Meta-Analysis of Anticoagulation Therapy for the Prevention of Cardiovascular Events in Patients With Peripheral Arterial Disease

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Peripheral artery disease (PAD) remains a major cause of morbidity and future cardiovascular events despite advancement in the surgical interventions and optimal medical therapy. The aim of our study is to evaluate the efficacy and safety of anticoagulation (AC) therapy for reducing cardiovascular and limb events in patients with PAD. PUBMED, Medline, and Cochrane Library were searched through 2020 for randomized clinical trials comparing major adverse cardiovascular events (MACE) and risk of major bleeding (MB), between AC and standard of care (SOC) therapy, among patients with PAD. Meta-analysis was performed using weighted pooled absolute risk difference (RD) with 95% confidence interval (CI) and fixed effects model for overall and sub-groups of full dose (FD) and low dose (LD) AC therapies. Amongst 17,684 patients from 7 different studies, the addition of AC to SOC therapy was associated with MACE reduction (RD -0.022, 95% CI -0.033 to -0.012, p <0.001) and increased MB (RD 0.02, 95% CI 0.014 to 0.025, p <0.001). For FD, MACE reduction was (RD -0.021, 95% CI -0.042 to 0.001, p = 0.061) and MB (RD 0.036, 95% CI 0.025 to 0.047, p <0.001). For LD, MACE reduction was (RD -0.023, 95% CI -0.035 to -0.011, p <0.001) and MB (RD 0.011, 95% CI 0.005 to 0.017, p <0.001). In conclusion, addition of AC to the current SOC therapy can mitigate future MACE events in patients with PAD albeit at risk of increased bleeding. LD AC is associated with an efficacy/safety net benefit compared to FD AC therapy. © 2021 Published by Elsevier Inc. (Am J Cardiol 2021;148:165−171)

Peripheral arterial disease (PAD) remains a major cause of morbidity, mortality, and disability across the world despite the recent advancement in medical, endovascular, and surgical therapies.[1−3] PAD patients are at a higher risk of cardiovascular and limb events despite optimal medical therapy.[4] Although current medical and surgical societal guidelines have advocated single or dual antiplatelet therapy (SAPT and DAPT) for these patients.[5,6] Recent randomized controlled trials (RCTs) have found superior outcomes with the addition of oral anticoagulation (AC) to antiplatelet.[7,8] Addition of AC to anti-platelet therapy in patients with PAD has been shown to provide an additional anti-ischemic benefit albeit at the cost of higher bleeding risk.[9−11] More recent randomized clinical trials have shown a similar reduction of ischemic events with the addition of low-dose rivaroxaban to antiplatelet therapy for patients with PAD.[7,8] Therefore, we constructed a study level meta-analysis, comparing AC combination therapy to the current standard of care (SOC) antiplatelet therapy. In addition, we aimed to evaluate full-dose (FD)[9−12] versus low-dose (LD)[7,8,13] AC on safety and efficacy outcomes.

Methods

A search was conducted in the MEDLINE, Cochrane Library, and the Embase database through 2020 and clinical trials were identified by searching the keywords, "peripheral artery disease," "peripheral artery intervention," and Boolean operator and "anticoagulation" by 2 independent authors (HK, RM). Studies were included if they were RCT by design, compared AC therapy to antiplatelet therapy, and reported individual cardiovascular and limb events. All studies in the SOC arm used either single antiplatelet or dual antiplatelet (ePAD[9] only), whereas the AC arm included AC with antiplatelet or without antiplatelet (Dutch BOA[11] trial only). Studies were excluded if they were observational, nonrandomized, retrospective, subgroup of the original study or abstract. Figure 1 depicts a summary of our systematic review for inclusion, exclusion, and final selection of studies for the meta-analysis whereas Table 1 summarizes inclusion and exclusion criteria for each individual study. The study did not require institutional review board approval being a systemic review of the

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See page 170 for disclosure information.

