocardial infarction), congestive heart failure (previous diagnosis of heart failure), renal impairment (serum creatinine > 170 µmol/L), CVA (prior stroke or TIA), or insulin-dependent diabetes mellitis. High-risk surgery defined as surgery with known cardiac risk of > 5 %, and included procedures with large fluid shifts such as oesophageal, liver, and pancreatic surgery. Intermediate-risk surgery defined as surgery with cardiac risk of 1% to 5%, and included head and neck surgery, intraperitoneal and intrathoracic surgery, orthopaedic surgery, and prostate surgery **Exclusion criteria** 1. Unstable CAD 2. Non-compensated congestive heart failure 3. Shock 4. Allergy to aspirin 5. < 18 years of age 6. History of gastrointestinal bleeding or intracranial haemorrhage, or treatment with warfarin, clopidogrel, or methotrexate 7. Undergoing vascular surgery **Type of surgery** 1. Abdominal

Oscarsson 2010 *(Continued)*

2. Urologic
3. Orthopaedic
4. Gynaecologic

Baseline characteristics

Continuation group

1. Age, mean (range): 71.8 (58 to 86) years
2. Gender, M/F: 69/40
3. BMI, mean (SD): 27.5 (± 4.58) kg/m^2
4. Type of surgery, n: abdominal: 24; urology: 33; orthopaedic: 47; gynaecology: 5
5. Type of anaesthesia, n: GA: 28; regional: 52; GA + epidural: 20
6. ASA score, n: ASA I: 1: ASA II: 65; ASA III: 37; ASA IV: 0
7. Participants with coronary stent, n: not reported. However, study authors report a 2006 amendment to inclusion criteria so that patients with intracoronary stents were excluded
8. Reason for having antiplatelet therapy: cardiac risk factor
9. Type of antiplatelet therapy prior to surgery: 90% of participants were on aspirin (dose not reported)
10. Duration of antiplatelet therapy prior to study: not reported

Discontinuation group

1. Age, mean (range): 72.6 (46 to 88) years
2. Gender, M/F: 70/41
3. BMI, mean (SD): 27.3 (± 4.85) kg/m^2
4. Type of surgery: abdominal: 28; urology: 28; orthopaedic: 49; gynaecology: 6
5. Type of anaesthesia, n: GA: 21; regional: 56; GA + epidural: 20
6. ASA score: ASA I: 0; ASA II: 61; ASA III: 45; ASA IV: 1
7. Participants with coronary stent, n: not reported. However, study authors report a 2006 amendment to inclusion criteria so that patients with intracoronary stents were excluded
8. Reason for having antiplatelet therapy: cardiac risk factor
9. Type of antiplatelet therapy prior to surgery: 90% of participants were on aspirin (dose not reported)
10. Duration of antiplatelet therapy prior to study: not reported

Country: Sweden

Setting: hospitals

Interventions	**Continuation group** 1. Number of randomized participants = 109; 0 losses (study authors report 4 did not comply with treatment, 4 had surgery postponed); 109 analysed participants 2. Details: participants discontinued any existing dose of aspirin at 7 days prior to surgery, then given 75 mg aspirin, until third postoperative day **Discontinuation group** 1. Number of randomized participants = 111; 0 losses (study authors report 6 did not comply with treatment, 3 had surgery postponed); 111 analysed participants 2. Details: participants discontinued any existing dose of aspirin at 7 days prior to surgery, then given placebo until third postoperative day
Outcomes	1. Postoperative myocardial damage 2. MACEs (including acute myocardial infarction, cardiac arrest, severe arrhythmia, or cardiovascular death) 3. Cardio-cerebrovascular complications (including MACE or stroke/TIA) 4. Perioperative blood loss and major bleeding (including postoperative bleeding, intracranial haemorrhage, or spinal/epidural haematoma)

