# Oral Anticoagulant and Antiplatelet Therapy for Peripheral Arterial Disease: A Meta-analysis of Randomized Controlled Trials

Clinical and Applied Thrombosis/Hemostasis Volume 27: 1-7 © The Author(s) 2021 Article reuse guidelines: sagepub.com/journals-permissions DOI: 10.1177/1076029621996810 journals.sagepub.com/home/cat



Tao Tang, PhD<sup>1,\*</sup>, Ming Zhang, PhD<sup>1,\*</sup>, Wendong Li, PhD<sup>1,\*</sup>, Nan Hu, PhD<sup>1</sup>, Xiaolong Du, PhD<sup>1</sup>, Feng Ran, PhD<sup>1</sup>, and Xiaoqiang Li, PhD<sup>1</sup>

#### Abstract

Peripheral artery disease (PAD) is a common disease affecting over 200 million people worldwide. PAD is associated with significant limb and cardiovascular morbidity and mortality which is reduced by antiplatelet and antithrombotic therapy. However, the optimal type, dose, and time of antithrombotic therapy is still uncertain.We searched 4 electronic databases from January I, 1990, to June I, 2020, for randomized controlled trials of patients who received oral anticoagulant and antiplatelet therapy for PAD. The primary outcome was a composite of acute limb ischemia, major amputation, myocardial infarction, ischemic stroke, death from cardiovascular events, or death from any cause. Secondary outcomes included major bleeding, fatal bleeding, and intracranial hemorrhage events.We identified 3 studies that satisfied inclusion and exclusion criteria. Compared with antiplatelet alone, oral anticoagulant plus antiplatelet therapy improved acute limb ischemia (p < 0.00001), stroke (p = 0.005), and major amputation events (p = 0.11). However, oral anticoagulant plus antiplatelet therapy was not effective for prevention of myocardial infarction (p = 0.23), death from cardiovascular events (p = 0.65), or death from any cause (p = 0.66). Additionally, a significant increase in major bleeding events was demonstrated (p < 0.00001). There was no significant difference in fatal bleeding (p = 0.16) or intracranial hemorrhage events. On the other hand, measuring myocardial infarction, death, fatal bleeding, or intracranial hemorrhage risk remains controversial.

#### **Keywords**

anticoagulant, antiplatelet, PAD

Date received: 27 January 2021; revised: 27 January 2021; accepted: 01 February 2021.

#### Introduction

Peripheral arterial disease (PAD) is associated with a substantial risk of disease progression, cardiovascular morbidity and mortality, and secondary prevention is recommended for most patients.<sup>1-2</sup> Evidence suggests the use of antiplatelet therapy for secondary prevention in patients with PAD to reduce the threat of cardiovascular diseases.<sup>1-2</sup> Moreover, antiplatelet and antith-rombotic therapy may increase the patency of revascularized vessels after interventions, and result in reduced acute limb ischemia risk, reintervention rates, and possibly reduced cardiovascular complications.<sup>3</sup> These advantages should be weighed against the risk of bleeding complications associated with anticoagulant and antiplatelet medicines. We therefore performed a meta-analysis of 3 randomized controlled trials (RCTs).<sup>4-5</sup> comparing oral anticoagulant plus antiplatelet

<sup>1</sup> Department of Vascular Surgery, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China. \*They contributed equally to this work.

#### **Corresponding Authors:**

Feng Ran and Xiaoqiang Li, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China. Emails: doctor\_ran@163.com; flytsg@126.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).



Figure 1. Flow chart of literature review.

therapy with antiplatelet alone for the treatment of PAD to resolve this discrepancy and provide evidence to clinical physicians.

# Methods

# Literature Search

Using PubMed, Embase, Web of Science, and Cochrane Library, we searched literature published between January 1, 1990, and June 1, 2020. The following search terms were included: anticoagulation (vitamin K antagonists or non-vitamin K antagonist oral anticoagulants (Direct oral anticoagulant DOACs)) or/and antiplatelet and PAD; and/or comparative studies or RCTs or cohort studies or retrospective or prospective studies. Inclusion criteria were (1) studies comparing oral anticoagulant plus antiplatelet (experimental group) with antiplatelet (control group) and (2) effectiveness of intact clinical data(include RCTs, intact patient demographics, follow-up time, outcomes). There were no language restrictions. We identified 3 studies that met our criteria (Figure 1).

Two investigators (Tang and Li) independently extracted data utilizing a data abstraction tool: number of patients in the experimental (oral anticoagulant plus antiplatelet) and control antiplatelet) groups, study quality, time of follow-up, and primary and secondary PAD outcomes. The primary outcome was a composite of acute limb ischemia, major amputation, myocardial infarction, ischemic stroke, and death from cardiovascular or any cause events, and the secondary outcome was a composite of acute limb ischemia, major amputation, myocardial infarction, ischemic stroke, and death from cardiovascular or any cause events.

# Data Extraction and Quality Assessment

Publication details, inclusion and exclusion criteria, enrolled patient demographics, interventions used, and outcomes (primary and secondary outcomes) were collected. Risk of bias in RCTs (including masking of participants, method of sequence generation and allocation concealment, intention-to-treat analysis, incomplete or unclear data, time to follow-up, and loss to follow-up) was assessed. Study quality was assessed using the Modified Jadad scale.<sup>6</sup> Any Disagreements between reviewers were resolved by consensus.

#### Statistical Analysis

Statistical analysis was performed using Review Manager (version 5.3; Cochrane Collaboration software). We used fixedeffects models for primary outcomes and secondary outcomes. Statistical heterogeneity was assessed by I<sup>2</sup>. The level of heterogeneity was distinguished as low (I<sup>2</sup> = 25%-49%), moderate (I<sup>2</sup> = 50%-74%), and high (I<sup>2</sup>  $\geq$ 75%) heterogeneity. Primary and secondary outcomes were analyzed using odds ratios, with a 2-sided statistical significance level of 5%.

# Results

### Study Characteristics and Quality

The initial search strategy identified 23 full-text articles, and 20 citations were initially screened. Of these, 3 trials met the appropriate criteria for inclusion in the review (Figure 1). The 3 RCTs<sup>3-5</sup> included experimental groups that received oral anticoagulant plus antiplatelet therapy for PAD and control groups that received antiplatelet therapy for PAD. The quality of RCTs was evaluated by modified Jadad score.<sup>6</sup> Table 1 shows the baseline characteristics for each study.