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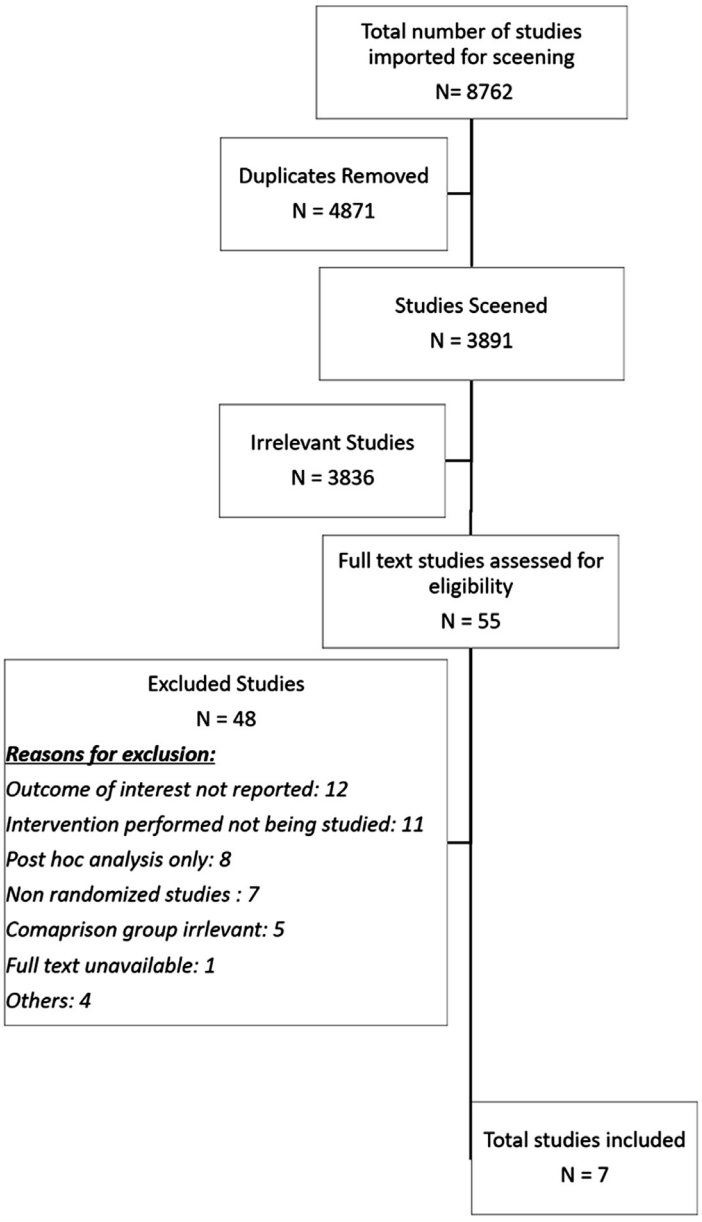

Figure 1. Study selection process: flow diagram depicting the process of screening and selection of final studies for the meta-analysis.

previously published RCT. The study is registered with international, prospective register for systematic review protocols (Prospero; CRD42020190815).

Qualified studies were reviewed by 2 independent authors (HK, RM) to assess suitability. A total of 7 studies were selected after discrepancies were resolved and mutual consensus among all the co-authors for final inclusion. Study characteristics and results were extracted by the authors and incorporated in a standardized form. Data extracted from the studies included the first author's name, publication year, country of origin, sample size, gender, and age of study participants. Also, years of follow-up, method to assess events, the number of cases, and participants in each treatment subgroup were recorded and summarized in Table 1. The data underlying in this article will be shared on reasonable request to the corresponding author.

Primary efficacy endpoint was defined as major adverse cardiovascular events (MACE) as a composite of cardiovascular death (CVD), myocardial infarction (MI), stroke (or cerebrovascular accident [CVA]), limb events (revascularization, amputation) and net benefit. Primary safety outcome was defined as major bleeding (MB) according to trial definition and summarized in supplementary data Table S1 whereas Supplementary Table S2 and S3 summarize individual outcomes of interest reported by each trial. Secondary endpoints include individual rates of all-cause death (ACD), cardiovascular death, CVA, target vessel/limb revascularization (TRL/TVR), and major amputation (AMP). The net clinical benefit (NCB) of AC compared