Oscarsson 2010 *(Continued)*

	5. Transfusion (packed red blood cells, plasma, and platelet) 6. Death All assessed within first 30 postoperative days
Notes	**Funding/declarations of interest:** supported by grants from: the Health Research Council in South-East of Sweden; European Society of Anaesthesiology; county council of Östergötland, Weden; Stina and Birger Johansson Foundation, Sweden; The Heart Foundation, Sweden; Linköping Medical Association; Pfizer Inc., Stokholm **Study dates:** November 2005 and December 2008. **Note** 1. Early stopping; reasons were due to publication of recommendations that aspirin was continued during perioperative period which affected investigators willing to randomize high-risk patients, and recruitment difficulties (particular after patients with coronary stents were excluded from 2006 onwards)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Unclear risk	No details describing methods to conceal allocation were provided in the published study report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo controlled trial, and we assume participants are unlikely to be aware of group allocation. We assumed that personnel were also unaware of group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Signs of myocardial ischaemia were assessed by a clinical physiologist who was blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss of 17 participants. Low number unlikely to influence outcome data. We noted that although ITT was used, study authors assumed that lost participants had no events
Selective reporting (reporting bias)	Low risk	Prospective clinical trial registration (Eudract CT no. 2004-005136-76). No evidence of selective reporting based on trial protocol
Other bias	Low risk	No other sources of bias identified

ASA: American Society of Anesthesiologists
BMI: body mass index
CAD: coronary artery disease
CT: computerized tomography
CVA: cerebrovascular accident
DAPT: dual antiplatelet therapy
ENT: ears, nose, and throat
GA: general anaesthesia
IQR: interquartile range
ITT: intention to treat
LA: local anaesthesia
M/F: male/female

MACE: major adverse cardiovascular event
n: number of participants
NSAIDs: nonsteroidal anti-inflammatory drugs
RCT: randomized control trial
SD: standard deviation
SPA: spinal anaesthesia
TIA: transient ischaemic attack
TURP: transurethral resection of the prostate

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

Study	Reason for exclusion
Ardekian 2000	RCT. Participants scheduled for dental extraction under local anaesthetic. Continuation of 100 mg aspirin versus discontinuation of aspirin 7 days before procedure. Outcomes included bleeding (mild: < 20 mL; moderate: 20 mL to 50 mL; severe: > 50 mL). We excluded this study because there was minimal bleeding risk in this type of surgery.
Assia 1998	RCT. Participants scheduled for cataract surgery under local anaesthetic. Continuation of aspirin, versus discontinuation of aspirin for 2 to 5 days before procedure versus discontinuation of aspirin for 7 to 10 days before procedure. We excluded this study because there was minimal bleeding risk in this type of surgery.
Danino 2007	RCT. Participants undergoing surgery for skin carcinoma. Continuation of antiplatelet agents compared with discontinuation; however participants in discontinuation group were given an alternative agent (flurbiprofen or isocoagulant fractionated heparin).
Devereaux 2014	RCT. Participants undergoing non-cardiac surgery were assigned to receive aspirin or placebo, or clonidine or placebo. Participants stratified according to whether they had been taking aspirin before the study. However, participants in the continuation group were required to stop taking aspirin at least 3 days before surgery. We excluded this because this was not comparable to other studies in which 'continuation' did not involve any interruption of antiplatelet agent before surgery.
Duygu 2010	RCT. Participant scheduled for dental surgery under local anaesthetic. Continuation of aspirin (75 mg to 300 mg) versus discontinuation for 7 days before procedure. Outcomes measured were bleeding time and haemostatic measures to control bleeding (e.g. gauze soaked with resorbable gelatin). We excluded this study because there was minimal bleeding risk in this type of surgery.
Eapen 2017	RCT. Participants scheduled for dental extraction under local anaesthetic. Continuation of 75 mg aspirin or discontinuation of aspirin for 5 days before procedure. Outcomes measured were bleeding times, prolonged bleeding, and need for local haemostatic measures to control bleeding. We excluded this study because there was minimal bleeding risk in this type of surgery.
Engheta 2016	RCT. Participants scheduled for skin tumour surgery under sedation. Continuation of aspirin (80 mg) versus placebo for 7 days before procedure. Outcomes measured volume of bleeding, need for early changing of dressings, development of haematoma or local anticoagulation disorders. We excluded this study because there was minimal bleeding risk in this type of surgery.
Gaspar 1999	RCT. Participants scheduled for dental surgery. Continuation of low-dose aspirin or discontinuation of aspirin for 1 week before procedure. Outcomes measured bleeding times, and use of haemostatic measures to control bleeding. We excluded this study because there was minimal bleeding risk in this type of surgery.
Medeiros 2011	RCT. Participants scheduled for single tooth extraction under local anaesthetic. Continuation of 100 mg aspirin of discontinuation of aspirin for 7 days before procedure. Outcomes measured volume of bleeding, need for haemostatic measures to control bleeding (e.g. use of sutures). We excluded this study because there was minimal bleeding risk in this type of surgery.