#### Primary Outcome

Primary and secondary outcomes are shown in Table 2. The 3 studies<sup>3-5</sup> included results of acute limb ischemia, myocardial infarction, stroke, death from cardiovascular events, and death from any cause. Results of major amputation events were included in 2 studies.<sup>4-5</sup> Meta-analysis indicated that oral anticoagulant plus antiplatelet therapy for PAD reduced the occurrence of acute limb ischemia (p < 0.00001;  $I^2 = 43\%$ ), stroke  $(p = 0.005; I^2 = 33\%)$ , and major amputation events (p = 0.11; $I^2 = 77\%$ ) compared to antiplatelet alone and did not result in a significant difference in myocardial infarction (p = 0.23;  $I^2 = 5\%$ ), death from cardiovascular(p = 0.65;  $I^2 = 29\%$ ) or death from any cause events (p = 0.66;  $I^2 = 0\%$ ) compared to antiplatelet therapy. This meta-analysis showed that oral anticoagulant plus antiplatelet therapy is more effective for reducing risk of acute limb ischemia, stroke, and major amputation than antiplatelet alone. Results of the meta-analysis of the primary outcomes are shown in Figure 2.

Table I. Baseline	Characteristics of Included Cli	nical Trials									
Study	Group	Sample	Follow-up	Mean age (years)	Female sex (%)	Diabetes (%)	Hypertension (%)	CAD (%)	Stroke (%)	ABI	Study quality score
WAVE 2007	AC(warfarin INR2.0-3.0)	1080	35 months	<b>63.9</b> ± 9.4	26.3	26.9	58.3	44.7	14.4	0.83	RCT
	+Aspirin Aspirin 81-325 mg qd	1081		<b>63.8</b> ± 9.5	26.5	27.6	58.1	44.9	16.4	0.84	Jadad: 7
VOYAGER 2020	AC(Rivaroxaban2.5 mg bid) + Asnirin 100 mg ad	3286	28 months	67	25.8	40	81.7	32	AN	0.56	RCT
	Aspirin 100 mg qd	3278		67	26.1	40. I	81.1	31	AN	0.56	Jadad: 7
COMPASS 2018	AC(Rivaroxaban2.5 mg bid) +Aspirin 100 mg ad	2492	21 months	<b>67.9</b> ± 8.45	29	44.1	78.9	66.5	6.9	ΑN	RCT
	Aspirin 100 mg qd	2504		$67.8 \pm 8.47$	29	44.1	80.6	65.5	6.2	٩N	Jadad: 7
Abbreviations—AC:	anticoagulant, ABI: ankle brachial ii	ndex, CAD:	coronary arter	y disease, RCT: r	andomized	controlled trial, N	IA: not available.				

Table 2. Primary and Secondary Outcomes in Clinical Trials.

•										
Study	Group	Acute limb ischemia events	Major amputation events	Myocardial infarction events	Stroke events	Cardiovascular death events	Death events	Major bleeding events	Fatal bleeding events	Intracranial hemorrhage events
WAVE 2007	AC(warfarin) +Aspirin	42	AN	20	24	66	66	74	01	4
	Aspirin	44	٩N	15	38	65	96	24	m	0
VOYAGER 2020	AC(Rivaroxaban) + Aspirin	144	103	103	71	661	321	140	6	13
	Aspirin	227	115	115	82	174	297	001	6	17
COMPASS 2018	AC(Rivaroxaban) + Aspirin	61	5	51	25	64	129	64	4	ъ
	Aspirin	34	17	67	47	78	142	54	m	6
Abbreviations—AC:	anticoagulant .NA: not available.									



Figure 2. Meta-analysis of primary outcomes of clinical trials.

### Secondary Outcomes

The 3 articles<sup>3-5</sup> contained data about major bleeding events, fatal bleeding, and intracranial hemorrhage events. A statistically significant increase in major bleeding events  $(p < 0.00001, I^2 = 83\%)$  was reported. We found that heterogeneity of major bleeding events was high ( $I^2 = 83\%$ ), suggesting the need to explore heterogeneity sources. We divided the major bleeding events into 2 types: AC (anticoagulant plus antiplatelet including warfarin): p < 0.00001,  $I^2 = 83\%$ ; and DOAC groups (anticoagulant plus antiplatelet excluding warfarin): p = 0.007,  $I^2 = 0\%$ ). There was no significant difference in fatal bleeding (p = 0.16;  $I^2 = 0\%$ ) or intracranial hemorrhage events (p = 0.43,  $I^2 = 77\%$ ). Because the heterogeneity of intracranial hemorrhage events was high, we will need to explore heterogeneity sources. For this study, we also divided intracranial hemorrhage events into 2 types: AC: p = 0.43,  $I^2 = 77\%$ ; and DOAC: p = 0.23,  $I^2 = 0\%$ ). Figure 3 shows the meta-analysis of bleeding events (major bleeding, fatal bleeding, and intracranial hemorrhage events).

# Discussion

PAD is most commonly caused by atherosclerosis and is widespread in the world.<sup>7</sup> Current guidelines recommend antiplatelet monotherapy for prevention of cardiovascular disease with a class IA recommendation. By comparison, dual antiplatelet therapy is regularly prescribed after stent placement in cardiovascular disease. Furthermore, these recommendations contain PAD subgroup analyses in cardiovascular trials. Through underlying antiplatelet therapy, patients with PAD are still at a high risk of atherothrombotic complications. Treatment strategies targeting the decline of cardiovascular morbidity or mortality in PAD have necessarily involved the use of antithrombotic treatment. However, the type, dose, time, and strength of antithrombotic treatment for PAD patients has not yet been determined. As time went on, 3 RCTs<sup>3-5</sup> provided evidences to antithrombotic treatment for PAD. So we use meta-analysis from 3 RCTs indicating that oral anticoagulant plus antiplatelet therapy for PAD may improve acute limb ischemia, major amputation, or stroke risk compared with antiplatelet therapy alone.

