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Full title: Antiplatelet therapy for peripheral arterial disease: an umbrella review and meta-analysis of preventative and treatment outcomes

Running head: Antiplatelet therapy in peripheral arterial disease

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Abstract

Objective: The literature on antiplatelet therapy for peripheral arterial disease has historically been summarised inconsistently, leading to conflict between international guidleines. An umbrella review and meta-analysis was performed to clearly summarise the literature, allow assessment of competing safety risks and clinical benefits, and identify weak areas for future research.

Methods: MEDLINE, EMBASE, DARE, PROSPERO and Cochrane databases were searched from inception until January 2019. All meta-analyses of antiplatelet therapy in peripheral arterial disease were included. Quality was assessed using Amstar scores, with GRADE analysis quantifying strength of evidence. Data were pooled using random-effects models.

Results: Twenty-eight meta-analyses were included. Thirty-three clinical outcomes and 41 antiplatelet comparisons in 72,181 patients were analysed. High-quality evidence showed antiplatelet monotherapy reduced non-fatal strokes and cardiovascular death in symptomatic patients (3 and 8 fewer per 1000 patients respectively, 95% CI 0–6 and 0–16), but increased risk of major bleeding (7 more per 1000, 95% CI 3–14). In asymptomatic patients, monotherapy reduced non-fatal strokes (5 fewer per 1000, 95% CI 0–8) but had no other clinical benefit. Dual antiplatelet therapy caused more major bleeding after intervention than monotherapy (37 more per 1000, 95% CI 8–102), with very low-quality evidence of improved endovascular patency (Relative Risk 4.00, 95% CI 0.91–17.68).

Conclusions: Antiplatelet monotherapy has minimal clinical benefit for asymptomatic peripheral arterial disease, and limited benefit for symptomatic disease, with clear risk of major bleeding. There is a lack of evidence to guide antiplatelet prescribing after peripheral endovascular intervention which needs addressing by adequately powered randomised trials.

Study registration: PROSPERO 2017 CRD42017084223

Key words: Antiplatelet therapy; Peripheral arterial disease; Systematic review; Meta-analysis

Introduction

Peripheral arterial disease (PAD) affects over 200 million people worldwide and is predicted to increase with the global diabetes expansion.[1,2] Guideline groups in the UK,[3] USA[4] and Europe[5] recommend antiplatelet therapy for patients with PAD. However, the specific recommendations in these guidelines are inconsistent.

The National Institute for health and Care Excellence (NICE)[3] in the UK and the American College of Cardiology/ American Heart Association (ACC/AHA)[4] in the USA recommend antiplatelet monotherapy for secondary prevention of cardiovascular events in all patients with PAD. The joint European Society for Vascular Surgery (ESVS) / European Society of Cardiology (ESC)[5] guidelines restrict this to symptomatic PAD. Dual antiplatelet therapy after peripheral intervention “may be reasonable to use” in the ACC/AHA guidelines and is recommended after lower limb stenting and prosthetic bypass by the ESC. NICE do not make a recommendation. There is currently a trend towards prescribing dual antiplatelet therapy after endovascular lower limb intervention based mainly on the coronary stenting literature.[6-8] There are problems with this practice; flow dynamics and patterns of atherosclerosis are different in the coronary and peripheral arteries, and the risks and benefits of dual antiplatelet therapy compared to monotherapy are far less clear in the PAD literature than the coronary literature.

PAD antiplatelet guidelines conflict with one another because data were variably aggregated from heterogeneous trials of multiple antiplatelet regimes and agents, some of which were discontinued decades ago. The PAD populations in the trials were also a mixture of patients with claudication and critical ischaemia, who are

different both in terms of cardiovascular risk and the risk of thrombosis of the interventions.[5,9]

Randomised trials in the peripheral arterial population are more relevant than ever for several reasons: Clopidogrel, which is recommended by guidelines is now off patent;[3] several new antiplatelet agents and anticoagulants have become available and are being investigated in this population,[10,11] and calls for trials of cheap commonly prescribed drugs in the peripheral arterial population are being published.[12]

Patients with PAD are at high risk of cardiovascular events,[13] so it is important that we clarify the best ways to optimize their management, but before high quality future trials can be designed, the literature must be systematically assessed so that the quality of data and strength of effect for all antiplatelet outcomes in PAD can be examined and compared. The best way to assimilate such a large amount of data is using umbrella review methodology.[14] This is because while individual outcomes and/or antiplatelet agents have been meta-analysed extensively in the past, there has never been a critical comparison of all available outcomes.

The aim of this study was to definitively assess the evidence from randomised trials of antiplatelet therapy in patients with PAD. This will both facilitate the clarification of international guidelines and define the areas where further research is required.

Methods

For this study, a systematic umbrella review of meta-analyses examining antiplatelet therapy for any outcome in patients with PAD was performed. This allows an in-depth overview of a broad topic and facilitates comparisons between outcomes to examine the relative importance of each.[14,15] It also highlights deficiencies in the literature. The study was registered on PROSPERO on 14th December 2017 (PROSPERO 2017 CRD42017084223 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017084223). As there are no internationally accepted guidelines for reporting umbrella reviews, both PRISMA,[16] and the most recent framework evaluation for reporting of overviews of systematic reviews (umbrella reviews)[15] were followed.

Literature search

MEDLINE and EMBASE were searched via Ovid from inception until January 2019 for meta-analyses involving patients with peripheral arterial disease on any antiplatelet therapy for any treatment outcome (Appendix A). The DARE, PROSPERO and Cochrane collaboration databases were searched separately. The related articles function on PubMed was used for every included meta-analysis, and reference lists of included meta-analyses were hand-searched. All publication types and languages were eligible. Two researchers (UC and CPT) independently screened titles and abstracts of articles for full text review. A third researcher (GKA) resolved differences. Full text articles were again double-reviewed. Cohort studies were excluded from analysis.

Eligibility criteria

All meta-analyses involving subjects with PAD where any antiplatelet therapy was compared with another therapy were included. No restriction was made on the comparator group. Combination therapies were also included. Any outcome was allowed. Meta-analyses were included when they pooled any combination of relative risks, odds ratios, relative rates or hazard ratios comparing the same exposure with the same outcome. Studies which did not perform systematic review before meta-analysis or did not perform meta-analysis were excluded.

