

# Antithrombotic treatment in lower extremity artery disease: A Systematic Review of the literature

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## Abstract:

**Introduction:** Lower extremity artery disease (LEAD) affects more than 200 million people worldwide and it is considered as a predictor of mortality. The aim of the study was to assess the effectiveness of antithrombotic therapy in preventing major adverse cardiovascular events (MACE) and major adverse limb events (MALE) as well as their safety in terms of bleeding.

**Methods:** We performed a systematic review of the literature including Randomized Controlled Trials (RCTs), meta-analyses and guidelines for antithrombotic therapy in patients with stable LEAD, from 1996-2020. Data extracted from the eligible papers were summarized based on year of release, type of antithrombotic therapy administered and compared, number of patients and percentage of statistically significant effects of antithrombotics on the primary endpoints of the studies (MACE, MALE) as well as their safety (bleeding).

**Results:** 10 RCTs, 5 meta-analyses and 4 guidelines met the inclusion criteria. Single antiplatelet therapy (SAPT) has a limited effect and it is not recommended in patients with asymptomatic LEAD. On the contrary, in symptomatic LEAD, SAPT is effective in preventing MACE with mild evidence towards superiority of clopidogrel versus aspirin. The use of dual antiplatelet therapy (DAPT) has no strong evidence of superiority in stable LEAD, while it is associated with an increased risk of major bleeding. The combination of coumadins and antiplatelets failed to show any benefit, while it is associated with an increased fatal-bleeding risk and is therefore contraindicated. The combination of a low dose of rivaroxaban 2.5mg twice daily, with aspirin is a novel strategy in antithrombotic treatment for LEAD with a potential application in patients with multivascular disease. The risk of ischemic complications (MACE, MALE) and the overall mortality seems to be reduced without increasing the risk of fatal bleeding.

**Conclusion:** SAPT is effective in symptomatic LEAD, while the use of dual antiplatelet therapy (DAPT) is not recommended at the moment. The combination of a very low dose rivaroxaban with aspirin seems promising in the management of LEAD with a possible application in patients with multivascular disease. Future guidelines should assess its role.

## INTRODUCTION

Lower Extremity Artery Disease (LEAD) is an atherosclerotic chronic disease that progresses gradually, causing narrowing or blockage of the vascular lumen of the peripheral lower limbs arteries.<sup>1,2</sup> The term LEAD was first introduced to European Guidelines, distinguishing it from Peripheral Artery Disease (PAD), which includes all arteries except the coronary arteries, aorta and intracranial arteries.<sup>2</sup> The American Heart Association has no specific term for LEAD as it defines PAD as peripheral artery disease of the upper and lower extremities.<sup>3</sup> In the present review, according to the recent European guidelines<sup>2</sup>, the term LEAD refers to the patients with PAD of the lower extremities.

More than 200 million people live with LEAD worldwide,<sup>4</sup> including almost 15% of people over the age of 70.<sup>5</sup> LEAD is associated with all major atherosclerotic risk factors such as smoking,<sup>6</sup> hypertension<sup>7</sup> and dyslipidemia.<sup>7,8</sup> The first and main

clinical symptom of the disease is intermittent claudication<sup>1</sup> which can progressively lead to critical limb ischemia (CLI) and amputation.<sup>9</sup> In addition to local manifestations in the lower extremities, LEAD is clinically equivalent to Coronary Artery Disease (CAD) in terms of risk of vascular death.<sup>1</sup> Atherosclerotic disease affects many vascular beds, making patients with LEAD at high risk for acute myocardial infarction, stroke, and vascular death.<sup>10,11</sup> LEAD is a prognostic indicator of poor mortality.<sup>5,7</sup>

The goal of LEAD treatment is to treat lower extremity symptoms, improve quality of life, and reduce the risk of major cardiovascular events as well as limb events.<sup>11</sup> Measures, such as smoking cessation, healthy eating, regular exercise and weight loss, along with the use of drugs, such as antihypertensives, antilipidemics, antidiabetics and anticoagulants, are used in this direction.<sup>2</sup> The role of antithrombotic therapy, which includes antiplatelets and anticoagulants, in patients with LEAD is double. On one hand, it aims to reduce overall cardiovascular death or morbidity due to stroke or acute myocardial infarction and on the other hand, it aims to prevent thromboembolic complications from peripheral arteries. In addition, it is used after endovascular or open peripheral revascularization surgery to maintain artery or conduit patency.<sup>1</sup>

During the last decades interesting clinical trials, reviews and meta-analyses as well as guidelines for antithrombotic treatment in LEAD patients have been published.<sup>2</sup> Nevertheless, the optimal antithrombotic regimen for long-term use in patients with stable LEAD remains unclear.

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The aim of our study was to assess the effectiveness of antithrombotic therapy in reducing major adverse cardiovascular events (MACE) and major adverse limb events (MALE) as well as their safety in terms of bleeding.