In the WAVE (Warfarin Antiplatelet Vascular Evaluation) trial,<sup>5</sup> the study compared the effectiveness and safety of combination antithrombotic therapy with oral anticoagulant (warfarin) plus antiplatelet therapy with antiplatelet therapy alone for PAD. The results showed that the combination of oral anticoagulant (warfarin) plus antiplatelet therapy was no more effective than antiplatelet therapy alone in preventing primary cardiovascular complications. In contrast, anticoagulant (warfarin) plus antiplatelet therapy was associated with a substantial excess of moderate or life-threatening bleeding events. The WAVE trail's results emphasize the need to appraise alternatives to warfarin in patients with PAD. A low dosage Factor Xa inhibitor (rivaroxaban) plus antiplatelet therapy has been shown to lower cardiovascular ischemia risk. The COMPASS

(Cardiovascular Outcomes for People Using Anticoagulation Strategies) study<sup>4</sup> demonstrated that patients with PAD who were enrolled in the COMPASS trial and received the combination of rivaroxaban 2.5 mg twice a day plus 100 mg of aspirin a day had a 28% reduction in major adverse cardiovascular events, a 46% reduction in major adverse limb events, and a 31% reduction in the composite of major adverse cardiovascular or limb events, compared with the aspirin alone group. Although this combination was associated with an increased risk of major bleeding, there was no excess in fatal or critical organ bleeds. The European Society for Vascular Surgery (ESVS) 2020 guidelines<sup>8</sup> have added recommendations in acceptance of the COMPASS study for PAD patients with chronic limb threatening ischemia.

Acute limb ischemia (ALI) is a common complication in PAD and lower extremity vascular reconstruction is an effective measure for preventing limb loss.9-11 However, new evidence suggests that patients who had lower limb recanalization had a quadruple increased risk of ALI and higher risk of cardiovascular events, including an almost 30% increased risk of myocardial infarction.<sup>12-13</sup> Acute limb ischemia is a complication that is combined with long hospital stays and high risk of amputation, disability, and death.14-17 On the basis of COMPASS study, the Vascular Outcomes study of ASA along with rivaroxaban in endovascular or surgical limb revascularisation for peripheral artery disease (VOYAGER PAD)<sup>3</sup> was designed to assess the effectiveness and safety of 2.5 mg twice daily rivaroxaban plus aspirin in high risk PAD patients at high risk for lower extremity vascular reconstruction compared with aspirin alone. A low dose of rivaroxaban with added aspirin was associated with a significantly lower morbidity of ALI. major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes compared to aspirin alone. The incidence of TIMI (Thrombolysis in Myocardial Infarction) major bleeding did not significantly differ between the 2 groups. The incidence of ISTH (International Society on Thrombosis and Haemostasis) major bleeding was significantly higher in the rivaroxaban plus aspirin group.

Previous studies for antithrombotic therapy in endovascular and surgical revascularization were not definitive, as they were premised on subgroups of patients with coronary artery disease or extensive atherosclerosis patients.<sup>18-20</sup> The VOYAGER PAD study provides new, high-quality evidence that the benefits for long-term use of this novel dual pathway regimen reduces the risk of acute cardiovascular events and ALI events after lower limb revascularization. The data from the VOYA-GER PAD study complements the COMPASS study, which revealed a significant reduction in cardiovascular events and ALI events in PAD patients. Our meta-analysis has highlighted a new antithrombotic therapy for patients with PAD. Platelet inhibition plus low-dose anticoagulant would depend on status to balance ischemic and bleeding risks when selecting type, dose, and intensity of antithrombotic treatment for PAD.<sup>21-23</sup> Our study has some limitations. In this meta-analysis, the number of RCT trials was low and major bleeding events are a severe problem for antithrombotic therapy. Because the studies