The primary objective was to provide an overview of all safety and efficacy outcomes included in at least one meta-analysis, for patients randomized to any antiplatelet regime.

Data extraction

CPT and CAW independently extracted data as per the protocol registered on PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=84223). A standardised data collection proforma was used to improve reproducibility.

After extraction, individual study data from each meta-analysis was re-analysed with data from multiple other analyses. When a meta-analysis had been updated (such as Cochrane reviews, which are regularly updated), the most up to date version was used. If a randomised trial had data discrepancies between different meta-analyses the original trial reference was examined and the data re-extracted.

Risk of bias (quality) assessment

The AMSTAR measurement tool was used to assess the quality of included meta-analyses.[17,18] AMSTAR is a validated measurement tool to assess the methodological quality of systematic reviews, and ranges from 0 to 11 points.

The GRADE classification was used to assess the quality of the evidence for each outcome.[19] GRADE classifies the quality of evidence from included studies into: “high,” “moderate,” “low” and “very low” quality. This allows the overall strength of evidence for each individual meta-analysed outcome to be assessed.

Strategy for data synthesis

In order to give an overall picture of the effect of different antiplatelet strategies on a broad range of outcomes we grouped antiplatelet strategies into three main categories.

1. Single antiplatelet therapy vs. placebo or no antiplatelet therapy
2. Single antiplatelet therapy vs. dual antiplatelet therapy
3. Single antiplatelet therapy vs. anticoagulation

Single antiplatelet therapy was used as the baseline strategy as most guidelines currently recommend it for patients with PAD. Meta-analysis was performed for these groupings, with pooled estimates calculated for overall summary effects and also subgroup analysis for specific antiplatelet agents. It was not possible to compare by dose or duration of antiplatelet therapy because of a lack of data from included meta-analyses and heterogeneity between included trials.

Subgroup analysis

Subgroup analysis was performed by antiplatelet agent/regime (described above) and by clinical subgroups. In order to provide more detailed information about the benefits and risks of a particular antiplatelet strategy for these subgroups, we performed the following subgroup analyses, where data was available:

1. Asymptomatic patients
2. Symptomatic patients
3. Patients with intermittent claudication alone
4. Patients undergoing endovascular intervention
5. Patients undergoing open surgical intervention
6. Patients undergoing any type of intervention

It was not possible to examine patients with critical limb ischaemia separately as data was not available for this subgroup, though many trials included these patients.

Because of the large number of analyses this produced, in order to report significant results clearly, each of the main results sections (above) were divided into:

1. Safety and secondary prevention outcomes
2. Limb outcomes

Statistical analysis

Trial outcomes extracted from included meta-analyses were reanalysed using the DerSimonian and Laird random effects model.[20] The Paule and Mandel method was used to calculate the between-study variance and its uncertainty for dichotomous data, and the restricted maximum likelihood estimator was used for continuous data,[21,22] as these estimators have been shown in simulation studies to have reliable performance for these types of data.[23] Higgins' I^2 statistic was used to quantify heterogeneity.[24] Where more than 10 trials were available for analysis, Egger's regression test was used to look for evidence of publication bias.[25] All outcomes where an effect was significant at the 10% level were presented, as both risk ratios and also absolute event rates per 1000 patients. Analysis was performed within the R statistical programming environment version 3.5.1, using the metafor package version 2.0-0 for meta-analysis. Patency results are presented in the standard way, where events are losses of patency and thus more events signify a worse patency rate.

Patient involvement

The study was informed by feedback from qualitative patient interviews conducted as part of a randomised trial of patients undergoing major lower limb amputation for peripheral arterial disease,[26] who were taking antiplatelet medication for a mixture of secondary and/or tertiary prevention. This preliminary data showed enthusiasm for trials of antiplatelet agents in this population.

Results

The search yielded 1503 unique studies, from which 28 meta-analyses were included:[9,27-53] 21 including randomised trials alone,[9,27-35,38-40,42-46,48,52,53] and 7 including randomised trials and cohort studies (Figure 1, Appendix A).[36,37,41,47,49-51] These included data from 121 randomised trials involving 72,181 patients (Supplementary Table 1). The median number of included studies per meta-analysis was 15 (range 6 to 195). When meta-analyses with peripheral arterial patients only are considered the median was 14 with range 6-52. The median AMSTAR score was 8 (range 3-11). The higher quality meta-analyses were all published by the Cochrane collaboration.[28,29,32,35,48] We reanalysed 33 unique safety and efficacy outcomes from the 121 included studies.

There were 41 discrete antiplatelet comparisons. Including subgroup analysis, we ran 1271 meta-analyses (referred to as 'analyses') in total. All analyses are shown in the supplementary resources. Trials investigating secondary prevention were generally larger when compared to trials of tertiary prevention after intervention. Trials examining antiplatelet strategy following peripheral endovascular intervention in particular were small and lower quality.

There were five trials with discrepancies in patient and/or event numbers between meta-analyses, requiring data re-extraction.[54-58] No included meta-analysis authors had to be contacted for data queries.

Antiplatelet monotherapy vs. placebo or no antiplatelet therapy

Table 1 shows summary data for the most beneficial and harmful effects of antiplatelet monotherapy when compared to placebo or nothing, for all outcomes with an effect which is significant at the 10% level.

Safety and secondary prevention outcomes

Overall, there was high-quality evidence that antiplatelet monotherapy reduced non-fatal strokes (3 fewer per 1000 patients, 95% CI 0–6; P=0.019), but at a cost of a significantly increased risk of major bleeding (4 more per 1000, 95% CI 1–8; P=0.009).

In asymptomatic patients the only secondary prevention outcome where any benefit was found was for non-fatal stroke, where moderate quality evidence of a small absolute reduction was found (5 fewer per 1000 patients, 95% CI 0–8; P=0.055).