Table 1
Summary of trial design and outcomes for the multicenter studies

	VOYAGER PAD[8]	COMPASS[7]	ePAD[9]	Wave[10]	Jivegard[13]	Johnson[12]	Dutch BOA[11]
Year	2020	2018	2018	2007	2005	2002	2000
Sample size	6,564	4,996	203	2,161	284	831	2,690
Median follow-up, (years)	2.3	1.7	0.5	2.9	1	3	1.8
Age, (years)	67 ± 6	67.6 ± 8.5	67.3 ± 9.5	64	73.5 ± 9	64 ± 8	69 ± 10
Male	74%	71%	71%	73.6%	55.2%	99%	63%
Aspirin dose	100 mg	100 mg	100 mg	81-325 mg	75 mg	325 mg	80 mg
AC type and dose	Rivaroxaban (2.5mg)	Rivaroxaban (2.5mg)	Edoxaban (60mg)	VKA (INR 2-3)	Dalteparin (5000 IU)	VKA (INR 1.4-2.8)	VKA (INR: 3-4.5)
Composite primary efficacy outcome (MACE)	CVD, CVA, MI, ALI, AMP	CVD, CVA, MI, ALI	CVD, CVA, MI, TLR, AMP	CVD, CVA, MI, ALI, AMP	(-)	(-)	CVD, CVA, MI, AMP
Primary safety outcome (major bleeding)	+	+	+	+	+	+	+

AC = anticoagulation; ALI = acute limb ischemia; AMP = major amputation; CVD = cardiovascular death; CVA = cardiovascular accident; DAPT = dual antiplatelet therapy; ICH = intracranial hemorrhage; INR = international normalized ratio; IU = international unit; MACE = major adverse cardiovascular events; MI = myocardial infarction; mg = milligrams; SAPT = single antiplatelet therapy; SOC = standard of care; TLR = target lesion revascularization; USA = United states of America, VKA = vitamin K antagonist; (-) = not available; + = reported/available.

with SOC was calculated using the following formula: NCB = (MACE rate $_{\text{on AC}}$ - MACE rate $_{\text{on SOC}}$) − (major bleeding rate $_{\text{on AC}}$ - major bleeding rate $_{\text{on SOC}}$).

The data were analyzed using the Comprehensive Meta-Analysis package V3 (Biostat, Englewood, NJ, USA). The Mantel-Haenszel method was used for calculating the weighted pooled absolute risk difference under the fixed effects model.[14] The data are reported as RD with 95% confidence interval (CI). To access the heterogeneity of the treatment effect among the different RCT included, Cochran's Q and I^2 statistic were calculated under the random effects model and reported for each individual outcome in the results section respectively.[15] Publication bias was assessed using the Egger's test and a p value < 0.05 considered significant for potential bias (Supplementary Table S4). Sensitivity analysis was performed using the one study removed technique to explore the effect of individual study on overall outcomes (Supplementary Table S5 and Supplementary Figure 4 to 11). To further evaluate the effect of dose of AC used, we also conducted a sub-group analysis for FD and low dose LD AC therapy. Forest plots were used to represent within group, and overall effect size along with their respective 95% CI. A p value <0.05 was considered significant for our analysis.

Results

A total of 7 studies were included in the final analysis. Figure 1 summarizes the selection criteria for the final studies included in the meta-analysis while Figure 2 represents the summary of primary efficacy (MACE) and safety (MB) outcomes with their respective forest plots. Figure 3 represents the NCB or harm associated with AC as compared to SOC therapy. The basic demographic parameters of the AC and SOC groups and a summary of the trials included in the study is summarized in Table 1. The individual mortality, ischemic, and limb events are presented in the supplementary material. The study included a total of 17, 684 subjects, of whom 8,843 were assigned to AC group and 8,841 to SOC group, mean age 68 +/- 3 years. There are 4 studies in the FD and 3 studies in the LD AC group.

MACE was reported by 5 studies, including 8,284 patients in the AC and 8,288 in the SOC group (Figure 2). Overall, MACE on AC was (RD -0.022, 95% CI -0.033 to -0.012, p <0.001), for FD (RD -0.021, 95% CI -0.042 to 0.001, p = 0.061) and for LD (RD -0.023, 95% CI -0.035 to -0.011, p <0.001). There was no statistically significant heterogeneity (Q 1.14, I^2 0%, p = 0.89). MB was reported by all 7 studies, including 8,813 subjects in the AC and 8,811 in the SOC group (Figure 2). Overall, MB on AC was (RD 0.02, 95% CI 0.014 to 0.025, p <0.001), for FD (RD 0.036, 95% CI 0.025 to 0.047, p <0.001) and for LD (RD 0.011, 95% CI 0.005 to 0.017, p <0.001). There was moderate heterogeneity observed (Q 17.93, I^2 66.5%, p = 0.0069).

