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SYSTEMATIC REVIEW ARTICLE

Efficacy and Safety of Antiplatelet Therapies in Symptomatic Peripheral Artery Disease: A Systematic Review and Network Meta-Analysis

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Abstract: ***Background*:** Clopidogrel monotherapy is guideline-recommended in symptomatic peripheral artery disease (PAD). The advent of new antithrombotic strategies prompts an updated analysis of available evidence on antiplatelet therapy for PAD.

***Methods*:** We searched MEDLINE, Embase and CENTRAL through January 2019 for randomised controlled trials and observational studies comparing antiplatelet therapies as monotherapy, dual therapy, or combination with anticoagulants. Efficacy (major adverse cardiovascular events, acute or chronic limb ischaemia, vascular amputation, peripheral revascularisation) and safety (all-cause mortality and overall bleeding) outcomes were evaluated via Bayesian network meta-analyses.

***Results*:** We analysed 26 randomised controlled trials. Clopidogrel (hazard ratio, HR, 0.78; 95% credible interval [CrI] 0.65-0.93) and ticagrelor (HR 0.80; 95% CrI 0.65-0.98) significantly reduced major adverse cardiovascular events risk compared with aspirin. No significant difference was observed for dual antiplatelet therapy with clopidogrel and aspirin. Vorapaxar significantly reduced limb ischaemia and revascularisation compared with placebo, while dual antiplatelet therapy with clopidogrel and aspirin showed a trend for reduced risk of amputation compared with aspirin (risk ratio 0.68; 95% CrI 0.43-1.04). For all-cause mortality, picotamide, vorapaxar, dipyridamole with aspirin, and ticlopidine showed a significantly lower risk of all-cause mortality vs aspirin. Clopidogrel and ticagrelor showed similar overall bleeding risk vs aspirin, while dual antiplatelet therapy with clopidogrel and aspirin significantly increased bleeding risk.

***Conclusion*:** This updated network meta-analysis confirms that clopidogrel significantly decreases the risk of major adverse cardiovascular events compared with aspirin, without increasing bleeding risk. Clopidogrel should remain a mainstay of PAD treatment, at least in patients at higher bleeding risk.

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1. INTRODUCTION

Peripheral artery disease (PAD) is a chronic, progressive, and debilitating disease representing a manifestation of atherosclerosis. In 2010, 202 million people around the world were living with PAD [1]. Most of the patients are asymptomatic or undiagnosed, and about 30% of PAD patients present with symptoms such as intermittent claudication, atypical leg pain, and chronic limb-threatening ischaemia [2]. Antiplatelet treatment is essential for increasing patient quality of life and functional status, as well as reducing the risk of cardiovascular (CV) and limb adverse events associated with PAD. Initiation of antiplatelet treatment using aspirin or clopidogrel is recommended for patients with symptomatic PAD, by both the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) [2, 3]. Importantly, the 2017 ESC guidelines favour clopidogrel over aspirin with a class IIb recommendation and level B evidence [2], based on the results of a *post-hoc* analysis of an older trial of clopidogrel *vs* aspirin (Clopidogrel *versus* Aspirin in Patients at Risk of Ischaemic Events trial [CAPRIE]) [4], and on those of a more recent trial (Examining Use of Ticagrelor in Peripheral Artery Disease [EUCLID]) in which

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clopidogrel proved non-inferior to the newer antiplatelet agent ticagrelor [5].

In this study, we conducted a systematic literature review and network meta-analysis (NMA) to evaluate the efficacy and safety of antiplatelet therapies in patients with symptomatic PAD.

2. MATERIALS AND METHODS

A systematic literature review was conducted according to guidelines provided by the Cochrane Collaboration's Handbook for Systematic Reviews of Interventions [6]. Study eligibility criteria were developed by using the Population, Intervention, Comparator, and Outcome (PICO) framework (Table **S1**). Randomised controlled trials (RCTs) and observational studies comparing antiplatelet therapies as monotherapy, dual antiplatelet therapy (DAPT), or in combination with anticoagulants in adult patients with symptomatic PAD were included in this review. Symptomatic PAD was defined by symptoms including intermittent claudication and limb ischaemia, or by surgical intervention for PAD. In this study, only lower extremity artery disease (LEAD) [2] was of interest; however, since the term 'peripheral artery disease' (PAD) is still commonly used in the literature to refer to the condition, we retained the use of 'PAD' in the present paper.

Search strategies for MEDLINE, EMBASE and Cochrane CENTRAL (*via* OvidSP) were created based on the study eligibility criteria (Table **S2**) and were conducted from inception to January 2019. Conference abstracts from 2017 onwards were also searched for relevant studies. Handsearching was also performed on the reference lists of previously published systematic literature reviews on the same topic.

All abstracts identified from the search were reviewed by 2 investigators, and eligible references were advanced to full-text screening. Investigators reconciled discrepancies *via* discussion. A third senior investigator intervened to reach a consensus on any unresolved discrepancies. Articles deemed eligible after full-text screening were included in the review. Study characteristics, interventions, patient characteristics, and the reported outcomes of interest in the included studies were extracted into the Digital Outcome Conversion (DOC) Data version 2.0 software platform (Doctor Evidence, LLC, Santa Monica, CA, USA). Characteristics of interest were age, gender, smoking status, comorbidities, and concomitant medications. Efficacy outcomes included MACE (defined as the composite of CV mortality, myocardial infarction, and stroke), acute or chronic limb ischaemia, limb amputation due to vascular causes, and peripheral revascularisation, while safety outcomes included bleeding and all-cause mortality.

The Cochrane Collaboration's tool for assessing the risk of bias in randomised trials was used to assess the studies with a randomised study design [7]. This instrument is used to evaluate 7 domains of bias: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias.

The NMA was conducted to pool trial results, when appropriate. We used the standard practice models described by the National Institute for Health and Care Excellence Decision Support Unit, Technical Support Documents series [8]. All analyses were performed in a Bayesian framework and involved a model with parameters, data, a likelihood distribution, and prior distributions. The NMA was performed for efficacy and safety outcomes at the final follow-up time point. The analyses were performed for the outcomes of interest that formed a connected evidence network.

Both hazard ratio (HR) and binary outcomes were used for NMA because the data was not consistently reported across trials. The NMA of reported HRs assuming proportional hazards between treatments was performed using a regression model with a contrast-based normal likelihood for the log HR of each trial in the network [8]. For binary outcomes, the NMA was performed based on the proportion of patients experiencing the event of interest using a regression model with a binomial likelihood and logit link. Relative treatment effects were expressed as risk ratio (RR) with corresponding credible intervals (CrI). When feasible, RR estimates were plotted for the efficacy and safety outcomes to provide a visual benefit-harm profile of the various antiplatelet therapies.

Both fixed and random-effects models were conducted; the fixed-effect results are reported based on the model selection (*i.e.* deviance information criterion and residual plots). All analyses were performed on R (version 3.0.3) by using the "gemtc" package implemented in JAGS on the DOC DATA 2.0 web-based platform (Doctor Evidence LLC, Santa Monica, USA).

3. RESULTS

The systematic literature search identified 5,467 unique records, of which 163 were accepted after title/abstract screening. Based on a review of the full texts, a total of 52 publications met PICO criteria and were selected for the descriptive analysis, including 49 publications on 35 RCTs and 3 observational studies.

Nine publications [9-17] on 6 RCTs were excluded from the NMA evidence base due to involving anticoagulants in treatment comparison. Three RCTs were excluded from analysis assessment since the PAD subgroup was only a *post-hoc* population but not defined by the inclusion criteria [18-20]. Three additional publications were excluded from the quantitative analysis due to being observational studies [21-23]. Overall, from 52 publications initially included, 37 publications [4, 5, 24-58] pertaining to 26 unique RCTs were included for a feasibility assessment of NMA among antiplatelet therapies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the study selection procedure is presented in Fig. (**1**).