In symptomatic patients there was again minimal evidence of benefit for antiplatelet monotherapy on secondary prevention outcomes, with a significant reduction in events at the 5% level only found for cardiovascular death. Even these benefits are offset by a significant increase in the risk of major bleeding; 8 cardiovascular deaths were prevented per 1000 patients (95% CI 0–16; P=0.05), but there were 7 additional major bleeds (95% CI 3–14; P=0.002). There was no evidence of any secondary prevention benefit for aspirin or aspirin plus dipyridamole for any outcome other than non-fatal stroke. Many of the most beneficial effects for antiplatelet monotherapy were from trials using Ticlopidine as the antiplatelet agent

(Supplementary resources 1 and 2) , which has been withdrawn from market in many regions due to reports of thrombocytopenia, neutropenia and aplastic anaemia.

Limb outcomes

The most significant beneficial effects of monotherapy were generally limb-related and for patients undergoing intervention (Table 1): both vein and prosthetic bypass had primary patency benefits from antiplatelet therapy.

Dual antiplatelet therapy vs. monotherapy

Table 2 shows summary data for the most beneficial and harmful effects of dual antiplatelet therapy vs. antiplatelet monotherapy, for all outcomes with an effect which is significant at the 10% level. These were generally of lower GRADE quality than the outcomes of monotherapy vs. placebo or nothing, mainly as a result of imprecision.

Safety and systemic outcomes

Dual antiplatelet therapy resulted in significantly more major bleeding then monotherapy (Table 2). This is especially the case after intervention, where 37 more major bleeds per 1000 patients were caused by dual antiplatelet therapy (95% CI 8–102; P=0.0048).

Limb outcomes

Only two outcomes showed significant benefit at the 5% level with dual antiplatelet therapy, which were for prosthetic bypass patency at 24 months and amputation (low and moderate GRADE quality respectively, Table 2). There was very low quality evidence for dual antiplatelet therapy over monotherapy for endovascular intervention patency at 6 months from one trial (RR 4.00 95% CI 0.91–17.68, P=0.07).[59] All meta-analyses are shown in Supplementary resources 1 and 3.

Antiplatelet therapy vs. anticoagulation

There were only eight trials examining this comparison (Table 3). Most of the analyses were informed by patients included in two trials.[60,61] Major bleeding was not significantly different between the two groups and there were no significant differences in secondary prevention outcomes, although the trials were not powered to detect the latter.

Patients undergoing vein bypass had better patency rates from anticoagulation than antiplatelet monotherapy (81 events per 1000 patients prevented at 24 months, 95% CI 25–157; P=0.0024 GRADE quality moderate), whereas patients undergoing bypass using prosthetic grafts benefitted more from antiplatelet monotherapy than anticoagulation (81 events per 1000 patients prevented, 95% CI 25–128; P=0.0058 GRADE quality moderate). All meta-analyses are shown in Supplementary resources 1 and 4.

Other antiplatelet comparisons

Significant individual safety, secondary prevention and limb outcomes are described in detail in Appendix B. Multiple other antiplatelet comparisons have been examined in randomised trials. Details of all effect size estimates for different comparisons are given in Supplementary Resources 1–4. Only four single trials found significant differences between trial treatments, and each trial had a different antiplatelet comparison. These are shown in Supplementary Table 2.

The CAPRIE trial recruited 11592 patients with symptomatic PAD, randomising them to either aspirin or clopidogrel. They found significant benefit in terms of cumulative cardiovascular events and non-fatal myocardial infarction for patients treated with clopidogrel.[54] The DAVID trial randomised 1209 patients with diabetes and PAD to aspirin or picotamide.[56] They found significant benefit in terms of all-cause mortality for patients treated with picotamide as well as fewer side effects for patients treated with picotamide. In the STOP-IC trial 163 patients were randomised to either aspirin and cilostozol or aspirin and ticlopidine following endovascular intervention to femoropopliteal lesions.[62] They found significantly fewer losses of primary patency at 12 and 24 months with aspirin and cilostazol. There was no significant difference in rates of major bleeding between trial treatments in any of these studies.

Discussion

This analysis has shown that the benefits for antiplatelet therapy in PAD may historically have been overstated, and that the risks of harm have been understated. There is no secondary prevention benefit for patients with asymptomatic PAD taking antiplatelet monotherapy, but there is a significant increase in the risk of major bleeding. The improvement in secondary prevention of cardiovascular events in symptomatic patients with PAD taking antiplatelet monotherapy is modest at best: For every 8 cardiovascular deaths prevented in 1000 patients with symptomatic PAD there were 7 major bleeds. The risk of death from major bleeding is unclear, but no benefit is seen in terms of all-cause mortality, suggesting that any benefit in terms of reducing cardiovascular death is balanced by the associated harm.

In the UK, NICE recommend clopidogrel monotherapy for all patients with PAD.[3] This includes asymptomatic patients, who in this analysis derive no secondary prevention benefit but experience a risk of major bleeding when treated with antiplatelet agents. NICE relies heavily on data from the CAPRIE trial comparing clopidogrel with aspirin.[54] The ESC guidelines also recommend antiplatelet monotherapy, more specifically for symptomatic patients.[5] This contradicts the NICE and ACC/AHA guidelines. These guidelines cite subgroup analyses from large randomised trials, which are largely post-hoc analyses so need to be interpreted with caution. When combined in meta-analysis many of the significant results disappear. We would therefore suggest that even the benefit of antiplatelet monotherapy for symptomatic patients with PAD not undergoing intervention is unclear when balanced against the risk of major bleeding.

Antiplatelet therapy appears more beneficial following intervention for PAD, with more events prevented than for secondary cardiovascular prevention. The quality of the evidence for outcomes following intervention was of lower GRADE quality than the secondary prevention evidence discussed above, with trials of hundreds of patients for intervention compared with thousands for secondary prevention. The most beneficial effects of antiplatelet monotherapy are for prosthetic bypass patency, where several hundred graft loss events per 1000 patients are prevented. However, prosthetic bypass is a poor second choice to autologous vein and its use should therefore be relatively limited.[63] Anticoagulation is significantly more beneficial for vein bypasses than antiplatelet monotherapy, preventing 81 graft losses per 1000 patients at 2 years (Table 3, $p<0.0001$). It is possible that some of this benefit may be offset by higher bleeding risks with anticoagulation, but it is not possible to formally assess this as the two studies included in this analysis did not report this outcome for the subgroup of patients receiving a vein bypass rather than a prosthetic bypass.