Study	Reason for exclusion
Varghese 2015	RCT. Participants scheduled for dental extraction under local anaesthetic. Continuation of antiplatelet therapy (aspirin or clopidogrel, or both) or discontinuation of antiplatelet therapy for 5 days before procedure. Outcomes measured bleeding (oozing or active) using haemostatic measures to control bleeding. We excluded this study because there was minimal bleeding risk in this type of surgery.

RCT: randomized controlled trial

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

NCT01806090

Trial name or title	Uninterrupted clopidogrel therapy before elective colonoscopy will increase the risk of post-polypectomy bleeding
Methods	RCT, parallel design
Participants	**Target number of randomized participants:** 216 **Inclusion criteria** 1. On regular treatment with clopidogrel alone or in combination with other anti-platelet drugs (e.g. aspirin), elective colonoscopy for asymptomatic screening of bowel cancer or investigation of bowel symptoms (e.g. altered bowel habit, rectal bleeding, anaemia, polyp follow-up), ≥ 18 years of age, written informed consent **Exclusion criteria** 1. Coronary stent of any type placed within 30 days 2. Cardiac-vascular event within 3 months 3. Drug-eluting coronary stent placed within 6 months 4. Terminal illness 5. Concomitant use of anticoagulants 6. Congenital or acquired bleeding diathesis showing clinical bleeding tendency (e.g. haemophilia, decompensated cirrhosis) 7. Pregnancy or women of child-bearing age without regular use of contraception **Type of surgery:** colonoscopy **Country:** China **Setting:** hospital
Interventions	**Continuation group** 1. Participants continue taking clopidogrel therapy **Discontinuation group** 1. Participants substitute clopidogrel with a placebo for seven days before procedure
Outcomes	1. Delayed post-polypectomy bleeding up to 30 days after the procedure 2. Immediate post-polypectomy bleeding within 5 minutes of the procedure
Starting date	February 2012
Contact information	suenbingyee@surgery.cuhk.edu.hk

NCT01806090 *(Continued)*

Notes	

NCT02797548

Trial name or title	Perioperative antiplatelet therapy in patients with drug-eluting stent undergoing noncardiac surgery (ASSURE-DES)
Methods	RCT, parallel design
Participants	**Target number of randomized participants:** 2000 **Inclusion criteria** 1. Planned non-cardiac surgery at least after 6 months of implantation of DES, low or intermediate risk level surgery, written informed consent **Exclusion criteria** 1. Acute coronary syndrome within 1 month 2. Heart failure NYHA III to IV 3. Contraindication to aspirin 4. On anticoagulant therapy 5. Emergent surgery 6. Cardiac surgery 7. High bleeding risk surgeries (e.g. intra-cranial surgery, intra-spinal surgery, retinal surgery) 8. Pregnancy or breast-feeding 9. Life expectancy < 1 year **Type of surgery:** non-cardiac surgery **Country:** Republic of Korea **Setting:** hospital
Interventions	**Continuation group** 1. Aspirin during surgery **Discontinuation group** 1. No antiplatelet therapy during surgery (time of discontinuation not reported in clinical trials documents)
Outcomes	1. Composite event of all-cause death 2. Stent thrombosis 3. All-cause death 4. Cardiac death 5. Myocardial infarction 6. Stroke 7. Repeat revascularization 8. Bleeding event All outcomes measured at 30 days
Starting date	16 March 2017