## METHODOLOGY

A standard online search of the literature was conducted on PubMed, ScienceDirect and Google Scholar. Various combinations of the following keywords were used: 'lower extremity artery disease', 'peripheral arterial disease', 'antiplatelet therapy', 'anticoagulant therapy', 'antithrombotic therapy', 'aspirin', 'clopidogrel', 'ticagrelor', 'vorapaxar', 'single antiplatelet therapy', 'dual antiplatelet therapy', 'single antiplatelet therapy versus placebo', 'single antiplatelet therapy versus single antiplatelet therapy', 'single antiplatelet therapy versus dual antiplatelet therapy', 'anticoagulant plus antiplatelet therapy versus antiplatelet therapy', 'coumadins', 'novel oral anticoagulants', 'direct oral anticoagulants', 'anti-Xa factor', 'guidelines', 'clinical trials', 'literature reviews', 'meta-analyses'.

This paper is based on an investigation of literature data and contains trials, reviews and meta-analyses conducted over the past 25 years. It does not include any animal or human studies performed by the author. The inclusion criteria were the following:

1. Randomized Controlled Trials (RCTs)
2. Meta-analyses on the antithrombotic treatment and LEAD
3. Guidelines

Antithrombotic therapy was administered to patients with

stable LEAD, either symptomatic or asymptomatic. Stable LEAD stands for patients with none or no recent (6 months) intravascular or open peripheral artery revascularization surgery and no progressive signs of critical limb ischemia. Studies have recorded results such as: (i) Major Adverse Cardiovascular Events (MACE) including Myocardial Infarction (MI), stroke and cardiovascular death (ii) Major Adverse Limb Events including Acute Limb Ischaemia (ALI), Chronic Limb Ischaemia (CLI) and lower limb amputation, and (iii) major or life-threatening and minor bleeding.

Between November 1996 and November 2019 the studies included are:

8 RCTs (table 1)

5 Meta-analyses (table 2)

4 Guidelines of International (table 3) and Greek Societies (table 4):

- European Society of Cardiology - European Society for Vascular Surgery (ESC-ESVS)
- Society for Vascular Surgery (SVS)
- American College of Cardiology / American Heart Association (ACC / AHA)
- Greek guidelines for LEAD from the Institute for the Study and Education in Thrombosis and Antithrombotic Treatment (IMETHA).

The review excluded patients with Cerebrovascular/Carotid Artery Disease and Coronary Artery Disease (CAD). Results regarding antithrombotic therapy come from analysis of clinical trials or subgroups of patients with LEAD.

## RESULTS

### Randomized Controlled Trials (RCTs)

Randomized Controlled Trials	Patients	Treatment	Results
<b>POPADAD</b> <sup>12</sup>	1276 (asymptomatic LEAD and diabetes)	Aspirin 100 mg vs placebo or antioxidant	MACE: HR: 0.98, (0.76-1.26), p = 0.86 Bleeding (GI): HR: 0.90, (0.53-1.52), p = 0.69
<b>AAA</b> <sup>13</sup>	3350 (asymptomatic LEAD)	Aspirin 100 mg vs placebo	MACE: HR: 1.03, (0.84-1.27), p = NS Major bleeding: HR: 1.71, (0.99-2.97), p = NS
<b>CAPRIE</b> <sup>14</sup>	6452 (LEAD subgroup)	Clopidogrel 75mg vs Aspirin 325mg	MACE: HR: 0.76 (0.64-0.91), p = 0.003 Bleeding (GI): HR: 0.56 (0.52-0.93), p=0.05
<b>EUCLID</b> <sup>15</sup>	13885	Ticagrelor 90mg x2 vs Clopidogrel 75mg	MACE: HR: 1.02 (0.92-1.13), p = 0.65 MALE: HR: 1.03 (0.79-1.33), p = 0.85 Major bleeding: HR: 1.10 (0.84-1.43), p = 0.49
<b>CHARISMA</b> <sup>16</sup>	3096 (LEAD subgroup)	Clopidogrel 75mg plus Aspirin vs Aspirin alone	MACE: HR: 0.85 (0.66-1.08), p = 0.18 MALE: 3.8% vs 5.1%; p = 0.07 Major bleeding: HR: 0.97 (0.56-1.66), p = 0.90 Minor bleeding: HR: 1.62 (1.27-2.08), p < 0.001
<b>TRA2_P-TIMI 50</b> <sup>17</sup>	3787 (LEAD subgroup)	Vorapaxar+ Aspirin/ Clopidogrel vs Aspirin/ Clopidogrel	MACE: HR: 0.94 (0.78-1.14), p = 0.53 MALE: HR: 0.58 (0.39-0.86), p = 0.006 Moderate or major bleeding: HR: 1.62 (1.21-2.18), p = 0.001
<b>TRACER</b> <sup>18</sup>	936 (LEAD subgroup- patients with ACS)	Vorapaxar 2.5 mg vs placebo	MACE: HR: 0.85 (0.64-1.13), p = 0.865 Bleeding: HR: 1.47 (0.89-2.45), p = 0.921
<b>WAVE</b> <sup>19</sup> *	2161	Coumadins (INR target 2-3) + antiplatelet vs antiplatelet	MACE: HR: 0.92 (0.73-1.16), p = 0.48 MALE: HR: 0.96 (0.63-1.47), p = 0.86 Life-threatening bleeding: RR: 3.41 (1.84-6.35), p < 0.001