	Anticoagulant+	Aspirin	Aspir	rin		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
10.1.1 AC Subgroup							
COMPASS 2018	64	2492	54	2504	16.5%	1.20 [0.83, 1.73]	
/OYAGER 2020	140	3286	100	3278	30.0%	1.41 [1.09, 1.84]	
WAVE 2007	74	1080	24	1081	7.0%	3 24 12 03 5 18	
Subtotal (95% CI)		6858		6863	53.5%	1.59 [1.31, 1.92]	•
Total quanta	270	0050	170	0000	33.374	1100 [1101, 1102]	
Interesents	44.05 44-2/0-	0.0000.18	- 0.00				
Heterogeneity: Chir =	11.95, df = 2 (P =	0.003); 1-	= 83%				
est for overall effect:	Z = 4.73 (P < 0.00	0001)					
IG 4 2 NOAC Crown							
10.1.2 NOAC Group			14.5				-
COMPASS 2018	64	2492	54	2504	16.5%	1.20 [0.83, 1.73]	
/OYAGER 2020	140	3286	100	3278	30.0%	1.41 [1.09, 1.84]	
Subtotal (95% CI)		5778		5782	46.5%	1.34 [1.08, 1.65]	•
lotal events	204		154				
Heterogeneity: Chi <sup>2</sup> =	0.53, df = 1 (P = 0	).47); l <sup>2</sup> = (	96				
Test for overall effect.	Z = 2.68 (P = 0.00	07)					
Total (95% CI)		12636		12645	100.0%	1.47 [1.28, 1.69]	•
Fotal events	482		332				
Heterogeneity: Chi? =	13.54 df = 4 (P =	0.0000 12	= 70%				<b>├───</b>
Fact for overall effect:	7-622/0 -0.00	0.0000,1	- 70.0				0.01 0.1 1 10 100
Fest for overall effect.	Z = 5.32 (F = 0.00)	27 48-1	/D = 0.24	1 1 - 22	1 1 04		Favours Anticoagulant+Aspirin Favours Aspirin
est for subdroub dime	erences: Chi*= 1	.37. df = 1	(P = 0.24	1 = 21	.1%		
eta-analysis of ma	ajor bleeding e	vents (A	C grou	p (incl	ude wai	farin): p<0.00001	, I <sup>2</sup> =83%; NOAC group (exclude
	5 0						
arfarin): p=0.007,	$I^2=0\%$ ; total to	est:p<0.0	00001, I	2=70%	).		
	Anticoagulant	Aspirin	Aspi	rin		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
COMPASS 2018	4	2492	3	2504	25.0%	1.34 [0.30, 5.99]	
/OYAGER 2020	6	3286	6	3278	50.2%	1.00 (0.32, 3.10)	<b>_</b>
A/AVE 2007	10	1000		1001	24 004	2 26 10 02 42 241	
		1112011			2 A 25 7 A	5 50 11 97 17 741	_
WAYE 2007	10	1080	3	1001	24.070	3.30 [0.82, 12.24]	
Total (95% CI)	10	6959	3	6963	100.0%	1 67 [0 92 3 42]	
Total (95% CI)	20	6858	3	6863	100.0%	1.67 [0.82, 3.42]	-
Fotal (95% CI) Fotal events	20 200 df - 2/D-	6858	12	6863	100.0%	1.67 [0.82, 3.42]	-
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> =	20 2.00, df = 2 (P =	6858 0.37); I <sup>2</sup> =	3 12 0%	6863	100.0%	1.67 [0.82, 3.42]	0.01 0.1 1 10 10
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect:	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1	6858 0.37); I² = 6)	3 12 0%	6863	100.0%	1.67 [0.82, 3.42]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin
Fotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect:	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1	6858 0.37); I <sup>2</sup> = 6)	3 12 0%	6863	100.0%	1.67 [0.82, 3.42]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin
Fotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1	6858 0.37); I <sup>#</sup> = 6)	3 12 0%	6863	100.0%	1.67 [0.82, 3.42]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin
Fotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect.	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev	6858 0.37); I <sup>#</sup> = 6) ents (959	3 12 0% % confi	6863 dence i	100.0%	1.67 [0.82, 3.42] (CI) 0.82–3.42; p	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%).
Fotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Teta-analysis of fat	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev	6858 0.37); I <sup>2</sup> = 6) ents (95%	12 0% % confi	6863 dence i	100.0%	1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio
Fotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect reta-analysis of fat	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events	6858 0.37); I <sup>#</sup> = 6) ents (959 Aspirin Total	3 12 0% % confi Aspin Events	6863 dence i	100.0% nterval Weight	1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% Cl
Fotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect feta-analysis of fat	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events	6858 0.37); I <sup>2</sup> = 6) ents (9 <i>5</i> % Aspirin Total	3 12 0% 6 confi Aspin Events	6863 dence i tin Total	100.0% nterval Weight	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Teta-analysis of fat Study or Subgroup 9.1.1 AC Subgroup COMPACE 2012	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events	6858 0.37); I <sup>2</sup> = 6) ents (959 Aspirin Total	3 12 0% % confi Aspin Events	6863 dence i in <u>Total</u>	100.0% 100.0% Interval <u>Weight</u>	(CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Teta-analysis of fat Study or Subgroup 3.1.1 AC Subgroup COMPASS 2018 SUMOCE 2000	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5	6858 0.37); I <sup>z</sup> = 6) ents (95 <sup>c</sup> Aspirin <u>Total</u> 2492 2200	3 12 0% % confi <u>Events</u> 9	6863 dence i in Total	100.0% 100.0% nterval <u>Weight</u> 17.1%	<ul> <li>3.36 [0.32, 12.24]</li> <li>1.67 [0.82, 3.42]</li> <li>(CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI</li> <li>0.56 [0.19, 1.67]</li> <li>0.56 [0.19, 1.67]</li> </ul>	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Fotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect. Teta-analysis of fat Study or Subgroup 9.1.1 AC Subgroup COMPASS 2018 /OYAGER 2020	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13	6858 0.37); I <sup>#</sup> = 6) ents (95 <sup>c</sup> Aspirin Total 2492 3286	3 0% % confi <u>Aspin Events</u> 9 17	6863 dence i in <u>Total</u> 2504 3278	100.0% 100.0% interval <u>Weight</u> 17.1% 32.4%	<ul> <li>3.36 [0.92, 12.24]</li> <li>1.67 [0.82, 3.42]</li> <li>(CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57]</li> </ul>	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect teta-analysis of fat Study or Subgroup 3.1.1 AC Subgroup COMPASS 2018 /OYAGER 2020 MAVE 2007	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14	6858 0.37); I <sup>2</sup> = 6) ents (95 <sup>6</sup> Aspirin Total 2492 3286 1080	12 0% % confi <u>Aspin Events</u> 9 17 0	6863 dence i in <u>Total</u> 2504 3278 1081	100.0% 100.0% nterval 17.1% 32.4% 0.9%	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 29.41 [1.75, 493.60]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Teta-analysis of fat Study or Subgroup 0.1.1 AC Subgroup COMPASS 2018 VOYAGER 2020 VAVE 2007 Subtotal (95% CI)	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14	6858 6858 0.37); I <sup>a</sup> = 6) ents (95 <sup>c</sup> Aspirin