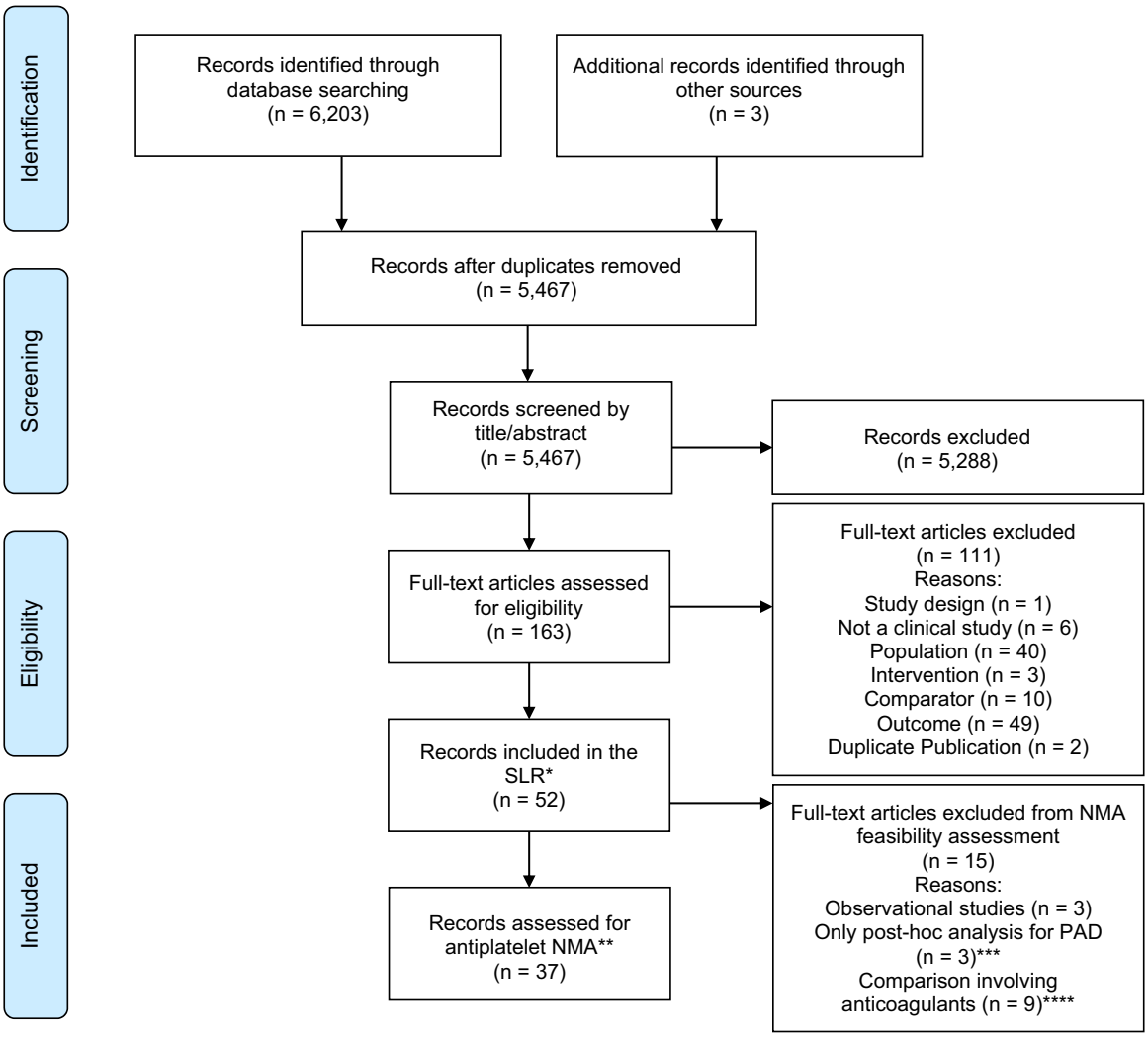


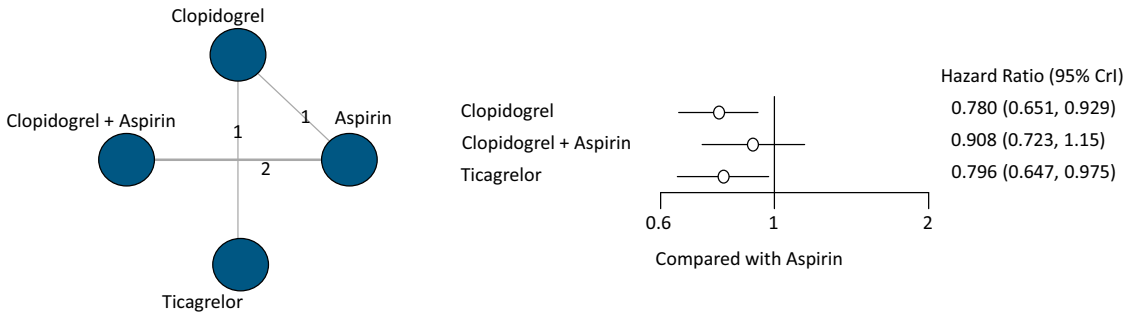
Fig. (1). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram. *The systematic review evidence base includes 52 publications — 49 publications on 35 unique RCTs and 3 publications on observational studies. ** The antiplatelet analysis evidence base includes 37 publications on 26 unique RCTs. *** 3 publications on 3 unique RCTs were excluded from NMA assessment since the PAD subgroup was only a post-hoc population but not defined by the study population inclusion criteria. **** 9 publications on 6 unique RCTs were excluded from NMA assessment since anticoagulants were involved in the treatment.

Network meta-analysis. Among the 26 RCTs of symptomatic PAD patients that were assessed in the NMA, 7 types of antiplatelets were evaluated as the study intervention, including clopidogrel (n=5) [4, 29, 33, 52, 58], cilostazol (n=9) [28, 38, 40, 43, 44, 49, 54-56], ticlopidine (n=6) [24, 25, 27, 34, 39, 45], picotamide (n=2) [26, 50], dipyridamole (n=2) [32, 47], ticagrelor (n=1) [5], and vorapaxar (n=1) [37]. Aspirin was used as DAPT with these study interventions, or as a monotherapy serving as the study comparator.

For 12 studies that were only included for qualitative review, 6 RCTs evaluated the combination of antiplatelets and anticoagulants, including 3 trials on warfarin [13, 15, 17], and 1 trial each on dalteparin [14], edoxaban [16], and rivaroxaban [9]. In 3 RCTs where PAD was only assessed as *post-hoc* analysis, ticagrelor was evaluated in 2 studies [18, 20] and vorapaxar was evaluated in 1 study [19]. Real world evidence was limited for the symptomatic PAD population — only 3 studies were identified as eligible according to the study protocol, with 1 study each reporting on cilostazol [21], ticlopidine [22] and DAPT [23].

The age of the population ranged from 58.8 to 74.0 years. The proportion of male patients ranged from 47.5% to 97.0%. While 3 studies reported a male population higher than 85% [24, 38, 52], there was little variation between the other trials in the reported proportion of males. For other PAD risk factors and characteristics, although not reported in all studies, differences in smoking status, hypertension, hyperlipidaemia, diabetes, myocardial infarction, stroke, and concomitant medications were observed across the studies, suggesting heterogeneity across studies.