NCT02797548 *(Continued)*

Contact information	sjpark@amc.seoul.kr
Notes	

NCT03184805

Trial name or title	STOPping versus continuing antiplatelet therapy during noncardiac surgery and procedures after next generation drug-eluting stent implantation
Methods	RCT, parallel design
Participants	**Target number of randomized participants:** 2400 **Inclusion criteria** 1. 19 to 85 years of age, planning of elective non-cardiac surgery or invasive procedure, at least 1 year interval between the surgery or procedure and last PCI with next generation DES, currently on antiplatelet therapy, adult non-cardiac surgery patients **Exclusion criteria** 1. PCI with BMS 2. First generation DES or bioresorbable vascular scaffold 3. Total length of inserted DES in the 3 vessels > 60 mm 4. History of stent thrombosis 5. History of coronary artery bypass grafting surgery, planned surgery or procedure with high bleeding risk (including followings: intracranial neurosurgery, spinal canal surgery, and eye posterior chamber surgery, EMR, ESD, ampullary resection, ERCP with endoscopic sphincterotomy plus large-balloon papillary dilation, EUS-FNA of cystic lesions) 6. Left ventricular ejection fraction < 40% 7. Myocardial infarction within 6 months 8. Any overt thromboembolism requiring medical surveillance and/or treatment, any clinically overt sign of haemorrhage within 3 months 9. Anticoagulant therapy for any reason 10. Need of continuation or discontinuation of antiplatelet therapy during surgery or procedure at the discretion of cardiologist or operator, any contraindication 11. Adverse drug reaction or hypersensitivity to aspirin 12. Pregnant women or women with potential childbearing 13. Inability to understand or read the informed content **Type of surgery:** elective non-cardiac surgery or invasive procedure **Country:** Republic of Korea **Setting:** hospital
Interventions	**Continuation group** 1. If participants taking other antiplatelet agents, these will be discontinued at least 7 days, 5 days, and 3 days before surgery. Participant to continue with 100 mg aspirin throughout **Discontinuation group** 1. Participants will discontinue all antiplatelet agents at 7 days, 5 days, and 3 to 5 days before surgery
Outcomes	1. Cardiac death 2. Non-fatal myocardial infarction

NCT03184805 *(Continued)*	3. CVA 4. Definite or probable stent thrombosis 5. Any revascularization 6. BARC ≥ 3 bleeding during hospitalisation All outcomes measured at 1 day after hospital discharge
Starting date	June 2017
Contact information	mkhong61@yuhs.ac
Notes	

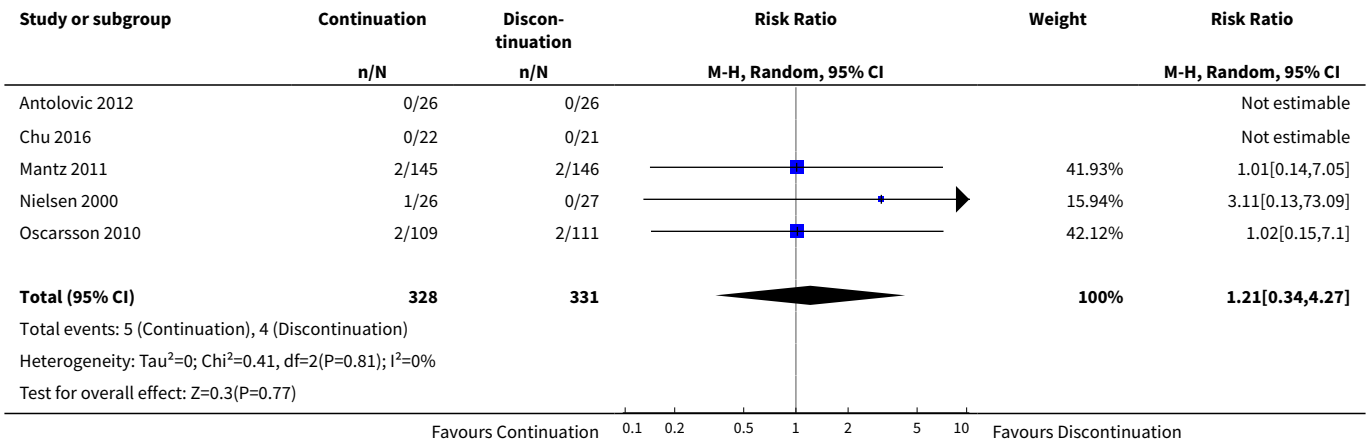
BARC: Bleeding Academic Research Consortium
BMS: bare-metal stent
CVA: cerebrovascular accident
DES: drug-eluting stent
EMR: endoscopic mucosal resection
ERCP: endoscopic retrograde cholangiopancreatography
ESD: endoscopic submucosal dissection
EUS-FNA: endoscopic ultrasonography-guided fine-needle aspiration
NYHA: New York Heart Association
PCI: percutaneous coronary intervention
RCT: randomized controlled trial