Total 2492 3286 1080 6858	3 12 0% K confi <u>Aspin</u> <u>Events</u> 9 17 0	6863 dence i in 2504 3278 1081 6863	100.0% 100.0% interval <u>Weight</u> 17.1% 32.4% 0.9% 50.5%	<ul> <li>3.36 [0.32, 12.24]</li> <li>1.67 [0.82, 3.42]</li> <li>(CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI</li> <li>0.56 [0.19, 1.67]</li> <li>0.76 [0.37, 1.57]</li> <li>29.41 [1.75, 493.60]</li> <li>1.23 [0.73, 2.05]</li> </ul>	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: ieta-analysis of fat Study or Subgroup COMPASS 2018 /OYAGER 2020 //AVE 2007 Subtotal (95% CI) Total events	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 32	6858 0.37); I <sup>z</sup> = 6) ents (959 Aspirin Total 2492 3286 1080 6858	3 12 0% 6 confi <u>Aspin</u> <u>Events</u> 17 0 26	6863 dence i in 2504 3278 1081 6863	100.0% 100.0% nterval 17.1% 32.4% 0.9% 50.5%	<ul> <li>3.36 [0.32, 12.24]</li> <li>1.67 [0.82, 3.42]</li> <li>(CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI</li> <li>0.56 [0.19, 1.67]</li> <li>0.76 [0.37, 1.57]</li> <li>29.41 [1.75, 493.60]</li> <li>1.23 [0.73, 2.05]</li> </ul>	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Teta-analysis of fat Study or Subgroup COMPASS 2018 /0YAGER 2020 NAVE 2007 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> =	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 8.54, df = 2 (P = 0	6858 0.37); I <sup>2</sup> = 6) ents (959 Aspirin Total 2492 3286 1080 6858 0.01); I <sup>2</sup> = 7	3 0% % confi Aspin Events 9 17 0 26 7%	6863 dence i in <u>Total</u> 2504 3278 1081 6863	100.0% 100.0% nterval <u>Weight</u> 17.1% 32.4% 0.9% 50.5%	<ul> <li>3.36 [0.32, 12.24]</li> <li>1.67 [0.82, 3.42]</li> <li>(CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57]</li> <li>29.41 [1.75, 493.60]</li> <li>1.23 [0.73, 2.05]</li> </ul>	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Test for overall effect: Test for overall effect: Test for overall effect: ACMPASS 2018 ACMPASS 201	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 2 8.54, df = 2 (P = 0.43 Z = 0.78 (P = 0.43	6858 0.37); I <sup>z</sup> = 6) ents (959 Aspirin Total 2492 3286 1080 6858 0.01); I <sup>z</sup> = 7 3)	3 0% % confi <u>Aspin Events</u> 9 17 0 26 7%	6863 dence i in 2504 3278 1081 6863	100.0% 100.0% nterval <u>Weight</u> 17.1% 32.4% 0.9% 50.5%	<ul> <li>3.36 [0.32, 12.24]</li> <li>1.67 [0.82, 3.42]</li> <li>(CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI</li> <li>0.56 [0.19, 1.67]</li> <li>0.76 [0.37, 1.57]</li> <li>29.41 [1.75, 493.60]</li> <li>1.23 [0.73, 2.05]</li> </ul>	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Teta-analysis of fat Study or Subgroup 3.1.1 AC Subgroup COMPASS 2018 /OYAGER 2020 NAVE 2007 Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect:	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 2 8.54, df = 2 (P = 0 Z = 0.78 (P = 0.4)	6858 0.37); I <sup>2</sup> = 6) ents (95 <sup>c</sup> Aspirin Total 2492 3286 1080 6858 0.01); I <sup>2</sup> = 7 3)	3 0% 6 confi <u>Aspin Events</u> 9 17 0 26 7%	6863 dence i in <u>Total</u> 2504 3278 1081 6863	100.0% 100.0% interval <u>Weight</u> 17.1% 32.4% 0.9% 50.5%	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 29.41 [1.75, 493.60] 1.23 [0.73, 2.05]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Teta-analysis of fat Study or Subgroup OMPASS 2018 AVYAGER 2020 AVAVE 2007 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: 0.1.2 NOAC Group	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 32 8.54, df = 2 (P = 0 Z = 0.78 (P = 0.43)	6858 0.37); I <sup>#</sup> = 6) ents (95 <sup>c</sup> Aspirin Total 2492 3286 1080 6858 0.01); I <sup>#</sup> = 7 3)	3 0% % confi Aspin Events 9 17 0 26 7%	6863 dence i in <u>Total</u> 2504 3278 1081 6863	100.0% nterval <u>Weight</u> 17.1% 32.4% 0.9% 50.5%	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 29.41 [1.75, 493.60] 1.23 [0.73, 2.05]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Teta-analysis of fat Study or Subgroup OMPASS 2018 /OYAGER 2020 VAVE 2007 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: 3.1.2 NOAC Group COMPASS 2018	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 32 8.54, df = 2 (P = 0 Z = 0.78 (P = 0.4)	6858 0.37); I <sup>2</sup> = 6) ents (959 Aspirin Total 2492 3286 1080 6858 0.01); I <sup>2</sup> = 7 3)	3 0% % confi <u>Aspin Events</u> 9 17 0 26 7% 26	6863 dence i in <u>Total</u> 2504 3278 1081 6863	100.0% 100.0% Interval Weight 17.1% 50.5%	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 29.41 [1.75, 493.60] 1.23 [0.73, 2.05] 0.56 [0.19, 1.67]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: ieta-analysis of fat Study or Subgroup OMPASS 2018 /OYAGER 2020 NAVE 2007 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: OMPASS 2018 /OYAGER 2020	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 32 8.54, df = 2 (P = 0 Z = 0.78 (P = 0.4) 5 13	6858 0.37); I <sup>2</sup> = 6) ents (959 Aspirin Total 2492 3286 1080 6858 0.01); I <sup>2</sup> = 7 3) 2492 3286	3 0% % confi <u>Events</u> 17 0 26 7% 9 17	6863 dence j in <u>Total</u> 2504 3278 1081 6863	100.0% 100.0% Interval 17.1% 32.4% 17.1% 32.4%	<ul> <li>3.36 [0.32, 12.24]</li> <li>1.67 [0.82, 3.42]</li> <li>(CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57]</li> <li>29.41 [1.75, 493.60]</li> <li>1.23 [0.73, 2.05]</li> <li>0.56 [0.19, 1.67]</li> <li>0.56 [0.19, 1.67]</li> <li>0.76 [0.37, 1.57]</li> </ul>	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect eta-analysis of fat Study or Subgroup 0.1.1 AC Subgroup COMPASS 2018 /OYAGER 2020 NAVE 2007 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: 3.1.2 NOAC Group COMPASS 2018 /OYAGER 2020 Subtotal (95% CI) Subtotal (95% CI)	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 32 8.54, df = 2 (P = 0.4 5 13	6858 0.37); I <sup>#</sup> = 6) ents (95% Aspirin Total 2492 3286 1080 6858 0.01); I <sup>#</sup> = 7 3) 2492 3286 5778	3 0% 6 confi <u>Aspin Events</u> 9 17 0 26 7% 26 7% 9 17	6863 dence i in 2504 3278 1081 6863 2504 3278 5782	100.0% 100.0% Interval Weight 17.1% 32.4% 0.9% 50.5% 17.1% 32.4% 0.9% 50.5%	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 29.41 [1.75, 493.60] 1.23 [0.73, 2.05] 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 0.76 [0.37, 1.57] 0.76 [0.37, 1.57]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Teta-analysis of fat Study or Subgroup COMPASS 2018 YOYAGER 2020 VAVE 2007 Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: St.1.2 NOAC Group COMPASS 2018 YOYAGER 2020 Subtotal (95% CI) Events Compass 2018 YOYAGER 2020 Subtotal (95% CI) Events Subtotal (95% CI) Subtotal (95% CI) Subtotal (95% CI) Subtotal (95% CI) Subtotal (95% CI) Subtotal (9	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 8.54, df = 2 (P = 0 Z = 0.78 (P = 0.4) 5 13 14 8.54, df = 2 (P = 0.4) 5 13 14 8.54, df = 2 (P = 0.1) 5 13 14 8.54, df = 2 (P = 0.1) 5 13 14 13 14 13 14 13 14 13 14 13 14 13 14 13 13 14 13 14 13 14 13 14 13 14 13 14 13 13 14 13 14 13 14 13 14 13 14 13 14 13 14 13 14 13 14 13 14 13 14 13 14 13 13 14 14 13 14 13 13 14 13 14 13 14 13 14 15 15 15 15 15 15 15 15 15 15	6858 6858 0.37); I <sup>2</sup> = 6) ents (95% Aspirin Total 2492 3286 1080 6858 0.01); I <sup>2</sup> = 7 3) 2492 3286 5778	3 0% % confi <u>Aspin Events</u> 17 0 26 7% 9 17 26 7%	6863 dence i in 2504 3278 1081 6863 2504 3278 5782	100.0% 100.0% interval <u>Weight</u> 17.1% 32.4% 50.5%	<ul> <li>3.36 [0.32, 12.24]</li> <li>1.67 [0.82, 3.42]</li> <li>(CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI</li> <li>0.56 [0.19, 1.67]</li> <li>0.76 [0.37, 1.57]</li> <li>29.41 [1.75, 493.60]</li> <li>1.23 [0.73, 2.05]</li> <li>0.56 [0.19, 1.67]</li> <li>0.76 [0.37, 1.57]</li> <li>0.69 [0.38, 1.26]</li> </ul>	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Test for overall effect: Test for overall effect: Test for overall effect: COMPASS 2018 AVAVE 2007 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: COMPASS 2018 AVAVE 2018 AVAVE 2007 Subtotal (95% CI) Total events AUX AVAVE 2020 Subtotal (95% CI) Total events AUX AVAVE 2020 AUX AVAVE 2020 Subtotal (95% CI) Total events AUX AVAVE 2020 Subtotal (95% CI) AUX AVAVE 2020 Subtotal (95% CI) Total events AUX AVAVE 2020 AUX AVAVE 2020 A	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 32 8.54, df = 2 (P = 0 Z = 0.78 (P = 0.43) 5 13 14 22 13 14 22 13 14 22 13 14 22 13 14 22 13 14 22 13 14 22 13 14 22 14 24 24 24 24 24 24 24 24 24 2	6858 0.37); I <sup>2</sup> = 6) ents (95 <sup>4</sup> Aspirin Total 2492 3286 1080 6858 0.01); I <sup>2</sup> = 7 3) 2492 3286 5778	3 0% 6 confi <u>Aspin Events</u> 9 17 0 26 7% 9 17 26	6863 dence i in 2504 3278 1081 6863 2504 3278 5782	100.0% 100.0% Interval 17.1% 32.4% 0.9% 50.5% 17.1% 32.4% 49.5%	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 29.41 [1.75, 493.60] 1.23 [0.73, 2.05] 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 0.76 [0.37, 1.57] 0.69 [0.38, 1.26]	=0.16; I <sup>2</sup> =0%). Odds Ratio M.H. Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Test for overall effect: Test for overall effect: Test for overall effect: OVAGER 2020 VAVE 2007 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: OMPASS 2018 VOYAGER 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Total events Heterogeneity: Chi <sup>2</sup> =	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 2 8.54, df = 2 (P = 0 Z = 0.78 (P = 0.4) 5 13 18 0.222, df = 1 (P = 0	6858 0.37); I <sup>2</sup> = 6) ents (959 Aspirin Total 2492 3286 1080 6858 0.01); I <sup>2</sup> = 7 328 5778 0.64); I <sup>2</sup> = 0	3 0% 20% 26 26 26 26 26 26 26 26	6863 dence i in 2504 3278 1081 6863 2504 3278 5782	100.0% 100.0% nterval 17.1% 32.4% 50.5% 17.1% 32.4% 49.5%	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 29.41 [1.75, 493.60] 1.23 [0.73, 2.05] 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 0.69 [0.38, 1.26]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% Cl
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Teta-analysis of fat Study or Subgroup COMPASS 2018 /OYAGER 2020 NAVE 2007 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: 3.1.2 NOAC Group COMPASS 2018 /OYAGER 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Heterogeneity: Chi <sup>2</sup> =	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 32 8.54, df = 2 (P = 0.4 5 13 14 32 8.54, df = 2 (P = 0.4) 5 13 13 14 0.22, df = 1 (P = 0.2) 13 14 13 13 14 13 14 13 14 13 14 13 13 14 13 13 14 13 14 13 14 13 14 13 14 13 14 13 14 13 13 14 13 14 13 14 13 14 13 13 13 13 13 13 14 13 13 13 13 13 13 13 13 13 13	6858 0.37); I <sup>#</sup> = 6) ents (95% Aspirin Total 2492 3286 1080 6858 0.01); I <sup>#</sup> = 7 3296 5778 0.64); I <sup>#</sup> = (3)	3 0% 6 confi <u>Aspin</u> <u>Events</u> 9 17 0 26 7% 26 17 26 17 26	6863 dence i in 2504 3278 1081 6863 2504 3278 5782	100.0% 100.0% nterval <u>Weight</u> 17.1% 32.4% 50.5% 17.1% 32.4% 49.5%	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 29.41 [1.75, 493.60] 1.23 [0.73, 2.05] 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 0.76 [0.37, 1.57] 0.69 [0.38, 1.26]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Teta-analysis of fat Study or Subgroup COMPASS 2018 /OYAGER 2020 NAVE 2007 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 32 8.54, df = 2 (P = 0 Z = 0.78 (P = 0.42 5 13 14 0.22, df = 1 (P = 0.22) 13 14 13 14 13 14 25 13 14 25 13 14 27 20 20 20 20 20 20 20 20 20 20	6858 0.37); I <sup>2</sup> = 6) ents (95% Aspirin Total 2492 3286 1080 6858 0.01); I <sup>2</sup> = 7 3286 5778 0.64); I <sup>2</sup> = (3)	3 12 0% % confi Aspin Events 9 17 0 26 7% 9 17 26 17 26 17 26 17 26	6863 dence i in 2504 3278 1081 6863 2504 3278 5782	100.0% 100.0% Interval Weight 17.1% 32.4% 0.9% 50.5% 17.1% 32.4% 49.5%	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 29.41 [1.75, 493.60] 1.23 [0.73, 2.05] 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 0.69 [0.38, 1.26]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Teta-analysis of fat Study or Subgroup COMPASS 2018 /OYAGER 2020 AVAVE 2007 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Fost for overall effect:	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 32 8.54, df = 2 (P = 0 Z = 0.78 (P = 0.43) 5 13 18 0.22, df = 1 (P = 0.23) 2 = 1.20 (P = 0.23)	6858 0.37); I <sup>2</sup> = ents (95 <sup>c</sup> Aspirin Total 2492 3286 1080 6858 0.01); I <sup>2</sup> = 7 3296 5778 0.64); I <sup>2</sup> = (9 12636	3 12 0% 6 confi Aspin Events 9 17 0 26 17 26 18 18 12 12 12 12 12 12 12 12 12 12	6863 dence i in <u>Total</u> 2504 3278 1081 6863 2504 3278 5782 12645	100.0% 100.0% Interval Weight 17.1% 32.4% 0.9% 50.5% 17.1% 32.4% 49.5% 100.0%	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 29.41 [1.75, 493.60] 1.23 [0.73, 2.05] 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 0.69 [0.38, 1.26] 0.96 [0.65, 1.42]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: ieta-analysis of fat Study or Subgroup OMPASS 2018 COMPASS 2018 COMPASS 2017 Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: OMPASS 2018 ACYAGER 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Fotal events Fotal (95% CI) Fotal events	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 32 8.54, df = 2 (P = 0 Z = 0.78 (P = 0.43) 5 13 18 0.22, df = 1 (P = 0 Z = 1.20 (P = 0.23) 50	6858 0.37); I <sup>2</sup> = 6) ents (95' Aspirin Total 2492 3286 1080 6858 0.01); I <sup>2</sup> = 7 329 2492 3286 5778 0.64); I <sup>2</sup> = (0) 12636	3 12 0% 6 confi Aspin Events 9 17 0 26 7% 9 17 0 26 17 26 17 26 17 26 52	6863 dence i in <u>Total</u> 2504 3278 1081 6863 2504 3278 5782	100.0% 100.0% Interval Weight 17.1% 32.4% 0.9% 50.5% 17.1% 32.4% 49.5% 100.0%	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 29.41 [1.75, 493.60] 1.23 [0.73, 2.05] 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 0.76 [0.38, 1.26] 0.96 [0.65, 1.42]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Test for overall effect: Test for overall effect: Test for overall effect: COMPASS 2018 AVAVE 2007 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: COMPASS 2018 AVAVE 2007 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> =	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 32 8.54, df = 2 (P = 0 Z = 0.78 (P = 0.4) 5 13 18 0.22, df = 1 (P = 0 Z = 1.20 (P = 0.2) 8.35, df = 4 (P = 0	6858 0.37); I <sup>2</sup> = 6) ents (959 Aspirin Total 2492 3286 1080 6858 0.01); I <sup>2</sup> = 7 3286 5778 0.64); I <sup>2</sup> = 0 12636 0.03); I <sup>2</sup> = 0	3 12 0% 6 confi Aspin Events 9 17 0 26 7% 9 17 0 26 17 26 17 26 52 52 52	6863 dence i in <u>Total</u> 2504 3278 1081 6863 2504 3278 5782 12645	100.0% 100.0% Interval Weight 17.1% 32.4% 9% 50.5% 17.1% 32.4% 49.5% 100.0%	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 29.41 [1.75, 493.60] 1.23 [0.73, 2.05] 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 0.69 [0.38, 1.26] 0.96 [0.65, 1.42]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
Fotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Teta-analysis of fat Study or Subgroup 3.1.1 AC Subgroup COMPASS 2018 AOYAGER 2020 MAVE 2007 Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: 3.1.2 NOAC Group COMPASS 2018 AOYAGER 2020 Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Fotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: Fotal (95% CI)	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 32 8.54, df = 2 (P = 0.4) 5 13 13 0.22, df = 1 (P = 0.4) 5 13 0.22, df = 1 (P = 0.2) 50 8.35, df = 4 (P = 0.4) 50 8.35, df = 4 (P = 0.4) 50 50 50 50 50 50 50 50 50 50	6858 0.37); I <sup>2</sup> = 6) ents (95% Aspirin Total 2492 3286 1080 6858 0.01); I <sup>2</sup> = 7 3296 5778 0.64); I <sup>2</sup> = (0) 12636 0.08); I <sup>2</sup> = 5	3 12 0% 6 confi <u>Aspin</u> <u>Events</u> 9 17 0 26 7% 26 17 26 17 26 17 26 17 26 52 52 52	6863 dence i in 2504 3278 1081 6863 2504 3278 5782 12645	100.0% 100.0% Interval Weight 17.1% 32.4% 0.9% 50.5% 17.1% 32.4% 49.5% 100.0%	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 29.41 [1.75, 493.60] 1.23 [0.73, 2.05] 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 0.69 [0.38, 1.26] 0.96 [0.65, 1.42]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M.H, Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Fest for overall effect: eta-analysis of fat <u>Study or Subgroup</u> (01/1 AC Subgroup (01/2 Comparison of the subgroup) (01/2 Comparis	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1 tal bleeding ev Anticoagulant+ Events 5 13 14 32 8.54, df = 2 (P = 0 Z = 0.78 (P = 0.43) 5 13 0.22, df = 1 (P = 0 Z = 1.20 (P = 0.23) 50 8.35, df = 4 (P = 0 Z = 0.20 (P = 0.84) erences: Chi <sup>2</sup> = 2	6858 0.37); I <sup>2</sup> = 6) ents (959 Aspirin Total 2492 3286 1080 6858 0.01); I <sup>2</sup> = 7 3286 5778 0.64); I <sup>2</sup> = (0) 12636 0.08); I <sup>2</sup> = 5 0.02, df = 1	3 12 0% 6 confi Aspin Events 9 17 0 7% 26 7% 9 17 26 17 17 17 26 17 17 17 17 17 17 17 17 17 17	6863 dence i in 2504 3278 1081 6863 2504 3278 5782 12645	100.0% 100.0% Interval Weight 17.1% 32.4% 0.9% 50.5% 17.1% 32.4% 49.5% 100.0%	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 29.41 [1.75, 493.60] 1.23 [0.73, 2.05] 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 0.69 [0.38, 1.26] 0.96 [0.65, 1.42]	0.01 0.1 1 10 10 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M-H, Fixed, 95% CI
initial (95% CI)         initial events         leterogeneity: Chi <sup>2</sup> =         rest for overall effect:         eta-analysis of fat         itudy or Subgroup         ch1 AC Subgroup         ch1 AC Subgroup         ch1 AC Subgroup         ch1 AC Subgroup         ch4 ASS 2018         OYAGER 2020         VAVE 2007         subtotal (95% CI)         otal events         leterogeneity: Chi <sup>2</sup> =         est for overall effect:         otal events         leterogeneity: Chi <sup>2</sup> =         est for overall effect:         otal events         leterogeneity: Chi <sup>2</sup> =         est for overall effect:         otal events         leterogeneity: Chi <sup>2</sup> =         est for overall effect:         otal events         leterogeneity: Chi <sup>2</sup> =         est for overall effect:         est for overall effect:	20 2.00, df = 2 (P = Z = 1.40 (P = 0.1) tal bleeding ev Anticoagulant+ Events 5 13 14 32 8.54, df = 2 (P = 0 Z = 0.78 (P = 0.42) 5 13 18 0.22, df = 1 (P = 0 Z = 1.20 (P = 0.22) 50 8.35, df = 4 (P = 0 Z = 0.20 (P = 0.84) erences: Chi <sup>a</sup> = 2	6858 6858 $0.37); I^{2} = 6)$ ents (95% Aspirin Total 2492 3286 1080 6858 $0.01); I^{2} = 7$ 2492 3286 5778 $0.64); I^{2} = (0)$ 12636 $0.08); I^{2} = 5$ $0.08); I^{2} = 5$	3 12 12 13 14 15 16 17 17 17 17 17 17 17 17 17 17	6863 dence i in Total 2504 3278 1081 6863 2504 3278 5782 12645 0. I <sup>a</sup> = 50	100.0% 100.0% Interval <u>Weight</u> 17.1% 32.4% 0.9% 50.5% 17.1% 32.4% 49.5% 100.0%	3.36 [0.32, 12.24] 1.67 [0.82, 3.42] (CI) 0.82–3.42; p= Odds Ratio M-H, Fixed, 95% CI 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 29.41 [1.75, 493.60] 1.23 [0.73, 2.05] 0.56 [0.19, 1.67] 0.76 [0.37, 1.57] 0.69 [0.38, 1.26] 0.96 [0.65, 1.42]	0.01 0.1 1 10 11 Favours Anticoagulant+Aspirin Favours Aspirin =0.16; I <sup>2</sup> =0%). Odds Ratio M.H, Fixed, 95% CI