A summary of the quality assessment for the 35 RCTs included for quantitative assessment is presented in Table **S3** and Fig. (**S1**). Most studies tended towards low risk of bias



Clopidogrel + Aspirin	1.14 (0.84, 1.59)	1.16 (0.88, 1.57)	0.91 (0.72, 1.15)
0.88 (0.63, 1.18)	Ticagrelor	1.02 (0.91, 1.14)	0.80 (0.65, 0.97)
0.86 (0.64, 1.13)	0.98 (0.88, 1.09)	Clopidogrel	0.78 (0.65, 0.93)
1.10 (0.87, 1.38)	1.26 (1.03, 1.55)	1.28 (1.08, 1.54)	Aspirin
Hazard ratio are reported for each intervention (row) versus comparator (column) combination.			

Fig. (2). Network meta-analysis for major adverse cardiac events using reported hazard ratios. Network diagram, forest plot and league table of the network meta-analysis for Major Adverse Cardiac Events (composite of cardiovascular death, myocardial infarction and stroke) using reported hazard ratios. The numbers by the vertices of the network diagram indicate how many trials reported the comparison between the connected nodes. Hollow circles represent hazard ratios; the 95% credible intervals (CrI) are denoted by lines. The table reports Hazard Ratios for each intervention (drug name in the row) *vs*. comparator (drug name in the column). Meta-analysis is performed by fixed effects model. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

across the 7 domains, except for the blinding of participants and personnel (performance bias) and incomplete outcome data (attrition bias) categories, where 23% of the studies presented a high risk of bias. For blinding of participants and personnel, 8 studies were reported as open label [13-17, 44, 54, 55], thus rated as high risk of bias; for the incomplete outcome data category, 8 studies were rated as high risk of bias since >20% of patients were dropped out from the study or imputation was used for missing data [15, 27, 33, 38, 40, 43, 44, 56]. Six studies had unclear risk since the analysis population was not well specified [14, 18-20, 29, 37]. In other categories, 66-91% of the studies presented a low risk of bias, 0-34% presented unclear risk, while only 0-9% of the studies presented a high risk.

Efficacy outcomes. Efficacy outcomes of interest were reported in 28 studies in the review, including MACE (n=12), amputation (n=21), peripheral revascularisation (n=11) and limb ischaemia (n=8). Efficacy outcomes from the included studies are presented in Table **S4** through Table **S8**. For MACE outcomes, 4 trials were included in the NMA. Treatment with clopidogrel 75 mg daily significantly reduced the risk of MACE compared with aspirin monotherapy (HR: 0.78, 95% CrI: 0.65-0.93) [4]. Treatment with ticagrelor 90 mg twice daily significantly reduced the risk of MACE compared with aspirin monotherapy (HR: 0.80, 95% CrI: 0.65-0.98, indirect treatment comparison using data from CAPRIE and EUCLID trials) (Fig. **2**) [4, 5]. DAPT with clopidogrel and aspirin did not show a significant difference from aspirin monotherapy. Full league table of HR data analysis results is also presented in Fig. (**2**). An NMA using binary data from the same studies further confirmed this finding (Fig. **S2**).

For limb amputation, no analysis was feasible with HR data, so the NMA was performed using binary data. No significant differences were observed among clopidogrel with aspirin, picotamide, placebo, ticlopidine, or vorapaxar *versus* aspirin across 5 trials (Fig. **3a**). Although not reaching statistical significance, clopidogrel with aspirin showed a reduced risk of amputation compared with aspirin monotherapy (RR: 0.68, 95% CrI: 0.43-1.04). The only statistically significant finding was that ticlopidine reduced the risk of amputation compared with placebo (Fig. **S3**; RR: 0.19, 95% CrI: 0.03-0.80).

For limb ischaemia and revascularisation, only 2 studies each were eligible for the indirect treatment comparison, and vorapaxar was found to reduce the risk of limb ischaemia (RR: 0.59, 95% CrI: 0.43-0.80) and revascularisation (RR: 0.89, 95% CrI: 0.80-0.99) compared with placebo (Figs. **3b** and **3c**, respectively). Clopidogrel was not available for NMA on these outcomes. Network diagrams and league tables for limb amputation, limb ischaemia, and peripheral revascularisation are presented in Fig. (**S3**).

Safety outcomes. Safety outcomes of interest were reported in 35 studies in the review, including all-cause mortality (n=30) and bleeding (n=19). Safety outcomes from the included studies are presented in Table **S9** to Table **S12**. The definition of bleeding for the different trials included is reported in Table **S13**.

For all-cause mortality, HR analysis observed no statistically significant difference among cilostazol, vorapaxar and placebo across 2 trials (Fig. **4a**). The NMA using binary data included 9 trials; when compared with aspirin, picotamide and ticlopidine both showed a significantly lower risk of all--cause mortality (Fig. **4b**). Picotamide, vorapaxar, dipyridamole with aspirin, and ticlopidine also showed a significantly lower risk of all-cause mortality when compared to DAPT with clopidogrel and aspirin. Network diagrams and league tables for all-cause mortality are presented in Fig. (**S4**).

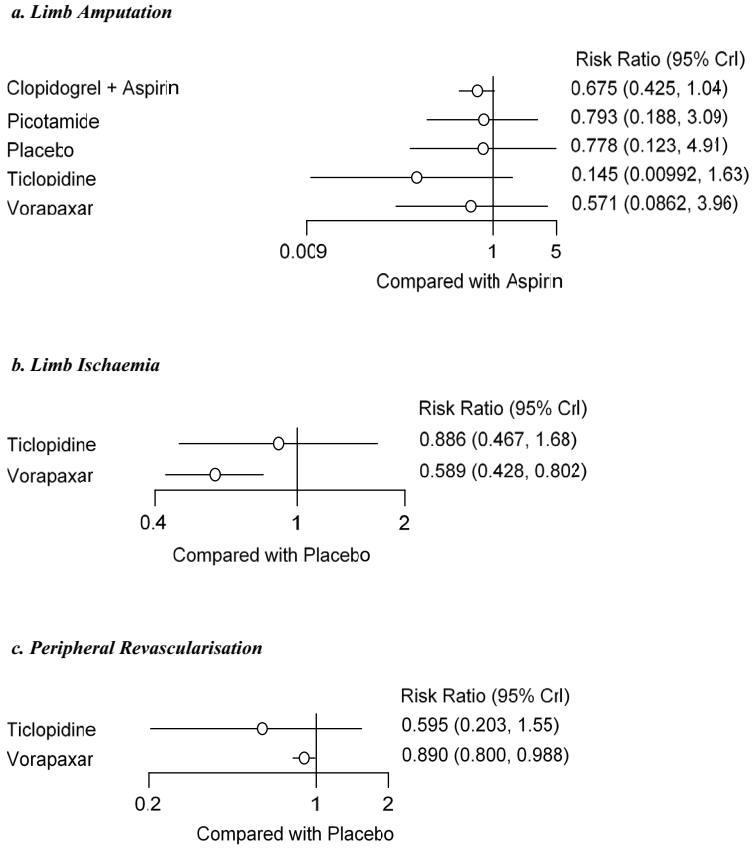


Fig. (3). Network meta-analysis for limb amputation, limb ischaemia, and peripheral revascularisation using reported binary data. Forest plot of the network meta-analysis for limb amputation (**a**), limb ischaemia (**b**), and peripheral revascularisation (**c**). Explanation of the graph, as in Fig. (**2**).