MI was reported by all 7 studies, including 8,843 patients in the AC groups and 8,841 in the SOC group (Supplementary Figure 1). Overall, MI on AC was (RD -0.006, 95% CI -0.012 to -0.001, p = 0.039), for FD (RD -0.006, 95% CI -0.016 to 0.005, p = 0.296) and for LD (RD -0.006, 95% CI -0.013 to 0.001, p = 0.071). There was no statistically significant heterogeneity (Q 3.51, I^2 0%, p = 0.74).

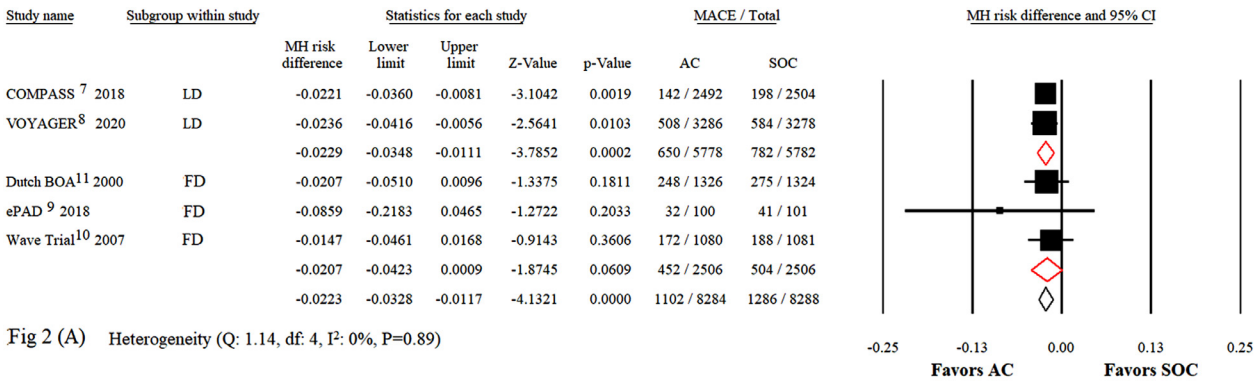

Fig 2 (A) Heterogeneity (Q: 1.14, df: 4, I^2: 0%, P=0.89)

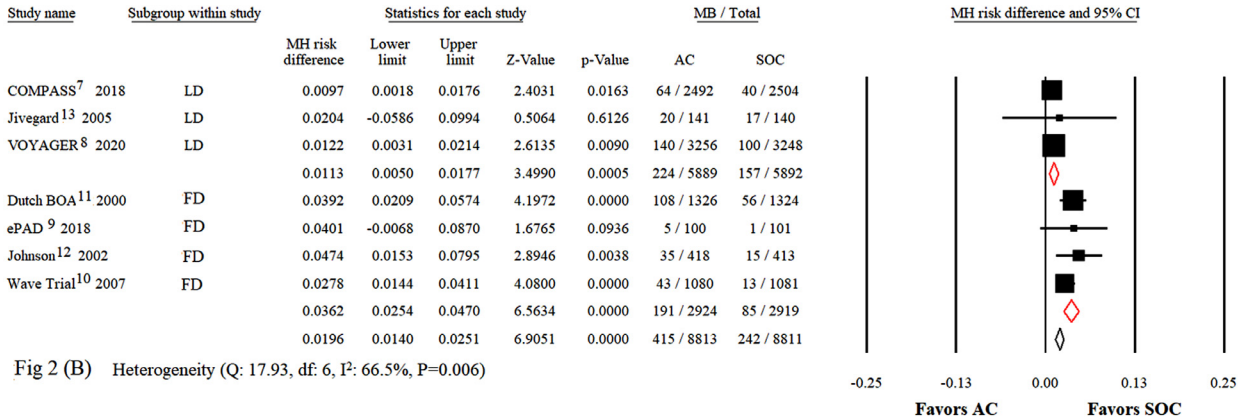

Fig 2 (B) Heterogeneity (Q: 17.93, df: 6, I^2: 66.5%, P=0.006)