Outcomes following endovascular intervention deserve special mention. The past decade has seen a huge expansion in peripheral endovascular interventions, with cases increasing threefold in England over the past decade from around 12,000 cases in 2004-5 to over 33,000 in 2014-15 according to Hospital Episode Statistics. There is a trend towards dual antiplatelet prescribing after peripheral arterial intervention, the practice being extrapolated from coronary intervention data.[64] However there is currently no clear evidence of benefit for dual antiplatelets compared to monotherapy after peripheral intervention, but a clear risk of major bleeding: 37 more bleeds per 1000 patients ($p=0.0048$). As endovascular procedure

volume is predicted to continue increasing rapidly in line with the prevalence of diabetes,[65,66] the benefits of dual antiplatelet therapy in patients undergoing endovascular therapy requires urgent evaluation.[12]

There have been few recent trials of antiplatelet agents in PAD. The EUCLID trial comparing ticagrelor with clopidogrel showed no difference between the agents in the PAD (critical ischemia) subgroup.[67] The COMPASS trial was a 3-arm trial comparing the combination of low-dose rivaroxaban and aspirin with rivaroxaban or aspirin alone for secondary prevention of cardiovascular events and found in favour of combination therapy.[10] COMPASS showed that the combination of rivaroxaban and aspirin prevented 18 major adverse cardiovascular events per 1000 patients, while causing 12 additional major bleeds when compared to aspirin alone.[10] The effect size is again relatively small for an expensive on-patent drug; by way of comparison, CAPRIE showed that clopidogrel prevented 9 cumulative cardiovascular events over aspirin alone 20 years ago, with no significant difference in rates of major bleeding.[54] Clopidogrel is now off patent and as such is significantly cheaper (Tariff price in the UK £1.40 per month) than the on-patent rivaroxaban (Tariff price £50.40 per month).[68]

Umbrella review methodology has the benefit of giving a broad overview of a topic and the ability to compare the significance of event rates between a broad range of outcomes. However, because it relies on meta-analyses, trials not yet included in meta-analysis will be missed. This is the case in this analysis for the new trials of the direct oral anticoagulants.[10,69] We have, however, converted these trials' results into event rates using the same statistical methods for the discussion. There are also newer antiplatelet agents which have some individual trials not included in

the analysis, the most prominent being the EUCLID trial comparing ticagrelor with clopidogrel. This, however, showed no difference between the two agents for any outcome.[11,67,70,71] A further limitation of extracting data from meta-analyses is that it is difficult to correct for some deficiencies that are present in all available meta-analyses. A deficiency common to all of the included meta-analyses is that no information on the duration of follow-up is given for outcomes other than patency. It is therefore unclear over what period of time we should expect to find the calculated event rates. As the same studies generally presented both secondary prevention and safety outcomes, however, calculations which weigh the benefits of prevention against the harms of additional bleeding should remain valid as they are likely to have occurred over the same time period.

One strength of this umbrella review is that we have re-analysed the data. Standard umbrella review methodology extracts risk ratios intact and compares them. However when the literature is as extensive as it is in this field, meta-analyses included different studies and none could be viewed as definitive. Even the high quality meta-analyses included in this analysis had data discrepancies which were handled in this review by re-extracting primary trial data, and missing studies which were included by extracting the data from all analyses in this study.

There is a general lack of clinically meaningful data for outcome measures such as amputation-free survival and quality of life. This is a problem in the peripheral arterial literature in general, and newer lower limb trials are better designed to look at clinically meaningful, patient-centred outcomes.[72] We were not able to separate data by interventions known to have different outcomes such as different types or techniques of endovascular intervention because the literature in

those areas was so poor. Some trial data will be confounded by patients having multiple types of arterial disease and therefore alternative indications for antiplatelet therapy, so the benefit may be greater than in patients with isolated PAD. This links in to the additional problem that some of the included trials were post-hoc subgroups of larger trials ostensibly examining outcomes for different types of arterial disease. We have presented appropriate clinical subgroups separately in order to provide treating clinicians with data which is as granular as possible, but the PAD populations recruited into large trials were a heterogenous group of patients with carotid disease, claudication and critical limb ischaemia, so there remain a number of areas (such as those undergoing lower limb endovascular therapy) where the available data is severely limited and further trials are needed.

In addition to the heterogeneity in patient groups, the differences in antiplatelet agents and regimes/doses between trials made analysis challenging, although we tried to correct for this and explore the effect of different agents in subgroup analysis. No other high quality meta-analysis has attempted this previously, making this a more thorough exploration of the literature.

Another limitation of our analysis is that the definition of major bleeding is heterogeneous between studies. This is an established problem in cardiovascular trials and has resulted in several attempts to develop unifying definitions,[73,74] with only limited success. Reassuringly, despite these different definitions, the statistical heterogeneity on meta-analysis was not excessive for this outcome (Supplementary Resources 1—4).

In summary, antiplatelet monotherapy should not be prescribed for patients with isolated asymptomatic peripheral arterial disease as it has no proven secondary

prevention benefit, and there may be a significant risk of major bleeding. Monotherapy only has modest secondary cardiovascular prevention benefits in patients with symptomatic peripheral arterial disease but also increases the risk of major bleeding; patients with no other indication for antiplatelet therapy should be counselled carefully for shared decision making. Antiplatelet monotherapy is effective in maintaining the patency of prosthetic lower limb bypass grafts while anticoagulation is more beneficial for vein grafts. There is a lack of evidence to guide antiplatelet prescribing after peripheral arterial endovascular intervention, which needs addressing urgently by adequately powered randomised trials.

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References

1. Herrington W, Lacey B, Sherliker P, Armitage J, Lewington S. Epidemiology of Atherosclerosis and the Potential to Reduce the Global Burden of Atherothrombotic Disease. *Circ Res.* 2016;118(4):535-46.

2. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG*, et al.* Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg.* 2007;45 Suppl S:S5-67.

3. National Institute for Health and Care Excellence (NICE). Peripheral Arterial Disease: diagnosis and management. 2018; https://www.nice.org.uk/guidance/cg147. Accessed 31st May 2019.

4. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE*, et al.* 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2017;135(12):e726-e79.

5. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T*, et al.* Editor's Choice - 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg.* 2018;55(3):305-68.

6. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and

stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ.* 1994;308(6921):81-106.

7. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy--II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. *BMJ.* 1994;308(6922):159-68.

8. Cuisset T, Verheugt FWA, Mauri L. Update on antithrombotic therapy after percutaneous coronary revascularisation. *Lancet.* 2017;390(10096):810-20.

9. Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;324(7329):71-86.

10. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P*, et al.* Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet.* 2018;391(10117):219-29.

11. Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P*, et al.* Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. *N Engl J Med.* 2017;376(1):32-40.

12. Coughlin PA, Rudd JHF. Optimizing medical management in peripheral artery disease. *Br J Surg.* 2018;105(9):1079-81.

13. van Haelst STW, Koopman C, den Ruijter HM, Moll FL, Visseren FL, Vaartjes I*, et al.* Cardiovascular and all-cause mortality in patients with intermittent claudication and critical limb ischaemia. *Br J Surg.* 2018;105(3):252-61.

14. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc.* 2015;13(3):132-40.

15. Lunny C, Brennan SE, McDonald S, McKenzie JE. Toward a comprehensive evidence map of overview of systematic review methods: paper 1-purpose, eligibility, search and data extraction. *Syst Rev.* 2017;6(1):231.

16. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097.

17. Pieper D, Mathes T, Eikermann M. Can AMSTAR also be applied to systematic reviews of non-randomized studies? *BMC Res Notes.* 2014;7:609.

18. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J*, et al.* AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J Clin Epidemiol.* 2009;62(10):1013-20.

19. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J*, et al.* GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011;64(4):383-94.

20. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7(3):177-88.

21. Paule RC, Mandel J. Consensus values, regressions, and weighting factors. *J Res Natl Inst Stand Technol.* 1989;94(3):197-203.

22. Raudenbush SW. Analyzing effect sizes: Random-effects models. In: Cooper H, Hedges LV, Valentine JC, eds. *The handbook of research synthesis and meta-analysis.* New York, NY, US: Russell Sage Foundation; 2009:295-315.

23. Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G*, et al.* Methods to estimate the between-study variance and its uncertainty in meta-analysis. *Res Synth Methods.* 2016;7(1):55-79.

24. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21(11):1539-58.

25. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315(7109):629-34.

26. Bosanquet DC, Ambler GK, Waldron CA, Thomas-Jones E, Brookes-Howell L, Kelson M*, et al.* Perineural local anaesthetic catheter after major lower limb amputation trial (PLACEMENT): study protocol for a randomised controlled pilot study. *Trials.* 2017;18(1):629.

27. Basili S, Raparelli V, Vestri A, Di Tanna GL, Violi F. Comparison of efficacy of antiplatelet treatments for patients with claudication. A meta-analysis. *Thromb Haemost.* 2010;103(4):766-73.

28. Bedenis R, Stewart M, Cleanthis M, Robless P, Mikhailidis DP, Stansby G. Cilostazol for intermittent claudication. *Cochrane Database Syst Rev.* 2014(10):CD003748.

29. Bedenis R, Lethaby A, Maxwell H, Acosta S, Prins MH. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database Syst Rev.* 2015(2):CD000535.

30. Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. *JAMA.* 2009;301(18):1909-19.

31. Collins TC, Souchek J, Beyth RJ. Benefits of antithrombotic therapy after infrainguinal bypass grafting: a meta-analysis. *Am J Med.* 2004;117(2):93-9.

32. De Schryver EL, Algra A, van Gijn J. Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. *Cochrane Database Syst Rev.* 2007(3):CD001820.

33. Elmariah S, Mauri L, Doros G, Galper BZ, O'Neill KE, Steg PG*, et al.* Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis. *Lancet.* 2015;385(9970):792-8.

34. Fanari Z, Malodiya A, Weiss SA, Hammami S, Kolm P, Weintraub WS. Long-term use of dual antiplatelet therapy for the secondary prevention of atherothrombotic events: Meta-analysis of randomized controlled trials. *Cardiovasc Revasc Med.* 2017;18(1):10-5.

35. Geraghty AJ, Welch K. Antithrombotic agents for preventing thrombosis after infrainguinal arterial bypass surgery. *Cochrane Database Syst Rev.* 2011(6):CD000536.

36. Girolami B, Bernardi E, Prins MH, ten Cate JW, Prandoni P, Hettiarachchi R*, et al.* Antithrombotic drugs in the primary medical management of intermittent claudication: a meta-analysis. *Thromb Haemost.* 1999;81(5):715-22.

37. Girolami B, Bernardi E, Prins MH, ten Cate JW, Prandoni P, Simioni P*, et al.* Antiplatelet therapy and other interventions after revascularisation procedures

in patients with peripheral arterial disease: a meta-analysis. *Eur J Vasc Endovasc Surg.* 2000;19(4):370-80.

38. Katsanos K, Spiliopoulos S, Saha P, Diamantopoulos A, Karunanithy N, Krokidis M*, et al.* Comparative efficacy and safety of different antiplatelet agents for prevention of major cardiovascular events and leg amputations in patients with peripheral arterial disease: a systematic review and network meta-analysis. *PLoS One.* 2015;10(8):e0135692.

39. Lievre M, Cucherat M. Aspirin in the secondary prevention of cardiovascular disease: an update of the APTC meta-analysis. *Fundam Clin Pharmacol.* 2010;24(3):385-91.

40. Mahmoud AN, Elgendy AY, Rambarat C, Mahtta D, Elgendy IY, Bavry AA. Efficacy and safety of aspirin in patients with peripheral vascular disease: an updated systematic review and meta-analysis of randomized controlled trials. *PLoS One.* 2017;12(4):e0175283.