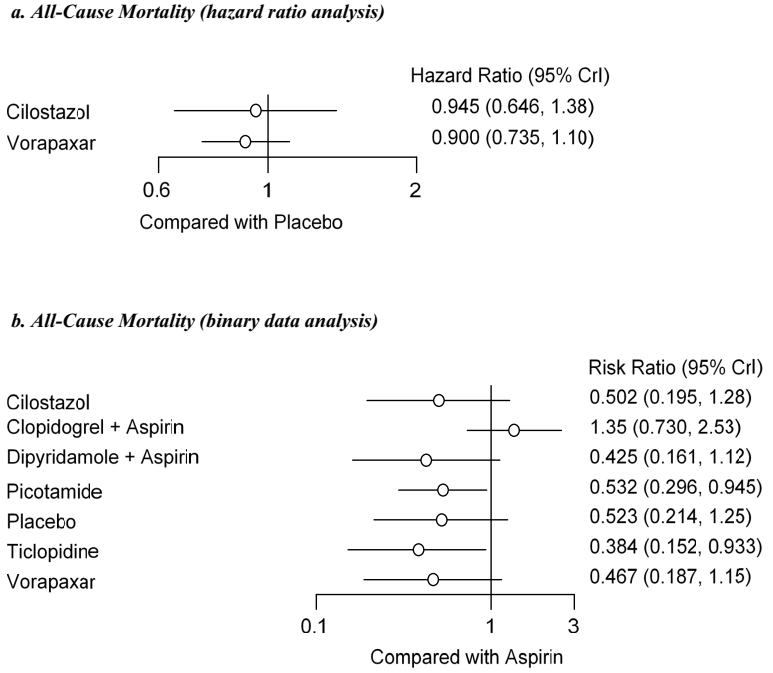


Fig. (4). Network meta-analysis for all-cause mortality. Forest plot of the network meta-analysis for all-cause mortality using reported hazard ratios (**a**) and binary data (**b**). Explanation of the graph, as in Fig. (**2**).

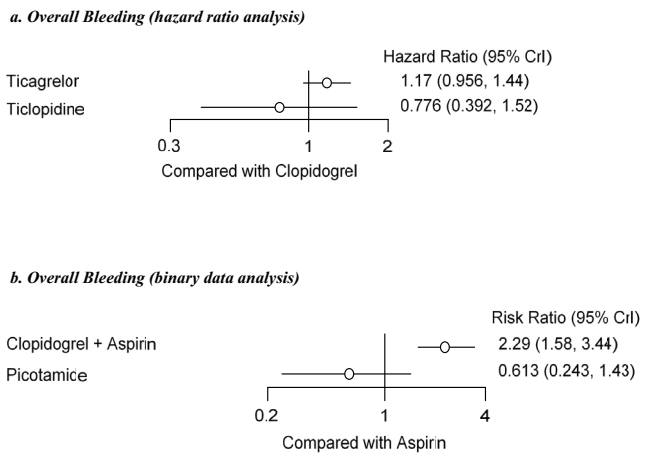


Fig. (5). Network meta-analysis for overall bleeding. Forest plot of the network meta-analysis for overall bleeding using reported hazard ratios (**a**) and binary data (**b**). Explanation of the graph, as in Fig. (**2**).

For overall bleeding, the indirect treatment comparison based on HR did not show a significant difference among clopidogrel, ticagrelor, and ticlopidine monotherapies (Fig. **5a**). Compared with aspirin, DAPT with clopidogrel and aspirin showed an increased risk (Fig. **5b**; RR: 2.29, 95% CrI: 1.58-3.44) [50]. In the indirect treatment comparison based on binary data from 2 trials, DAPT with clopidogrel and aspirin showed a significantly increased risk of overall bleeding when compared with picotamide (RR: 3.78, 95% CrI: 1.47-10.58). Network diagrams and league tables for overall bleeding are presented in Fig. (**S5**).

Plots of RR estimates for limb amputation and all-cause mortality for various therapies compared with aspirin are presented in Fig. (**S6**). Single antiplatelet treatment with the P2Y12-inhibitor ticlopidine had the most favourable harm-benefit profile, while DAPT with clopidogrel and aspirin was the only treatment associated with a higher risk of all-cause mortality. Clopidogrel and ticagrelor were not included in this plot as RR estimates for limb amputation *vs* aspirin are not available.

4. DISCUSSION

Antiplatelet therapies are essential for the long-term management of PAD. The various aspects of antiplatelet treatment in PAD, from the pathophysiology of thrombosis to the choice of antithrombotic regimen following peripheral revascularisation, were most recently reviewed in a Special Issue of this journal [59-61]. Previous meta-analyses reviewed the therapeutic evidence of antiplatelets for PAD [62], and compared antiplatelet therapies using pairwise meta-analyses in patients with claudication [63] or performed NMA in the overall PAD population [64]. However, the latter analysis also involved asymptomatic PAD patients and did not include the latest evidence (*e.g*. EUCLID trial).

The present study is the first to evaluate the comparative efficacy and safety among antiplatelet therapies in symptomatic PAD patients using Bayesian NMA, which allows for indirect comparison of different treatments that form a well-connected evidence network for the population, interventions, and outcomes of interest. However, due to limitations in the evidence network and the disconnection between treatments, some analyses were limited to 1 trial per comparison, clearly indicating the need for future clinical trials and observational studies with standardised outcome data and head-to-head comparisons in order to allow for more comprehensive assessment of the benefits and harms of different antiplatelet and anticoagulant therapies, helping physicians in the selection of the best therapy.

We found that clopidogrel or ticagrelor monotherapy significantly reduced the risk of MACE compared with aspirin treatment. While showing a similar effect with respect to MACE reduction, in 1 study clopidogrel presented a lower risk of bleeding events than ticagrelor, although not reaching statistical significance (HR: 0.85, 95% CrI: 0.69-1.05). In addition, ticagrelor is more expensive than clopidogrel and is currently not reimbursed for the treatment of PAD in most countries. Regarding DAPT with clopidogrel and aspirin, no significant difference was observed for MACE or limb amputation when compared with aspirin alone. Importantly, DAPT with clopidogrel and aspirin showed a significantly higher risk of all-cause mortality compared with picotamide, vorapaxar, dipyridamole combined with aspirin, and ticlopidine, most probably through an increase in major bleeding events, which are tightly associated with mortality. In fact, DAPT with clopidogrel and aspirin carries a higher risk of overall bleeding events compared with aspirin and with picotamide monotherapy. These findings contradict those of the meta-analysis by Navarese *et al*., comparing a pool of different DAPT regimens *vs* single antiplatelet therapy; in this study, DAPT significantly reduces mortality compared with single antiplatelet therapy, without increasing bleeding complications [62]. However, this meta-analysis has major limitations; firstly, the results are driven by non-adjusted estimates from 2 retrospective studies contributing 92.8% of the population, while relevant trials such as CASPAR [29] were not included; secondly, 93% of the patients had undergone a recent peripheral revascularisation, limiting the applicability of findings to the wider population of symptomatic PAD; thirdly, none of the studies included was an RCT of DAPT *vs* single antiplatelet therapy, with DAPT indication being unclear and its duration varying from 3 days to 60 months.

The increasing interest for PAD as a marker of higher CV risk across all types of medical treatment of atherosclerotic disease, including antiplatelets [20, 36], anticoagulants [10], lipid-lowering drugs [65, 66] and glucose-lowering drugs [67], calls for a more standardised and in-depth assessment of adverse limb events. The new composite endpoint of Major Adverse Limb Events (MALE) is increasingly used in randomised trials [10, 65], but its definition still lacks standardisation. Two recent meta-analyses investigated the effects of different antithrombotic treatments on MALE outcomes in PAD patients. The first, by Navarese *et al*., reported that DAPT was associated with a reduction in the risk of peripheral revascularisation in symptomatic PAD

patients (RR: 0.83, 95% CI: 0.73-0.94) [62]. In agreement with the present analysis, no statistically significant effect of a more intense antithrombotic treatment was found on MACE risk. The second meta-analysis, by Savarese *et al*. compared more intense antithrombotic therapy (DAPT or dual antithrombotic treatment) *vs* less intense antithrombotic therapy (single antiplatelet or oral anticoagulant) and reported a reduced risk of limb revascularisation (RR 0.89, 95% CI: 0.83–0.94) and limb amputation (RR 0.63, 95% CI 0.46-0.86) with more intense therapy [68]. The latter was associated with a higher risk of major bleeding (RR 1.23, 95% CI 1.04-1.44) without significant benefits in terms of MACE. In our opinion, it remains questionable whether the reduction of MALE at the expense of a potential increase in major bleeding should prompt the adoption of any of these combined antithrombotic regimens as the new standard of care for all symptomatic PAD patients.