Figure 2. (*A*, top): Primary efficacy outcomes: major adverse cardiovascular outcomes between anticoagulation and standard of care therapy. The diamond and its width indicate the pooled risk difference and corresponding 95% CI. M-H indicates Mantel-Haenszel. (*B*, bottom): primary safety outcomes: risk of major bleeding between anticoagulation and standard of care therapy. The diamond and its width indicate the pooled risk difference and corresponding 95% CI. AC = anticoagulation; FD = full dose; LD = low dose; MACE = major adverse cardiovascular events; MB = major bleeding; M-H = Mantel-Haenszel; SOC = standard of care.

All cause CVA was reported by 7 studies, including 8,843 in the AC and 8,841 in the SOC group (Supplementary Fig 1). Overall, CVA on AC was (RD -0.005, 95% CI -0.009 to -0.001, p = 0.046), for FD (RD -0.004, 95% CI -0.014 to 0.005, p = 0.383) and for LD (RD -0.005, 95% CI -0.01 to 0.001, p = 0.055). There was no statistically significant heterogeneity (Q 5.72, I^2 0%, p = 0.47). Ischemic CVA was reported by 3 studies, including 5,692 patients in the AC and 5,683 patients in the SOC group. Overall, ischemic CVA on AC was (RD -0.007, 95% CI -0.013 to -0.002, p = 0.009), for FD (RD -0.013, 95% CI -0.021 to -0.004, p = 0.003) and for the LD there was only one study available and thus no sub-group analysis was performed. There was no statistically significant heterogeneity (Q 2.78, I^2 28.32%, p = 0.25).

ACD was reported by 7 studies, including 8,834 subjects in the AC and 8,841 in the SOC group (Supplementary Figure 2). Overall ACD on AC was (RD 0.007, 95% CI -0.002 to 0.016, p = 0.119), for FD (RD 0.017, 95% CI -0.001 to 0.034, p = 0.066) and for LD (RD 0.002, 95% CI -0.007 to 0.012, p = 0.66). There was no statistically significant heterogeneity (Q 11.97, I^2 49.87%, p = 0.06). CVD was reported by 6 studies, including 8,702 subjects in the AC and 8,701 in the SOC group (Supplementary Figure 2). Overall, CVD on AC was (RD 0.001, 95% CI -0.006 to 0.008, p = 0.746), for FD (RD -0.001, 95% CI -0.015 to 0.014, p = 0.97) and for LD (RD 0.002, 95% CI -0.006 to 0.009, p = 0.623). There was no statistically significant heterogeneity (Q 5.15, I^2 2.9%, p = 0.4).

TLR/TVR was reported by 6 studies, including 6,351 patients in the AC and 6,337 in the SOC group (Supplementary Figure 3). Overall, TLR/TVR on AC was (RD -0.015, 95% CI -0.028 to -0.002, p = 0.022), for the FD (RD -0.009, 95% CI -0.026 to 0.009, p = 0.329) and for LD (RD -0.02, 95% CI -0.029 to -0.002, p = 0.031). There was no statistically significant heterogeneity (Q 3.69, I^2: 0%, p = 0.59). AMP was reported by 7 studies, including 8,843 patients in the AC group and 8,841 in the SOC group (Supplementary Figure 3). Overall, AMP on AC was (RD -0.004, 95% CI -0.009 to 0.001, p = 0.115), for FD (RD -0.002, 95% CI -0.012 to 0.008, p = 0.673) and for LD (RD -0.004, 95% CI -0.01 to 0.001, p = 0.079). There was no statistically significant heterogeneity (Q 2.79, I^2 0%, p = 0.83).

When LD and FD are both taken into consideration, the absolute risk reduction (ARR) for MACE was 2.2%, whereas the absolute risk increase (ARI) for MB was 1.9%. The net benefit was 0.3% in favor of AC as compared to SOC therapy and in the LD group, the NCB was higher at 1.2%, however in the FD, there was no clinical benefit noted (Figure 3).