41. Moher D, Pham B, Ausejo M, Saenz A, Hood S, Barber GG. Pharmacological management of intermittent claudication: a meta-analysis of randomised trials. *Drugs.* 2000;59(5):1057-70.

42. Pande RL, Hiatt WR, Zhang P, Hittel N, Creager MA. A pooled analysis of the durability and predictors of treatment response of cilostazol in patients with intermittent claudication. *Vasc Med.* 2010;15(3):181-8.

43. Peeters Weem SM, van Haelst ST, den Ruijter HM, Moll FL, de Borst GJ. Lack of evidence for dual antiplatelet therapy after endovascular arterial procedures: a meta-analysis. *Eur J Vasc Endovasc Surg.* 2016;52(2):253-62.

44. Qian J, Yang XH. A meta-analysis of randomized controlled trials on antiplatelet agents versus placebo/control for treating peripheral artery disease. *Medicine (Baltimore).* 2015;94(31):e1293.

45. Robertson L, Ghouri MA, Kovacs F. Antiplatelet and anticoagulant drugs for prevention of restenosis/reocclusion following peripheral endovascular treatment. *Cochrane Database Syst Rev.* 2012(8):CD002071.

46. Robless P, Mikhailidis DP, Stansby G. Systematic review of antiplatelet therapy for the prevention of myocardial infarction, stroke or vascular death in patients with peripheral vascular disease. *Br J Surg.* 2001;88(6):787-800.

47. Schmit K, Dolor RJ, Jones WS, Vemulapalli S, Hasselblad V, Subherwal S*, et al.* Comparative effectiveness review of antiplatelet agents in peripheral artery disease. *J Am Heart Assoc.* 2014;3(6):e001330.

48. Squizzato A, Bellesini M, Takeda A, Middeldorp S, Donadini MP. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular events. *Cochrane Database Syst Rev.* 2017;12:CD005158.

49. Tangelder MJ, Lawson JA, Algra A, Eikelboom BC. Systematic review of randomized controlled trials of aspirin and oral anticoagulants in the prevention of graft occlusion and ischemic events after infrainguinal bypass surgery. *J Vasc Surg.* 1999;30(4):701-9.

50. Vemulapalli S, Dolor RJ, Hasselblad V, Subherwal S, Schmit KM, Heidenfelder BL*, et al.* Comparative effectiveness of medical therapy, supervised exercise, and revascularization for patients with intermittent claudication: a network meta-analysis. *Clin Cardiol.* 2015;38(6):378-86.

51. Warner CJ, Greaves SW, Larson RJ, Stone DH, Powell RJ, Walsh DB*, et al.* Cilostazol is associated with improved outcomes after peripheral endovascular interventions. *J Vasc Surg.* 2014;59(6):1607-14.

52. Wave Investigators. The effects of oral anticoagulants in patients with peripheral arterial disease: rationale, design, and baseline characteristics of the Warfarin and Antiplatelet Vascular Evaluation (WAVE) trial, including a meta-analysis of trials. *Am Heart J.* 2006;151(1):1-9.

53. Wong PF, Chong LY, Stansby G. Antiplatelet therapy to prevent cardiovascular events and mortality in patients with intermittent claudication. *JAMA.* 2013;309(9):926-7.

54. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet.* 1996;348(9038):1329-39.

55. Janzon L, Bergqvist D, Boberg J, Boberg M, Eriksson I, Lindgarde F*, et al.* Prevention of myocardial infarction and stroke in patients with intermittent claudication; effects of ticlopidine. Results from STIMS, the Swedish Ticlopidine Multicentre Study. *J Intern Med.* 1990;227(5):301-8.

56. Neri Serneri GG, Coccheri S, Marubini E, Violi F, Drug Evaluation in Atherosclerotic Vascular Disease in Diabetics Study Group. Picotamide, a combined inhibitor of thromboxane A2 synthase and receptor, reduces 2-year mortality in diabetics with peripheral arterial disease: the DAVID study. *Eur Heart J.* 2004;25(20):1845-52.

57. Patel MR, Becker RC, Wojdyla DM, Emanuelsson H, Hiatt WR, Horrow J*, et al.* Cardiovascular events in acute coronary syndrome patients with peripheral arterial disease treated with ticagrelor compared with clopidogrel: data from the PLATO Trial. *Eur J Prev Cardiol.* 2015;22(6):734-42.

58. Schneider E, Brunner U, Bollinger A. Medikamentose rezidivprophylaxe nach femoro-poplitealer arterienrekonstruktion. *Angio.* 1979;2:73-7.

59. Tepe G, Bantleon R, Brechtel K, Schmehl J, Zeller T, Claussen CD*, et al.* Management of peripheral arterial interventions with mono or dual antiplatelet therapy--the MIRROR study: a randomised and double-blinded clinical trial. *Eur Radiol.* 2012;22(9):1998-2006.

60. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (the dutch bypass oral anticoagulants or aspirin study): a randomised trial. *Lancet.* 2000;355(9201):346-51.

61. Edmondson RA, Cohen AT, Das SK, Wagner MB, Kakkar VV. Low-molecular weight heparin versus aspirin and dipyridamole after femoropopliteal bypass grafting. *Lancet.* 1994;344(8927):914-8.

62. Iida O, Yokoi H, Soga Y, Inoue N, Suzuki K, Yokoi Y*, et al.* Cilostazol reduces angiographic restenosis after endovascular therapy for femoropopliteal lesions in the sufficient treatment of peripheral intervention by cilostazol study. *Circulation.* 2013;127(23):2307-15.

63. Ambler GK, Twine CP. Graft type for femoro-popliteal bypass surgery. *Cochrane Database Syst Rev.* 2018;2:CD001487.

64. Singh P, Harper Y, Oliphant CS, Morsy M, Skelton M, Askari R*, et al.* Peripheral interventions and antiplatelet therapy: role in current practice. *World J Cardiol.* 2017;9(7):583-93.