In the present analysis, we observed high heterogeneities in bleeding events. We included any bleeding events as reported in each study for the overall bleeding outcome, therefore the included events could range from minor to life-threatening bleeding. For major bleeding events, different classifications were used across the RCTs, hindering comparisons. In the NMA, only results with similar qualifiers were used to ensure a reasonable comparison. For bleeding outcomes, only overall bleeding was feasible for analyses; other bleeding outcomes were not feasible for NMA due to the lack of network connectivity.

Anticoagulants have also been investigated for their effect in PAD management. In this review, we identified 6 trials evaluating anticoagulants, including warfarin, dalteparin, edoxaban and rivaroxaban. Considering the differences in mechanisms of action and patient selection, these studies were not included in the NMA for quantitative analysis.

Although vitamin K antagonists and low-molecular weight heparins failed to become a first-line antithrombotic therapy for PAD, in 2018, a low dose of the direct oral anticoagulant rivaroxaban (2.5 mg twice daily) in combination with aspirin proved superior to aspirin monotherapy in the "Cardiovascular Outcomes for People Using Anticoagulation Strategies" (COMPASS) trial which included a large predefined PAD subgroup [9].

In symptomatic patients with LEAD, there was a significant improvement in MACE outcomes (HR: 0.71, 95% CI: 0.53-0.97) and vascular amputation (HR: 0.42, 95% CI: 0.21–0.85) with the addition of rivaroxaban to aspirin [9, 10]. However, the risk of major bleeding was also increased with the dual therapy (HR: 1.71, 95% CI: 1.06-2.77) [9]. On the other hand, in the small ePAD trial, comparing full dose edoxaban (60 mg/day) in combination with aspirin *vs* DAPT with clopidogrel and aspirin in patients undergoing femoropopliteal endovascular treatment, no significant difference was observed for the efficacy and safety outcomes between the 2 treatment groups [16].

Considering the promising effect of MACE and amputation reduction by rivaroxaban/aspirin combination therapy, it would be of interest to further investigate the efficacy and safety profiles of rivaroxaban *vs* alternative antiplatelet treatments in symptomatic PAD patients. From a qualitative perspective, the magnitude of MACE reduction with clopidogrel in the CAPRIE trial was comparable with that observed with rivaroxaban + aspirin in the COMPASS trial (CAPRIE trial, clopidogrel *vs* aspirin, HR: 0.78, 95% CI: 0.65–0.93; COMPASS trial, rivaroxaban + aspirin *vs* aspirin, HR: 0.71, 95% CI: 0.53-0.97) [4, 9], thus supporting the use of clopidogrel as the mainstay of PAD treatment in most patients, at least in those at higher bleeding risk. In addition, our NMA showed that monotherapy with the oral P2Y12 inhibitor ticlopidine had the most favourable harm-benefit profile *vs.* aspirin in terms of limb amputation and all-cause mortality; currently, ticlopidine has largely been replaced by clopidogrel, due to its side effects. On the other hand, the benefits of clopidogrel in PAD come from a subgroup analysis of CAPRIE, which might not be statistically powered (*i.e*. a *post hoc* analysis) to produce accurate results for this population and might present a higher risk of heterogeneity.

There are some inherent limitations in this review. We included all studies feasible for antiplatelet analysis in the NMA. There are differences in the patient characteristics across the selected trials, especially in smoking status, comorbidities and concomitant medications, however, no meta-regression or sensitivity analysis was feasible due to the limited evidence base. In addition, only limited outcomes were available as HR data, so in an attempt to examine the indirect comparison across antiplatelets, RR analysis using binary outcomes were also performed. For the RR analysis, we compared the proportions of patients who have experienced the outcomes of interest but not the incidence rates. With the differences in study follow-up durations and potential risk of incomplete outcome reporting in some trials, this method can introduce bias. Lastly, analyses for limb ischaemia, revascularisation, and bleeding were only feasible with 2 studies, and the results should be interpreted with caution.

CONCLUSION

The present NMA demonstrated that clopidogrel monotherapy significantly decreased the risk of MACE compared with aspirin and presented a similar risk of overall bleeding compared with other antiplatelet agents. Clopidogrel and aspirin as DAPT did not significantly improve MACE outcome compared with clopidogrel monotherapy or aspirin, while increasing the risk of bleeding. Therefore, clopidogrel monotherapy should remain the mainstay of antithrombotic treatment in symptomatic PAD and still represents the preferable option in patients who cannot accept the additional bleeding risk entailed by new dual antithrombotic regimens.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA Guideline has been followed.

FUNDING

This study was funded by Sanofi. The study sponsor was not involved in the study design, collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

CONFLICT OF INTEREST

Marco De Carlo reports consultancy fees from Bayer and speaker fees from Amgen, Boehringer-Ingelheim, Bayer, Daiichi-Sankyo and Sanofi. Giovanni Di Minno reports consultancy fees from Sanofi-Aventis, Takeda, Novo Nordisk, Pfizer, Bayer and Sobi. Tobias Sayre reports employment by Doctor Evidence, LLC which was contracted by Sanofi to perform this work. Mir Sohail Fazeli and Gaye Siliman report employment or contract by Evidinno Outcomes Research Inc., respectively, which reports contract by Doctor Evidence, LLC. Claudio Cimminiello reports consultancy fees from Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Pfizer-BMS and Sanofi.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

APPENDIX A

The systematic review included publications from 1986 to 2018, reporting on 51,465 patients with symptomatic PAD. The study and patient characteristics of the included studies are summarised in Table **1** APPENDIX **(A)** and Table **2** APPENDIX **(B)**.

Table 1. Study characteristics.

Study Acronym	Author (Year)	Clinical Trial Number	Primary /Secondary Pub for PAD	Intervention	Comparator	Population	Surgery	PAD Study N	Follow-up Duration
CAPRIE	CAPRIE (1996)	NR	Primary	Clopidogrel 75	Aspirin	PAD subpopulation	-	6452	1.91 yr (Mean)
COOPER	Shigematsu H (2012)	NCT00862420	Primary	Clopidogrel 75	Ticlopidine	PAD, symptomatic	-	431	52 wk
CHARISMA	Bhatt DL (2007)	NCT00050817	Primary	Clopidogrel 75 + Aspirin	Aspirin	PAD subpopulation	-	3059	27.6 mo (Median)
CASPAR	Belch JJ (2010)	NCT00174759	Primary	Clopidogrel 75 + Aspirin	Aspirin	PAD, symptomatic	Unilateral below-knee bypass graft (IC)	851	24 mo
MIRROR	Tepe G (2012)	NCT00163267	Primary	Clopidogrel 75 + Aspirin	Aspirin	PAD, symptomatic	Percutaneous transluminal angioplasty (BL)	80	6 mo
	Strobl FF (2013)	NCT00163267	Secondary	Clopidogrel 75 + Aspirin	Aspirin	PAD, symptomatic		80	12 mo
NA	Money SR (1998)	NR	Primary	Cilostazol	Placebo	PAD, symptomatic	-	239	16 wk
NA	Beebe HG (1999)	NR	Primary	Cilostazol	Placebo	Intermittent claudication - PAD	-	516	24 wk
NA	Dawson DL (2000)	NR	Primary	Cilostazol	Placebo	Intermittent claudication - PAD	-	698	198 d
NA	Strandness DE Jr (2002)	NR	Primary	Cilostazol	Placebo	Intermittent claudication - PAD	-	394	6 mo
CASTLE	Hiatt WR (2008)	NR	Primary	Cilostazol	Placebo	PAD, symptomatic	-	1439	34 mo (Mean)
NA	Brass EP (2012)	NCT00783081	Primary	Cilostazol	Placebo	PAD, symptomatic	-	387	26 wk
NA	Soga Y (2009)	UMIN000001434	Primary	Cilostazol + Aspirin	Aspirin	Intermittent claudication - PAD	Endovascular therapy (BL)	78	24 mo
STOP-IC	Iida O (2013)	NCT00912756	Primary	Cilostazol + Aspirin	Aspirin	PAD, symptomatic	Percutaneous transluminal angioplasty (BL)	200	12 mo
	Soga Y. (2018)	NCT00912756	Secondary	Cilostazol + Aspirin	Aspirin	PAD, symptomatic		200	3 yr