There was no publication bias noted for any of the reported outcomes in our meta-analysis, suggesting an overall good quality of study selection (Supplementary Table S4). In regards to heterogeneity, only major bleeding

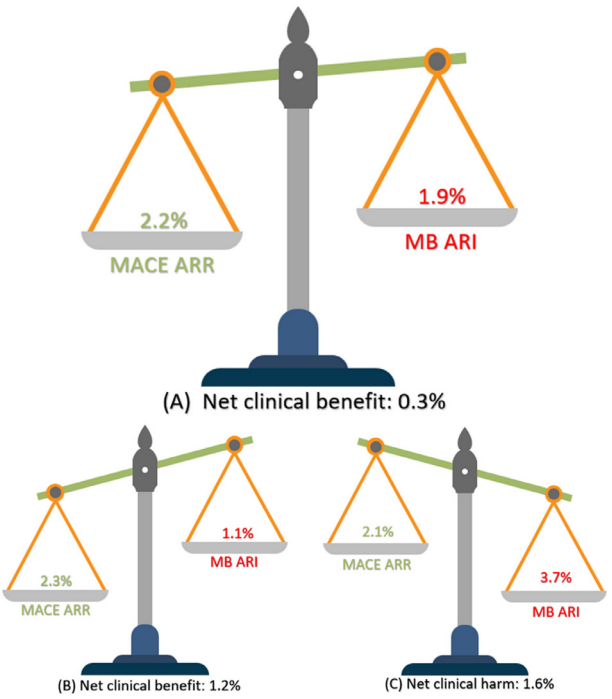

Figure 3. Net clinical benefit and harm: overall ischemic reduction and risk of bleeding associated with anticoagulation as compared to standard of care therapy. (*A*, top) Overall, (*B*, bottom left) low dose, and (*C*, bottom right) full dose anticoagulation therapy. ARI = absolute risk increase; ARR = absolute risk reduction; MACE = major adverse cardiovascular events; MB = major bleeding.

outcome displayed moderate heterogeneity. This was further explored using the sensitivity analysis (1 study removed: Dutch BOA trial) and confirmed our results for primary efficacy and safety outcomes. However, MI and CVA which were borderline significant in the core analysis, were no longer significant upon sensitivity analysis (Supplementary Table S5 and Supplementary Figure 4 to 11).

Discussion

PAD is a global burden with increasing incidence worldwide. Patients with PAD are at increased risk for cardiovascular and limb related events.[1–3] Current society guidelines recommend SAPT for all patients with PAD and DAPT for a limited duration after revascularization.[5,6] Despite the advancement in revascularization strategies, the risk of subsequent cardiovascular and limb events remains unacceptably high.[4] Several studies were performed to investigate strategies to mitigate this residual ischemic risk, those studies showed a lower risk for ischemic events and favorable graft patency rates when AC was added to or replaced antiplatelet therapy.[10–12]

Similarly, trials utilizing vorapaxar, a thrombin receptor antagonist, showed a significant reduction of risk of acute limb ischemia in patients with stable PAD.[16] The disadvantage, however, of the above-mentioned treatment strategies was a significantly higher rate of bleeding events.[10,11,16] Recent trials showed a favorable reduction of ischemic events with LD rivaroxaban in patients with PAD.[7,8] In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, LD AC resulted in a reduction of MACE at the cost of higher risk of bleeding according to a modified International Society on Thrombosis and Haemostasis (ISTH) definition.[8] In the VOYAGER trial, LD AC added to antiplatelet therapy resulted in a reduction of MACE with a non-significant increase in bleeding events.[7] Across these trials, the authors have used varied bleeding definitions, including thrombolysis in myocardial infarction (TIMI) bleeding criteria, bleeding academic research consortium (BARC), and ISTH.[7,17–19] The lack of standardization makes the comparison of bleeding events between studies challenging. Interestingly, earlier trials used individual definitions for bleeding events.[10–13] A comparison between several bleeding definitions has shown a fourfold difference in the rates when utilizing different bleeding definitions; however, one finding that remains consistent is that bleeding events are associated with worse outcomes.[20] This is likely due to the inherent hazard of bleeding but also to the subsequent interruption of anti-thrombotic therapy resulting in increased ischemic events.[21–23] Of note, when the ISTH definition was applied in numerous trials, AC therapy was associated with a significant higher risk of bleeding compared to SOC antiplatelet therapy.