DATA AND ANALYSES

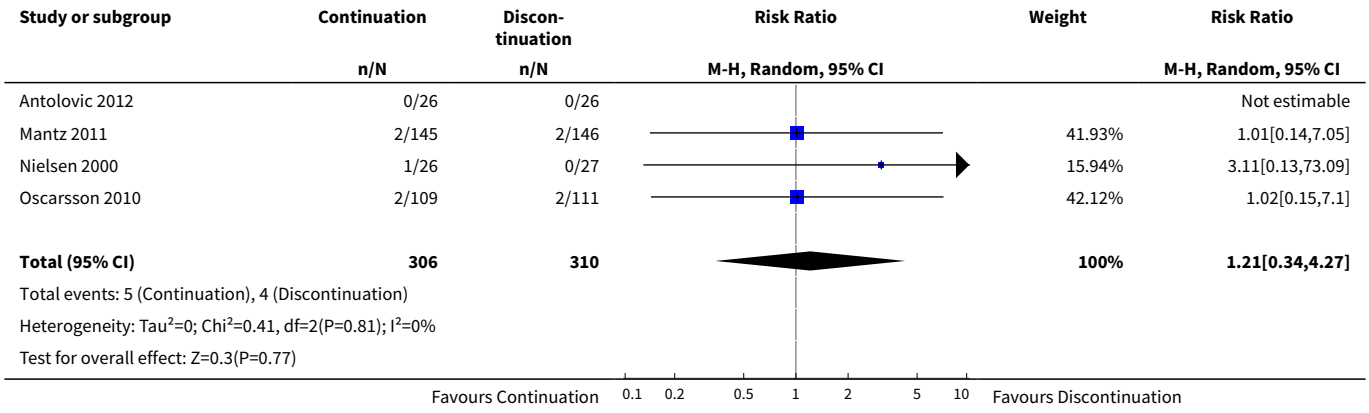
Comparison 1. Continuation vs discontinuation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality at end of follow up (up to six months)	5	659	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.34, 4.27]
2 All-cause mortality (up to 30 days)	4	616	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.34, 4.27]
3 Blood loss requiring transfusion of blood products (intraoperatively and postoperatively)	4	368	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.83, 2.26]
4 Blood loss requiring further surgical intervention (intraoperatively and postoperatively)	4	368	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.31, 7.58]
5 Risk of ischaemic events (within 30 days)	4	616	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.25, 1.77]