Table (1). contd....

CABBAGE	Soga Y (2017)	UMIN000007910	Primary	Cilostazol + Aspirin	Aspirin	PAD, symptomatic	Percutaneous transluminal angioplasty (BL)	53	3 mo
NA	Castelli P (1986)	NR	Primary	Ticlopidine	Placebo	Femoropopliteal procedures	Thromboendarterectomy (BL)	46	180 d
NA	Arcan JC (1988)	NR	Primary	Ticlopidine	Placebo	Intermittent claudication - PAD	-	169	24 wk
NA	Balsano F (1989)	NR	Primary	Ticlopidine	Placebo	Intermittent claudication - PAD	-	151	21 mo
STIMS	Janzon L (1990)	NR	Primary	Ticlopidine	Placebo	Intermittent claudication - PAD	-	687	5.6 yr (Median)
	Fagher B (1994)	NR	Secondary	Ticlopidine	Placebo	Intermittent claudication - PAD; Lund district	-	101	5.04 yr (Median)
EMATAP	Blanchard J (1994)	NR	Primary	Ticlopidine	Placebo	PAD, symptomatic	-	615	6 mo
NA	Becquemin JP (1997)	NR	Primary	Ticlopidine	Placebo	Femoropopliteal procedures	Below-knee bypass: femoropopliteal or femorotibial (IC)	243	24 mo
ADEP	Balsano F (1993)	NR	Primary	Picotamide	Placebo	PAD, symptomatic	-	2304	18 mo
	Milani M (1996)	NR	Secondary	Picotamide	Placebo	PAD, symptomatic; Diabetes	-	438	18 mo
DAVID	Neri Serneri GG (2004)	NR	Primary	Picotamide	Aspirin	PAD, symptomatic	-	1209	2 yr (Median)
NA	McCollum C (1991)	NR	Primary	Dipyridamole + Aspirin	Placebo	Femoropopliteal procedures	Femoropopliteal vein bypass (BL)	549	35 mo (Mean)
NA	Bergqvis D (1994)	NR	Primary	Dipyridamole + Aspirin	Placebo	PAD, symptomatic	Percutaneous transluminal angioplasty (BL)	223	12 mo
EUCLID	Hiatt WR (2017)	NCT01732822	Primary	Ticagrelor 90	Clopidogrel 75	PAD, symptomatic	-	13885	30 mo (Median)
	Hiatt WR (2017)	NCT01732822	Secondary	Ticagrelor 90	Clopidogrel 75	PAD, symptomatic	-	13885	30 mo (Median)
	Berger JS (2018)	NCT01732822	Secondary	Ticagrelor 90	Clopidogrel 75	PAD, symptomatic	-	13885	30 mo (Median)
	Jones WS (2017)	NCT01732822	Secondary	Ticagrelor 90	Clopidogrel 75	PAD, symptomatic; Prior lower extremity revascularisation	Revascularisation of the lower extremity (IC)	7875	30 mo (Median)
	Berger J. (2017)	NCT01732822	Secondary	Ticagrelor 90	Clopidogrel 75	PAD, symptomatic; Coronary artery disease	-	4032	30 mo (Median)
TRA2°P-TIMI 50	Bonaca MP (2013)	NCT00526474	Primary	Vorapaxar	Placebo	PAD subpopulation	-	3787	36 mo (Median)
	Bonaca MP (2016)	NCT00526474	Secondary	Vorapaxar	Placebo	PAD subpopulation	-	3787	2.5 yr (Median)
	Bonaca MP (2016)	NCT00526474	Secondary	Vorapaxar	Placebo	PAD subpopulation - PAD history regardless of other trial inclusion criteria	-	5845	2.5 yr (Median)
	Qamar A. (2018)	NCT00526474	Secondary	Vorapaxar	Placebo	PAD subpopulation - PAD regardless of CAD or stroke history	-	6146	2.5 yr (Median)
Trials with anticoagulants (given in combination with antiplatelet)									

Table (1). contd....

Veterans Affairs (VA) Cooperative Study #362	Johnson WC (2002)	NR	Primary	Warfarin + Aspirin	Aspirin	Femoropopliteal or other PAD procedures	Axillofemoral, femorofemoral, femoropopliteal, or femorodital bypass surgery (IC)	831	39.3 mo (Average)
	Johnson WC (2004)	NR	Secondary	Warfarin + Aspirin	Aspirin	Femoropopliteal or other PAD procedures		831	38 mo (Mean)
	Jackson MR (2002)	NR	Secondary	Warfarin + Aspirin	Aspirin	Femoropopliteal procedures; Occlusion	Femoropopliteal bypass (IC)	100	39 mo (Mean)
NA	Monaco M (2012)	NR	Primary	Warfarin + Clopidogrel 75	Clopidogrel 75 + Aspirin	Femoropopliteal procedures	Femoropopliteal bypass (IC)	341	6.6 yr (Median)
NA	Li H (2013)	NR	Primary	Warfarin + Nadroparin + Clopidogrel 75	Clopidogrel 75	Femoropopliteal procedures	Endovascular treatment of the femoropopliteal artery (BL)	88	12 mo
NA	Koppensteiner R (2006)	NR	Primary	Dalteparin + Aspirin	Aspirin	Femoropopliteal procedures	Femoropopliteal angioplasty (IC)	275	12 mo
ePAD	Moll F (2018)	NCT01802775	Primary	Edoxaban + Aspirin	Clopidogrel 75 + Aspirin	PAD, symptomatic	Femoral or above-knee popliteal artery endovascular treatment (IC)	203	6 mo
COMPASS	Anand SS (2017)	NCT01776424	Primary	Rivaroxaban 2.5 + Aspirin	Aspirin	PAD subpopulation - symptomatic	-	6048	21 mo (Median)
	Anand SS (2018)	NCT01776424	Secondary	Rivaroxaban 2.5 + Aspirin	Aspirin	PAD subpopulation - lower extremity	-	6391	21 mo (Median)
Trials with PAD as post-hoc population									
PEGASUS-TIMI 54	Bonaca MP (2016)	NCT01225562	Primary	Ticagrelor 60 or 90 + Aspirin	Aspirin	Prior myocardial infarction + 1 of 4 high-risk features (post-hoc for PAD at baseline)	-	21162	3 yr
PLATO	Patel MR (2014)	NCT00391872	Primary	Ticagrelor 90 + Aspirin	Clopidogrel 75 + Aspirin	Acute coronary syndrome (post-hoc for PAD at baseline)	-	1144	NR
TRACER	Jones WS (2014)	NCT00527943	Primary	Vorapaxar	Placebo	Acute coronary syndrome + 1 of 4 risk-enrichment criteria (post-hoc for history of PAD)	-	12944	2 yr
Observational studies									
REAL-FP1000 Registry	Soga Y (2012)	NA	Primary	Cilostazol + Clopidogrel 75 + Aspirin	Clopidogrel 75 + Aspirin	PAD, symptomatic	Percutaneous transluminal angioplasty (BL)	861	25 mo (Mean, SD ± 15)
NA	Armstrong EJ (2015)	NA	Primary	DAPT (Clopidogrel or Prasugrel or Ticlopidine + Aspirin)	Aspirin	PAD, symptomatic	-	223	13 yr (Median)
NA	Fiotti N (2003)	NA	Primary	Ticlopidine	Aspirin	PAD, symptomatic	-	629	3 yr