65. Hinchliffe RJ, Brownrigg JR, Andros G, Apelqvist J, Boyko EJ, Fitridge R*, et al.* Effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral artery disease: a systematic review. *Diabetes Metab Res Rev.* 2016;32 Suppl 1:136-44.

66. Zimmet P, Alberti KG, Magliano DJ, Bennett PH. Diabetes mellitus statistics on prevalence and mortality: facts and fallacies. *Nat Rev Endocrinol.* 2016;12(10):616-22.

67. Norgren L, Patel MR, Hiatt WR, Wojdyla DM, Fowkes FGR, Baumgartner I*, et al.* Outcomes of patients with critical limb ischaemia in the EUCLID Trial. *Eur J Vasc Endovasc Surg.* 2018;55(1):109-17.

68. Joint Formulary Committee. British National Formulary (online). 2019; http://www.medicinescomplete.com. Accessed 31st May 2019.

69. Moll F, Baumgartner I, Jaff M, Nwachuku C, Tangelder M, Ansel G*, et al.* Edoxaban plus aspirin vs dual antiplatelet therapy in endovascular treatment of patients with peripheral artery disease: results of the ePAD Trial. *J Endovasc Ther.* 2018;25(2):158-68.

70. Baumgartner I, Norgren L, Fowkes FGR, Mulder H, Patel MR, Berger JS*, et al.* Cardiovascular outcomes after lower extremity endovascular or surgical revascularization: The EUCLID Trial. *J Am Coll Cardiol.* 2018;72(14):1563-72.

71. Jones WS, Baumgartner I, Hiatt WR, Heizer G, Conte MS, White CJ*, et al.* Ticagrelor compared with clopidogrel in patients with prior lower extremity revascularization for peripheral artery disease. *Circulation.* 2017;135(3):241-50.

72. Hunt BD, Popplewell MA, Davies H, Meecham L, Jarrett H, Bate G*, et al.* Balloon versus stenting in severe ischaemia of the leg-3 (BASIL-3): study protocol for a randomised controlled trial. *Trials.* 2017;18(1):224.

73. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J*, et al.* Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. *Circulation.* 2011;123(23):2736-47.

74. Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W*, et al.* Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost.* 2010;8(1):202-4.

Tables

Outcome	N	Trials	Events / 1000		RR	95% C.I.	P-value	I^2	Egger's P-value	Strength of Evidence (GRADE)
			SAPT	No APT						
Side-effects	3818	9	186	97	1.905	1.315—2.761	0.0007	50.1	NA	Low ⊕⊕OO Due to imprecision and inconsistency
Major bleeding in symptomatic patients	7648	37	16	9	1.730	1.220—2.453	0.0021	0	0.170	High ⊕⊕⊕⊕
Major bleeding	22996	46	15	11	1.349	1.079—1.686	0.0086	0	0.659	High ⊕⊕⊕⊕
Non-cardiovascular death after intervention	3160	14	12	2	1.781	0.972—3.262	0.0618	0	0.767	Moderate ⊕⊕⊕O Due to imprecision
Non-cardiovascular death after bypass	2437	11	13	7	1.788	0.922—3.470	0.0857	0	0.668	Moderate ⊕⊕⊕O Due to imprecision

Table 1a: Safety outcomes associated with antiplatelet monotherapy compared to placebo or nothing. N: Number of patients; SAPT: Single Antiplatelet Therapy; APT: Antiplatelet therapy

Outcome	N	Trials	Events / 1000		RR	95% C.I.	P-value	I^2	Egger's P-value	Strength of Evidence (GRADE)
			SAPT	No APT						
Non-fatal stroke	23559	46	14	17	0.787	0.644—0.962	0.0191	0	0.933	High ⊕⊕⊕⊕
Cardiovascular death in symptomatic patients	10042	43	26	34	0.776	0.625—0.964	0.0220	0	0.272	High ⊕⊕⊕⊕
Cumulative cardiovascular events in symptomatic patients	10151	45	57	66	0.869	0.755—1.001	0.0515	0	0.956	Moderate ⊕⊕⊕O Due to imprecision
Cumulative cardiovascular events	24428	55	54	60	0.908	0.823—1.001	0.0524	0	0.595	Moderate ⊕⊕⊕O Due to imprecision
Cardiovascular death after bypass	2437	11	27	41	0.665	0.439—1.007	0.0542	0	0.252	Moderate ⊕⊕⊕O Due to imprecision
Non-fatal stroke in asymptomatic patients	13542	4	14	19	0.773	0.595—1.005	0.0545	0	NA	Moderate ⊕⊕⊕O Due to imprecision
Cumulative cardiovascular events in claudicants	6288	26	65	76	0.860	0.729—1.015	0.0736	0	0.433	Moderate ⊕⊕⊕O Due to imprecision
Cardiovascular death in claudicants	6288	26	27	34	0.785	0.600—1.027	0.0772	0	0.766	Moderate ⊕⊕⊕O Due to imprecision

Table 1b: Secondary prevention outcomes associated with antiplatelet monotherapy compared to placebo or nothing. N: Number of patients; SAPT: Single Antiplatelet Therapy; APT: Antiplatelet therapy