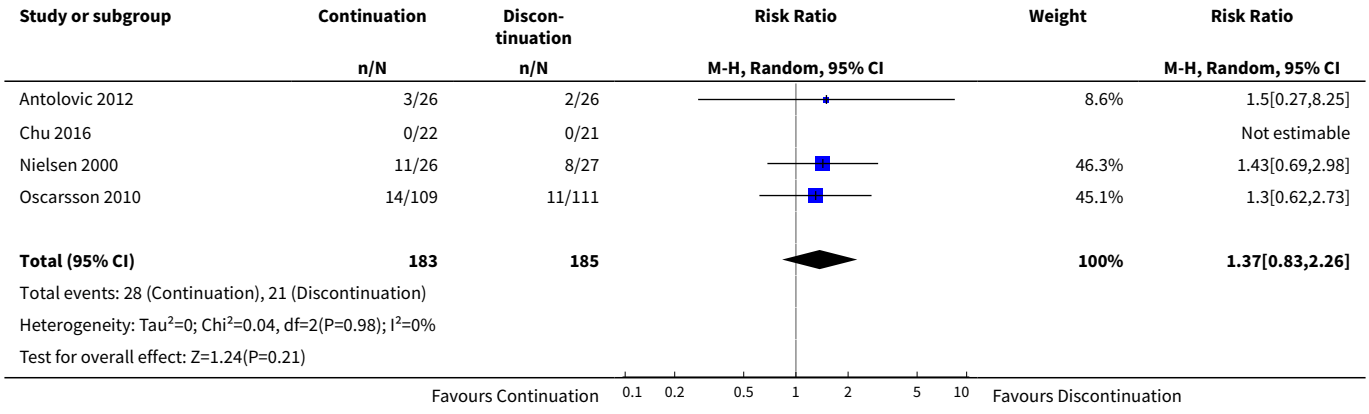
Analysis 1.1. Comparison 1 Continuation vs discontinuation, Outcome 1 All-cause mortality at end of follow up (up to six months).



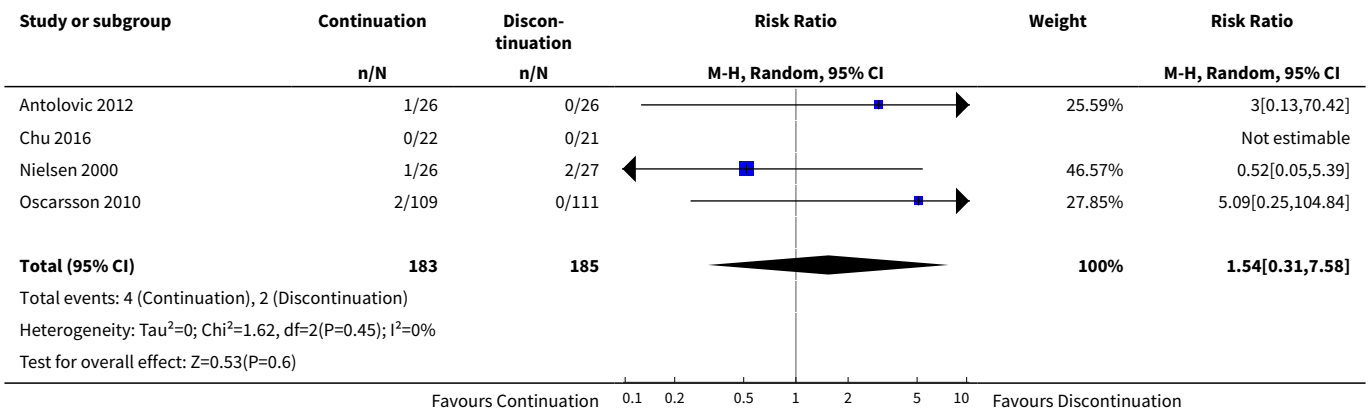
Analysis 1.2. Comparison 1 Continuation vs discontinuation, Outcome 2 All-cause mortality (up to 30 days).