*References with multiple publications of the same trial were only included if they differentiated in population type, outcomes, and time points available. BL = baseline; d = day; DAPT = dual antiplatelet therapy; IC = inclusion criteria; mo = month; NA = not applicable; NR = not reported; PAD = peripheral artery disease; Pub = publication; wk = week; yr = year.

APPENDIX B

Table 2. Patient characteristics.

Acronym	Author (Year)	Treatment	Group N	Smoking Status				Comorbidities							Concomitant Medication					
				Age, years	Male (%)	Current (%)	Former (%)	None (%)	Unknown (%)	HTN (%)	Hyper-lipidaemia (%)	DM (%)	MI (%)	Stroke (%)	Beta Blocker (%)	Other Anti--platelets (%)	Lipid Lowering (%)	ACE In-hibitor (%)	Diur-etics (%)	Statins (%)
CAPRIE	CAPRIE (1996)	Clopidogrel_75	9599	62.0	72.0	38.0	53.0	-	-	52.0	-	-	17.0	6.0	-	-	-	-	-	-
		Aspirin	9586	62.0	72.0	38.0	52.0	-	-	51.0	-	-	16.0	6.0	-	-	-	-	-	-
COOPER	Shigematsu H (2012)	Ticlopidine	216	70.2	88.9	23.6	63.0	-	-	74.1	54.6	32.4	2.8	18.1	-	61.0	-	-	-	-
		Clopidogrel_75	215	71.1	87.9	26.5	-	10.2	-	73.5	56.3	34.4	3.7	18.1	-	62.0	-	-	-	-
CHARISMA	Bhatt DL (2007)	Clopidogrel_75_Aspirin	4735	64.0	72.7	-	-	-	-		-	-		-	-	-	-	-	-	-
		Aspirin	4743	64.0	73.1	-	-	-	-		-	-		-	-	-	-	-	-	-
CASPAR	Belch JJ (2010)	Clopidogrel_75_Aspirin	425	66.5	75.5	38.8	-	-	-	70.1	50.4	37.4		-	37.0	-	-	47.0	34.0	47.8
		Aspirin	426	65.6	75.8	36.4	-	-	-	70.0	48.8	38.0		-	34.0	-	-	40.0	31.0	46.8
MIRROR	Tepe G (2012)	Clopidogrel_75_Aspirin	40	69.8	47.5	37.5	-	-	-	77.5	62.5	30.0		-	-	-	-	-	-	-
		Aspirin	40	70.2	57.5	42.5	-	-	-	77.5	62.5	45.0		-	-	-	-	-	-	-
NA	Money SR (1998)	Cilostazol	119	64.8	75.6	36.1	-	-	-		-	25.2		-	-	-	-	-	-	-
		Placebo	120	64.5	75.0	40.0	52.5	7.5	-		-	30.8		-	-	-	-	-	-	-
NA	Beebe HG (1999)	Cilostazol_100	175	64.3	74.3	34.9	-	6.9	-		-	26.3		-	-	-	-	-	-	-
		Cilostazol_50	171	64.5	76.6	36.3	57.3	-	-		-	29.8		-	-	-	-	-	-	-
		Placebo	170	65.1	77.1	44.1	-	6.5	-		-	28.2		-	-	-	-	-	-	-
NA	Dawson DL (2000)	Cilostazol	227	66.0	76.0	41.0	52.0	-	-	73.0	65.0	32.0		-	-	-	-	-	-	-
		Placebo	239	66.0	74.0	38.0	56.0	-	-	72.0	67.0	31.0		-	-	-	-	-	-	-
NA	Strandness DE Jr (2002)	Cilostazol_100	133	63.1	76.7	50.4	46.6	-	-		-	23.3		-	-	-	-	-	-	-
		Cilostazol_50	132	63.9	74.2	47.7	-	10.6	-		-	28.8		-	-	-	-	-	-	-
		Placebo	129	64.4	77.5	48.1	41.9	-	-		-	17.1		-	-	-	-	-	-	-
CASTLE	Hiatt WR (2008)	Cilostazol	717	66.5	65.6	28.6	56.6	14.8	-	82.4	82.0	37.8	29.3	10.3	-	-	-	-	-	70.6
		Placebo	718	65.9	65.5	31.3	-	-	-	81.1	78.0	33.7	28.9	10.6	-	-	-	-	-	70.9
NA	Brass EP (2012)	Cilostazol	89	64.5	94.6	51.4	39.2	-	-		-	14.9		-	-	88.0	-	-	-	-
		Placebo	87	62.9	89.7	61.5	-	9.0	-	-	-	15.4	-	-	-	74.0	-	-	-	-
NA	Soga Y (2009)	Ticlopidine_Aspirin	39	71.6	87.0	44.0	-	-	-	49.0	28.0	41.0	26.0	21.0	10.0	-	-	31.0	-	-
		Ticlopidine_Cilostazol_Aspirin	39	69.8	79.0	33.0	-	-	-	49.0	38.0	31.0	13.0	23.0	18.0	-	-	36.0	-	-
STOP-IC	Iida O (2013)	Aspirin	100	73.0	68.0	-	-	-	-	82.0	-	56.0	-	-	-	-	-	-	-	-
		Cilostazol_Aspirin	100	72.0	69.0	-	44.0	-	-	81.0	-	56.0	-	-	-	-	-	-	-	-
CABBAGE	Soga Y (2017)	Aspirin	26	73.0	76.0	8.0	52.0	40.0	-	96.0	60.0	80.0	-	-	-	-	-	-	-	-
		Cilostazol_Aspirin	27	73.0	72.0	20.0	-	-	-	80.0	40.0	68.0	-	-	-	-	-	-	-	-
NA	Castelli P (1986)	Placebo	23	59.0	78.2	-	-	-	87.0	21.7	30.4	17.4	-	-	-	-	-	-	-	-
		Ticlopidine	23	60.2	82.6	-	-	-	91.3	26.1	21.7	4.4	-	-	-	-	-	-	-	-
NA	Arcan JC (1988)	Placebo	86	58.8	97.0	41.9	-	-	-	31.4	17.4	-	-	5.8	-	-	-	-	-	-
		Ticlopidine	83	59.9	86.0	43.4	50.6	-	-	32.5	14.5	-	-	3.6		-	-	-	-	-
NA	Balsano F (1989)	Placebo	75	59.9	74.7	-	73.3	-	-	26.7	12.0	12.0	10.7	-	-	-	-	-	-	-
		Ticlopidine	76	59.5	71.1	-	-	-	-	40.8	21.1	14.5	5.3	-	-	-	-	-	-	-
STIMS	Janzon L (1990)	Placebo	341	60.2	76.2	67.2	-	-	-		-	-	19.0	3.2	-	-	-	-	-	-
		Ticlopidine	346	60.5	76.6	67.3	-	-	-		-	-	16.2	2.6	-	-	-	-	-	-
EMATAP	Blanchard J (1994)	Placebo	311	62.5	84.2	29.9	-	-	-	57.5	-	30.5	15.1	5.4	-	-	-	-	-	-
		Ticlopidine	304	63.3	85.2	23.3	-	-	-	55.3	-	28.9	16.5	2.6	-	-	-	-	-	-
NA	Becquemin JP (1997)	Placebo	121	67.7	76.0	19.0	-	-	-	53.7	25.6	21.5		-	-	-	-	-	-	-
		Ticlopidine	122	67.1	78.7	25.4	-	-	-	48.4	23.8	27.0		-	-	-	-	-	-	-
ADEP	Balsano F (1993)	Picotamide	1150	63.4	84.9	39.6	48.0	12.4	-	34.5	36.5	20.0	8.0	-	-	-	3.0	-	4.0	-
		Placebo	1154	62.9	83.6	37.1	-	-	-	37.2	35.8	18.1	7.4	-	-	-	3.0	-	3.0	-
DAVID	Neri Serneri GG (2004)	Aspirin	606	64.6	71.8	28.4	14.7	56.9	-	55.6	38.4	-	-	10.2	-	35.0	14.0	32.0	15.0	-
		Picotamide	603	63.8	73.5	30.5	-	-	-	58.2	38.0	-	-	10.4	-	31.0	15.0	32.0	10.0	-
NA	McCollum C (1991)	Dipyridamole_Aspirin	286	66.8	75.5	42.2	-	-	-	36.0	-	18.2	-	-	-	-	-	-	-	-
		Placebo	263	66.6	74.9	40.5	-	-	-	35.0	-	18.3	-	-	-	-	-	-	-	-
NA	Bergqvis D (1994)	Dipyridamole_Aspirin	108	65.0	60.2	76.0	-	-	-	39.0	-	32.0	-	-	-	-	-	-	-	-
		Placebo	115	66.0	67.0	77.0	-	-	-	33.0	-	21.0	-		-	-	-	-	-	-
EUCLID	Hiatt WR (2017)	Clopidogrel_75	6955	66.0	71.5	31.1	46.7	21.6	-	77.9	75.5	39.0	18.4	8.2	-	-		40.0	-	73.7
		Ticagrelor_90	6930	66.0	72.5	30.7	-	-	-	78.5	75.5	38.0	17.9	8.3		-	-	41.0	-	73.0
TRA2°P-TIMI 50	Bonaca MP (2013)	Vorapaxar	1892	66.0	71.0	-	-	-	-	84.0	87.0	37.0		14.0		-	-	-	-	-
		Placebo	1895	66.0	70.0	-	-	-	-	83.0	88.0	35.0		13.0	-	-	-	-	-	-
Veterans Affairs (VA) Coopera-tive Study #362	Johnson WC (2002)	Aspirin [Bypass, Prosthetic, History Of]	186	62.7	-	-	-	-	-		-	29.6	27.4	17.2	-	-	-	-	-	-
		Aspirin [Bypass, Venous, History Of]	227	64.8	-	-	-	-	-		-	51.8	23.5	17.6	-	-	-	-	-	-
		Warfarin_Aspirin [Bypass, Prosthetic, History Of]	187	63.4	-	-	-	-	-		-	31.0	30.0	16.6	-	-	-	-	-	-
		Warfarin_Aspirin [Bypass, Venous, History Of]	231	65.6	-	-	-	-	-		-	51.5	18.6	17.8	-	-	-	-	-	-
NA	Monaco M (2012)	Clopidogrel_75_Aspirin	168	66.2	72.6	26.8	-	-	-	83.3	-	50.0			-	-	-	-	-	-
		Clopidogrel_75_Warfarin	173	68.4	67.0	18.5	-	-	-	78.1	-	45.1			-	-	-	-	-	-
NA	Li H (2013)	Clopidogrel_75	42	73.0	68.0	60.0	-	-	-	65.0	20.0	40.0	8.0	16.0	-	-	-	-	-	-
		Clopidogrel_75_Nadroparin_Warfarin	46	74.0	64.0	52.0	-	-	-	72.0	28.0	44.0	8.0	24.0	-	-	-	-	-	-
NA	Koppensteiner R (2006)	Aspirin	138	70.2	60.0	64.0	-	-	-		61.0	32.0	-	-	-	-	-	-	-	-
		Dalteparin_Aspirin	137	69.9	56.0	70.0	-	-	-		63.0	30.0	-	-	-	-	-	-	-	-
ePAD	Moll F (2018)	Clopidogrel_75_Aspirin	102	66.7	76.5	35.3	-	-	-	83.3	-	39.2	-	-	-	-	-	-	-	-
		Edoxaban_Aspirin	101	68.0	66.3	34.7	46.5	18.8	-	82.2	-	40.6	-	-	-	-	-	-	-	-
COMPASS	Anand SS (2017)	Aspirin	2504	67.8	71.0	27.4	45.6	-	-	80.6	-	44.1	-	6.2	59.0	87.0	83.0	70.0	-	-
		Rivaroxaban_2_5	2492	67.9	71.0	27.4	46.0	-	-	78.9	-	44.1	-	6.9	59.0	86.0	84.0	69.0	-	-