Figure 3. Meta-analysis of bleeding events (secondary outcomes) of clinical trials.

used aspirin and rivaroxaban for antiplatelet/anticoagulant therapy, it is still unclear whether similar curative effect would be verified by other categories antiplatelet agents (P2Y12 inhibitors, phosphodiesterase inhibitors, glycoprotein IIb/IIIa receptor inhibitors) and DOACs (direct thrombin inhibitors). The efficacy/safety of rivaroxaban plus aspirin in patients with PAD compared with dual antiplatelet treatment is unknown. We hope that the questions we have raised will be addressed soon by additional trails.

# Conclusions

The results of our meta-analysis indicate that oral anticoagulant plus antiplatelet therapy for PAD may improve acute limb ischemia, major amputation, or stroke risk compared with antiplatelet therapy alone. The risk of myocardial infarction, death, fatal bleeding or intracranial hemorrhage remains debatable. However, it was evident that substantially more major bleeding events occurred in the oral anticoagulant plus antiplatelet group.

#### **Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

#### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

#### ORCID iD

Tao Tang ( https://orcid.org/0000-0002-9476-2684

#### References

- Kersting J, Kamper L, Das M, Haage P. Guideline-oriented therapy of lower extremity Peripheral Artery Disease (PAD)—Current data and perspectives. *Rofo.* 2019;191(4):311-322.
- Frank U, Nikol S, Belch J, et al. ESVM Guideline on peripheral arterial disease. VASA. 2019;48(Suppl 102):1-79.
- Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. N Engl J Med. 2020;382(21):1994-2004.
- Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebocontrolled trial. *Lancet*. 2018;391(10117):219-229.
- Anand S, Yusuf S, Xie C, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. N Engl J Med. 2007; 357(3):217-227.
- Oremus M, Wolfson C, Perrault A, Demers L, Momoli F, Moride Y. Interrater reliability of the modified Jadad quality scale for systematic reviews of Alzheimer's disease drug trials. *Dement Geriatr Cogn Disord*. 2001;12(3):232-236.
- Fowkes FG, Aboyans V, Fowkes FJ, McDermott MM, Sampson UK, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol*. 2017;14(3):156-170.

- Hamady M, Muller-Hulsbeck S. European Society for Vascular Surgery (ESVS) 2020 clinical practice guidelines on the management of acute limb ischaemia; a word of caution!. *CVIR Endovasc.* 2020;3(1):31.
- 9. Hess CN, Huang Z, Patel MR, et al. Acute limb ischemia in peripheral artery disease. *Circulation*. 2019;140(7):556-565.
- Olinic DM, Stanek A, Tataru DA, Homorodean C, Olinic M. Acute Limb Ischemia: an update on diagnosis and management. *J Clin Med.* 2019;8(8):1215.
- Wang JC, Kim AH, Kashyap VS. Open surgical or endovascular revascularization for acute limb ischemia. *J Vasc Surg.* 2016; 63(1):270-278.
- 12. Bonaca MP, Gutierrez JA, Creager MA, et al. Acute limb ischemia and outcomes with vorapaxar in patients with peripheral artery disease: results from the trial to assess the effects of vorapaxar in preventing heart attack and stroke in patients with Atherosclerosis-Thrombolysis in Myocardial Infarction 50 (TRA2 degrees P-TIMI 50). *Circulation*. 2016;133(10):997-1005.
- Sadat U, Hayes PD, Varty K.Acute limb ischemia in pediatric population secondary to peripheral vascular cannulation: literature review and recommendations. *Vasc Endovascular Surg.* 2015;49(5-6):142-147.
- Santistevan JR.Acute limb ischemia: an emergency medicine approach. *Emerg Med Clin North Am.* 2017;35(4):889-909.
- Lim S, Javorski MJ, Halandras PM, Kuo PC, Aulivola B, Crisostomo P. Epidemiology, treatment, and outcomes of acute limb ischemia in the pediatric population. *J Vasc Surg.* 2018;68(1): 182-188.
- Enezate TH, Omran J, Mahmud E, et al. Endovascular versus surgical treatment for acute limb ischemia: a systematic review and metaanalysis of clinical trials. *Cardiovasc Diagn Ther*. 2017; 7(3):264-271.
- Wang SK, Murphy MP, Gutwein AR, et al. Perioperative outcomes are adversely affected by poor pretransfer adherence to acute limb ischemia practice guidelines. *Ann Vasc Surg.* 2018; 50:46-51.
- Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med.* 2011; 365(8):699-708.
- Tsu LV, Dager WE. Safety of new oral anticoagulants with dual antiplatelet therapy in patients with acute coronary syndromes. *Ann Pharmacother*. 2013;47(4):573-577.
- 20. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med.* 2012; 366(1):9-19.
- Debus ES, Nehler MR. The Voyager PAD Trial—New Path for Post-revascularisation PAD Patients. *Eur J Vasc Endovasc Surg.* 2020;59(5):699-700.
- 22. Olinic DM, Tataru DA, Homorodean C, Spinu M, Olinic M. Antithrombotic treatment in peripheral artery disease. *VASA*. 2018;47(2):99-108.
- Koutsoumpelis A, Argyriou C, Tasopoulou KM, Georgakarakos EI, Georgiadis GS. Novel oral anticoagulants in peripheral artery disease: current evidence. *Curr Pharm Des.* 2018; 24(38):4511-4515.