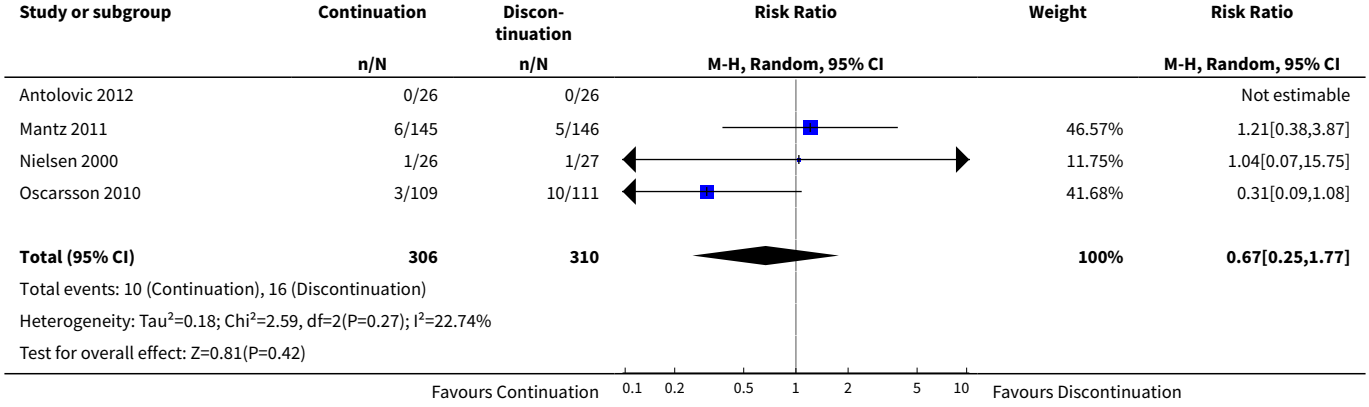
Analysis 1.3. Comparison 1 Continuation vs discontinuation, Outcome 3 Blood loss requiring transfusion of blood products (intraoperatively and postoperatively).



Analysis 1.4. Comparison 1 Continuation vs discontinuation, Outcome 4 Blood loss requiring further surgical intervention (intraoperatively and postoperatively).



Analysis 1.5. Comparison 1 Continuation vs discontinuation, Outcome 5 Risk of ischaemic events (within 30 days).



ADDITIONAL TABLES

Table 1. Data table

Outcome: major bleeding event			
Study	**Continuation group; n = 145**	**Discontinuation group; n = 146**	**Effect estimate***
Mantz 2011	10 participants had at least 1 major bleeding event	10 participants had at least 1 major bleeding event	OR 0.99, 95% CI 0.36 to 2.8; P = 1.0

* as reported by study authors
CI: confidence interval
n: number of randomized participants
OR: odds ratio

APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor: [Anticoagulants] explode all trees
#2	MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees
#3	MeSH descriptor: [Aspirin] explode all trees
#4	MeSH descriptor: [Thienopyridines] explode all trees
#5	#1 or #2 or #3 or #4
#6	anti?platelet* or anti platelet* or anti?thrombo* or anti thrombo* or anti?coagulant or anti coagulant or aspirin* or clopidogrel or prasugrel or ticagrelor or ticlopidine or (platelet and aggregation and inhibitor*) or (anti and thrombosis)
#7	#5 or #6
#8	MeSH descriptor: [General Surgery] explode all trees
#9	surgery or (operative and procedure*) or (operative and surgical and procedure*) or (surgical and procedure*)
#10	#8 or #9
#11	MeSH descriptor: [Hemorrhage] explode all trees
#12	bleeding or ischemi* or ischaemic*
#13	#11 or #12
#14	#7 and #10 and #13

Appendix 2. MEDLINE search strategy

1	Anticoagulants/ or Platelet Aggregation Inhibitors/ or Aspirin/ or Thienopyridines/
2	(anti?platelet* or anti platelet* or anti?thrombo* or anti thrombo* or anti?coagulant or anti coagulant or aspirin* or clopidogrel or prasugrel or ticagrelor or ticlopidine or (platelet and aggregation and inhibitor*) or (anti and thrombosis)).mp.
3	1 or 2
4	general surgery/
5	(surgery or (operative and procedure*) or (operative and surgical and procedure*) or (surgical and procedure*)).mp.

(Continued)

6	4 or 5
7	Hemorrhage/
8	(bleeding or isch?emia).mp.
9	7 or 8
10	3 and 6 and 9
11	((randomized controlled trial or controlled clinical trial).pt. or randomi*.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
12	10 and 11