Table (2). contd....

PEGASUS-TIMI 54	Bonaca MP (2016)	Aspirin	404	66.0	80.0	-	-	-	-	85.2	80.2	44.1	-	-	-		-	-	-	-
		Ticagrelor_60_Aspirin	368	66.0	74.5	-	-	-	-	84.2	81.0	42.1	-	-	-	-	-	-	-	-
		Ticagrelor_90_Aspirin	371	66.0	78.7	-	-	-	-	84.1	81.4	40.2	-	-	-	-	-	-	-	-
PLATO	Patel MR (2014)	Clopidogrel_75_Aspirin	578	66.0	75.1	-	-	-	-	78.2	-	39.3	33.4	-	-	-	-	-	-	
		Ticagrelor_90_Aspirin	566	66.0	74.7	-	-	-	-	79.9	-	36.0	34.1		-	-	-	-	-	-
TRACER	Jones WS (2014)	Total Population	934	-	-	-	-	-	-	85.4	78.5	45.6	43.9	10.0	-	-	-	-	-	-
REAL-FP1000 Registry	Soga Y (2012)	Cilostazol_Clopidogrel_75_Aspirin	492	72.9	70.8	29.6	-	-	-	85.4	-	61.9		-	-	-	-	-	-	37.3
		Clopidogrel_75_Aspirin	369	72.9	67.2	29.6	-	-	-	86.8	-	62.9		-	-	-	-	-	-	33.8
NA	Armstrong EJ (2015)	Aspirin	281	67.0	56.0	77.0	-	-	-	84.0	-	45.0	15.0	16.0	48.0	-	-	-	-	65.0
		Clopidogrel / Ticlopidine / Prasugrel_Aspirin	348	67.0	56.0	77.0	-	-	-	86.0	-	54.0	21.0	16.0	55.0	-	-	-	-	70.0
NA	Fiotti N (2003)	Aspirin	131	64.0	85.0	59.0	-	-	-	46.0	27.0	22.0	15.0	-	-	-	-	-	-	-
		Ticlopidine	92	63.0	68.0	59.0	-	-	-	46.0	25.0	35.0	17.0	-	-	-	-	-	-	-

ACE = angiotensin-converting enzyme; DM = diabetes mellitus; HTN = hypertension; MI = myocardial infarction; NA = not applicable; NR = not reported; PAD = peripheral artery disease; yr = year.

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