The major findings of the present study-level meta-analysis are the following. First, adding AC to a SOC antiplatelet treatment offers a reduction in MACE at the cost of higher risk of MB. The absolute risk for MACE was 2.2% at the cost of 1.9% absolute risk increase in MB. Second, LD AC provides a favorable balance between reduction of MACE and increased risk of MB. A net benefit of 1.2% reflects the beneficial effect of LD AC in this patient population. In the present analysis, we used either the individual trial definition or the ISTH definition to maintain consistency, since these were reported in most studies. The impact of dose of AC on MB events is a novel finding of the present analysis. LD compared to FD AC resulted in a favorable balance between MACE and MB. However, there is no risk score that has been validated to weigh the risk of ischemia and bleeding in patients with PAD. Thus, it is paramount for the clinician to identify patients with PAD who are at high risk for ischemic or bleeding events, in order to tailor the antithrombotic regimen after surgical or endovascular revascularization. It is important to mention the recently published meta-analysis by Saverese et al, who addressed the safety and efficacy of different combinations of antiplatelet and anthithrombotic therapies for the prevention of cardiovascular and limb events among patients with PAD.[24] Although, their findings are in line with ours, the current meta-analysis is focused on the addition of AC to SOC rather than investigating different strategies of antiplatelet drugs and regimens.

Several limitations should be taken into account while interpreting the results of the present study. First, there were variations in the type and dose of AC between the studies. Second, bleeding definition across the included trials were highly variable, which we attempted to standardize by using either ISTH or the individual trial definition. This likely represents the reason for the observed heterogeneity for the only MB outcome but did not change the overall results on sensitivity analysis. However, regardless of the

definition applied, MB is a risk factor for mortality and morbidity and associated with subsequent ischemic events.[20,22] Additionally, some trials included in the present analysis were designed to assess safety or major adverse limb events (MALE) and not MACE which makes it challenging for clinicians to make decisions with regards to adding AC to SOC therapy. Third, there was variability in the duration and follow-up of the included studies, therefore the long-term efficacy and safety of AC remains uncertain. Fourth, the majority of the FD AC trials were of relatively small sample size, and only one trial was powered to detect statistically significant differences in cardiovascular and ischemic endpoints.[9–11] Fifth, the age distribution of the included trials ranged from 64 to 74 ± 10 years and hence our results cannot be directly extrapolated to patients younger than 55 or older than 85 years of age. Finally, FD AC with warfarin is considered SOC for patients who underwent bypass surgery utilizing vein grafts, based on subgroup analyses of the Dutch BOA study and it does not represent high quality evidence. No sufficiently powered studies have been performed to investigate graft patency with LD AC. Therefore, our results cannot be directly extrapolated for this particular subset of PAD patients.

In conclusion, the addition of AC to SOC antiplatelet therapy in patients with PAD is associated with a lower risk for ischemic cardiovascular events but at the cost of higher bleeding risk. However, LD, compared to FD AC, has a favorable safety/efficacy ratio and should be applied in patients if bleeding risk is low.

Authors' Contribution

Haroon Kamran, MD: conceptualization, formal analysis, data curation, writing − original draft; Rohit Malhotra, MD: data curation − review & editing; Serdar Farhan, MD: conceptualization, methodology, writing − review & editing, supervision; Reza Masoomi, MD: data curation − review & editing; Aakash Garg, MD: data curation − review & editing; Amit Hooda, MD: data curation − review & editing; Reihonil Lascano, NP: writing − review & editing; Daniel Han, MD: writing − review & editing; Rami Tadros, MD: writing − review & editing; Arthur Tarricone, PHD: writing − review & editing; Usman Baber, MD: writing − review & editing; Roxana Mehran, MD: writing − review & editing; Kurt Huber, MD: conceptualization, methodology, writing − review & editing, visualization, supervision; Prakash Krishnan, MD: conceptualization, methodology, writing − review & editing, visualization, supervision

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.02.033.

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