Appendix 3. Embase search strategy

1	antithrombocytic agent/ or acetylsalicylic acid/ or anticoagulant agent/
2	(anti?platelet* or anti platelet* or anti?thrombo* or anti thrombo* or anti?coagulant or anti coagulant or aspirin* or clopidogrel or prasugrel or ticagrelor or ticlopidine or (platelet and aggregation and inhibitor*) or (anti and thrombosis)).mp.
3	1 or 2
4	general surgery/
5	(surgery or (operative and procedure*) or (operative and surgical and procedure*) or (surgical and procedure*)).mp.
6	4 or 5
7	exp bleeding/ or bleeding.mp. or ischaemic.mp.
8	3 and 6 and 7
9	((crossover procedure or double blind procedure or single blind procedure).sh. or (crossover* or cross over*).ti,ab. or placebo*.ti,ab,sh. or (doubl* adj blind*).ti,ab. or (controlled adj3 (study or design or trial)).ti,ab. or allocat*.ti,ab. or trial*.ti,ab. or randomized controlled trial.sh. or random*.ti,ab.) not ((exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.))
10	8 and 9

WHAT'S NEW

Date	Event	Description
4 October 2018	Amended	Acknowledgement section amended to include Sign-off Editor

CONTRIBUTIONS OF AUTHORS

Sharon R Lewis (SL), Oliver Schofield-Robinson (OSR), Michael W Pritchard (MP), Phil Alderson (PA), Andrew F Smith (AS)

Co-ordinating the review: SL.

Undertaking manual searches: SL, OSR.

Screening search results: SL, OSR.

Organizing retrieval of papers: SL, OSR.

Screening retrieved papers against inclusion criteria: SL, OSR.

Appraising the quality of papers: SL, OSR.

Abstracting data from papers: SL, OSR.

Managing data for the review: SL.

Entering data into Review Manager 5 (Review Manager 2014): SL.

Analysing RevMan statistical data: SL, PA, AS.

Interpreting data: SL, OSR, PA, AS.

Making statistical inferences: SL, PA, AS.

Writing the review: SL, MP.

Securing funding for the review: AS.

Serving as guarantor for the review (one review author): AS.

Reading and checking the review before submission: SL.

DECLARATIONS OF INTEREST

Sharon Lewis: see Sources of support.

Oliver Schofield-Robinson: see Sources of support.

Michael Pritchard: see Sources of support.

Andrew Smith: see Sources of support.

Phil Alderson: see Sources of support.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR Cochrane Collaboration Programme Grant, UK.

  'Back to normal': speed and quality of recovery after surgery, major injury and critical care. Project ref. 13/89/16

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol (Lewis 2017).

1. Review authors: we added two new review authors (Michael W Pritchard and Oliver J Schofield-Robinson).
2. Objectives: we edited the objectives to reflect changes made to types of participants, and to specify that discontinuation was required for at least five days before surgery.

3. Types of participants: we excluded people scheduled for minor surgeries under local anaesthetic or sedation because we anticipated that clinical heterogeneity would be too great between minor surgery under local anaesthetic or sedation and other surgery under general, spinal or regional anaesthesia). We added an inclusion criteria by type of anaesthesia (people scheduled for surgery under general, spinal or regional anaesthesia) in order to distinguish between studies in which minor surgery was performed under local anaesthetic or sedation.
4. Types of interventions: we clarified exclusion of studies which assessed drugs others than antiplatelet agents because this review aimed to specifically address continuation or discontinuation of antiplatelets therapy.
5. Types of outcome measures: for clarity, we edited the wording of the time points for mortality data collection for the primary outcomes 1 and 2. We collected mortality data at the longest follow-up time point reported by study authors (up to six months) for outcome 1, and at a time point up to 30 days for outcome 2.
6. We added a time point (intraoperatively and postoperatively) to the outcome 'Blood loss requiring further surgical intervention'.
7. Sensitivity analysis: we added an additional sensitivity analysis using an alternative meta-analytic tool (trial sequential analysis) on our primary outcomes. We added this analysis because this method accounts for studies with zero events which we did not anticipate during preparation of the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

*Elective Surgical Procedures [mortality]; *Withholding Treatment; Aspirin [administration & dosage]; Cause of Death; Clopidogrel; Hemorrhage [*chemically induced] [therapy]; Ischemia [*chemically induced] [therapy]; Platelet Aggregation Inhibitors [*administration & dosage]; Randomized Controlled Trials as Topic; Ticlopidine [administration & dosage] [analogs & derivatives]

MeSH check words

Adult; Humans