Outcome	N	Trials	Events / 1000		RR	95% C.I.	P-value	I^2	Egger's P-value	Strength of Evidence (GRADE)
			SAPT	No APT						
Prosthetic bypass patency 12 months	222	4	194	538	0.361	0.238—0.549	<0.0001	0	NA	Moderate ⊕⊕⊕O Due to imprecision
Prosthetic bypass patency 6 months	222	4	162	443	0.365	0.225—0.593	<0.0001	0	NA	Moderate ⊕⊕⊕O Due to imprecision
Combined bypass patency 6 months	1107	6	119	242	0.493	0.324—0.750	0.0010	51.7	NA	Low ⊕⊕OO Due to imprecision and inconsistency
Combined bypass patency 24 months	1195	7	200	353	0.566	0.387—0.827	0.0033	71.1	NA	Low ⊕⊕OO Due to imprecision and inconsistency
Combined bypass patency 12 months	1195	7	184	329	0.560	0.380—0.826	0.0034	69.7	NA	Low ⊕⊕OO Due to imprecision and inconsistency
Prosthetic bypass patency 3 months	222	4	104	255	0.408	0.216—0.773	0.0060	0	NA	Moderate ⊕⊕⊕O Due to imprecision
Prosthetic bypass patency 1 month	157	3	41	216	0.188	0.055—0.638	0.0074	0	NA	Moderate ⊕⊕⊕O Due to imprecision
Vein bypass patency 12 months	885	3	179	273	0.654	0.470—0.909	0.0115	25.7	NA	Moderate ⊕⊕⊕O Due to imprecision
Combined bypass patency 3 months	864	5	112	172	0.651	0.427—0.994	0.0469	19.7	NA	Moderate ⊕⊕⊕O Due to imprecision
Amputation in symptomatic patients	1819	5	51	79	0.647	0.390—1.073	0.0918	41.8	NA	Low ⊕⊕OO Due to imprecision and inconsistency
Ankle-brachial index	911	5	-	-	0.057	0.042—0.074	<0.0001	86.2	NA	Moderate ⊕⊕⊕O Due to inconsistency
Walking distance [a]	2629	12	-	-	44.65	25.44—63.87	<0.0001	81.8	$6.8x10^{-5}$	Moderate ⊕⊕⊕O Due to inconsistency

Table 1c: Limb outcomes associated with antiplatelet monotherapy compared to placebo or nothing. N: Number of patients; SAPT: Single Antiplatelet Therapy; APT: Antiplatelet therapy

[a] Walking distance is measured in metres, with positive numbers representing an improvement following antiplatelet monotherapy compared to placebo or nothing.

Outcome	N	Trials	Events per 1000		RR	95% C.I.	P-Values	I^2	Strength of Evidence (GRADE)
			SAPT	DAPT					
Major bleeding after intervention	931	2	21	58	0.368	0.183—0.737	0.0048	0	Moderate ⊕⊕⊕O Due to Imprecision
Major bleeding after bypass surgery	851	1	23	64	0.370	0.181— 0.754	0.0062	0	Low ⊕⊕OO Due to Imprecision, risk of bias
Major bleeding	20914	7	23	32	0.739	0.572— 0.954	0.0203	42.7	High ⊕⊕⊕⊕
Major bleeding in asymptomatic patients	2219	2	64	85	0.751	0.559—1.009	0.0577	0	Moderate ⊕⊕⊕O Due to imprecision
Cumulative cardiovascular events	19517	9	49	43	1.124	0.989— 1.277	0.0727	0	Moderate ⊕⊕⊕O Due to imprecision
Non-fatal Myocardial Infarction	16195	6	23	19	1.205	0.977— 1.486	0.0818	0	Moderate ⊕⊕⊕O Due to imprecision
Non-fatal Stroke in Claudicants	2966	1	10	5	0.469	0.192— 1.146	0.0966	0	Low ⊕⊕OO Due to imprecision, risk of bias
Vein bypass patency at 24 months	598	1	126	175	0.721	0.490—1.061	0.0971	0	Very Low ⊕⊕OO Due to Imprecision, risk of bias
Prosthetic bypass patency at 24 months	253	1	472	320	1.474	1.077—2.015	0.0152	0	Low ⊕⊕OO Due to Imprecision, risk of bias
Amputation	8115	3	15	11	1.453	1.000—2.112	0.0497	0	Moderate ⊕⊕⊕O Due to Imprecision
Endovascular Intervention patency at 6 months	80	1	200	50	4.000	0.905—17.681	0.0675	0	Very Low ⊕OOO Due to Imprecision, risk of bias
Amputation in patients undergoing intervention	891	2	103	70	1.468	0.952—2.264	0.0821	0	Low ⊕⊕OO Due to Imprecision
Amputation after bypass surgery	851	1	106	73	1.448	0.935—2.243	0.0970	0	Very Low ⊕OOO Due to Imprecision, risk of bias

Table 2: Safety, secondary prevention and limb outcomes associated with antiplatelet monotherapy compared to dual antiplatelet therapy. N: Number of patients; SAPT: Single Antiplatelet Therapy; DAPT: Dual Antiplatelet therapy

Outcome	N	Trials	Events per 1000		RR	95% C.I.	P-value	I^2	Strength of Evidence (GRADE)
			SAPT	Anti-Coag					
Side-effects	197	1	233	43	5.476	1.973—15.199	0.0011	0	Low ⊕⊕OO Due to imprecision, risk of bias
Vein bypass patency 24 months	1618	2	224	143	1.567	1.172—2.093	0.0024	0	Moderate ⊕⊕⊕O Due to imprecision
Vein bypass patency 12 months	1630	2	177	123	1.436	1.134—1.820	0.0027	0	Moderate ⊕⊕⊕O Due to imprecision
Vein bypass patency 6 months	1632	2	144	111	1.306	1.010—1.688	0.0416	0	Moderate ⊕⊕⊕O Due to imprecision
Prosthetic bypass patency 24 months	1104	1	329	410	0.804	0.688—0.939	0.0058	0	Moderate ⊕⊕⊕O Due to risk of bias
Prosthetic bypass patency 6 months	1104	1	157	214	0.732	0.569—0.940	0.0146	0	Low ⊕⊕OO Due to imprecision, risk of bias
Endovascular intervention patency 12 months	589	4	231	312	0.741	0.569—0.965	0.0261	0	Moderate ⊕⊕⊕O Due to imprecision
Prosthetic bypass patency 12 months	1104	1	244	301	0.811	0.668—0.984	0.0340	0	Low ⊕⊕OO Due to imprecision, risk of bias
Cumulative cardiovascular events after bypass surgery	2690	1	66	48	1.378	1.009—1.883	0.0440	0	Low ⊕⊕OO Due to imprecision, risk of bias

Table 3: Safety, secondary prevention and limb outcomes from antiplatelet monotherapy compared to anticoagulation. N: Number of patients; SAPT: Single Antiplatelet Therapy; Anti-Coag: Anti-coagulation.

Figure caption

Figure 1. Flowchart of selection of studies for inclusion in umbrella review on antiplatelet therapy and peripheral arterial disease.