**Table 1:** The above table summarizes key data from all the clinical trials in patients with LEAD presented in the review. Values in parentheses are 95% confidence interval

AAA: Aspirin for Asymptomatic Atherosclerosis, ACS: Acute coronary syndrome, CAPRIE: Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events, CHARISMA: Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance, EUCLID: Examining Use of Ticagrelor in Peripheral Artery Disease, GI: gastrointestinal, HR: hazard ratio, NS: not significant, POPADAD: Prevention of Progression of Arterial Disease and Diabetes, RR: risk ratio, TRA2\_P-TIMI 50: Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-Thrombolysis In Myocardial Infarction 50, TRACER: Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome, VKA: Vitamin K antagonist, WAVE: Warfarin Antiplatelet Vascular Evaluation.

\* WAVE trial deals with patients with PAD including LEAD and carotid artery disease

### SAPT and LEAD

Regarding asymptomatic LEAD the role of antiplatelet therapy and aspirin is limited. POPADAD and AAA trial found no difference in MACE and death. As a result, the efficacy of antiplatelet therapy in asymptomatic LEAD is questionable.<sup>12,13</sup> Aspirin monotherapy has long been accepted as the standard of care for patients with symptomatic LEAD.<sup>2,3</sup> This relies heavily on evidence from the Antithrombotic Trialists' Collaboration (ATC)<sup>20</sup> and Berger et al<sup>21</sup> meta-analyses which are analyzed below (table 2) and based on the guidelines, aspirin remains effective in preventing MACE in patients with symptomatic LEAD.<sup>2,3</sup>

The randomized, double-blind, CAPRIE trial showed a reduction of 8.7% (CI: 0.3-16.5%, p = 0.043) in primary end point with clopidogrel treatment in the overall trial and a reduction in MACE by 23.8% in subgroup of symptomatic LEAD patients. The trial showed that clopidogrel is more effective than aspirin in symptomatic LEAD as it was the only subgroup of vascular patients where clopidogrel had statistically significant potency over aspirin.<sup>14</sup>

More recently, the EUCLID trial which was designed exclusively for patients with symptomatic LEAD compared two different thienopyridine agents, ticagrelor and clopidogrel. The trial showed that ticagrelor did not appear to be superior to clopidogrel in reducing MACE and MALE and the bleeding rates were also similar in symptomatic LEAD.<sup>15</sup>

### DAPT and LEAD

The benefit of DAPT with thienopyridine added to aspirin was

first established in patients with CAD after the CURE study.<sup>22</sup> However, the CURE study did not investigate the effects of DAPT in patients with co-occurring LEAD. The combination of clopidogrel and aspirin has been tested in patients with chronic stable vascular disease in multiple vascular beds in the CHARISMA trial.<sup>23</sup> In the subgroup of LEAD patients, DAPT with clopidogrel and aspirin did not show statistically reduction in MACE and MALE while there was an increase in minor bleeding.<sup>16</sup>

Vorapaxar, a protease-activated receptor 1 (PAR-1) inhibitor, was added in TRA 2 ° P-TIMI 50 and TRACER trials as a second antiplatelet agent to the standard antiplatelet care. In the subgroup of LEAD patients in both trials, there was no reduction in the rates of MACE, while simultaneously vorapaxar was associated with higher rates of bleeding and it is not used in the clinical practice.<sup>17,18,24</sup>

### Coumadins and LEAD

Building upon the observation that anticoagulant therapy served as prevention in patients with cardiovascular disease,<sup>25</sup> coumadins in combination with antiplatelet therapy were evaluated in patients with LEAD. Specifically, in the WAVE trial patients with stable PAD including LEAD and carotid artery disease were randomized and it was shown that the combination of coumadins with antiplatelet therapy compared to SAPT did not reduce MACE or MALE while it was associated with statistically significantly more life-threatening bleeding.<sup>19</sup>

### Meta-analyses

Meta-analyses of RCTs	Patients	Treatment	Results
ATC <sup>20</sup>	9214 (42 RCTs)	Antiplatelet vs placebo	MACE: antiplatelets 5.8% vs placebo 7.1%, 23% odds reduction (SE 8%) , p=0.004
Berger et al. <sup>21</sup>	5269 (18 RCTs)	Aspirin 100-1500mg and/without dipyridamole vs placebo	MACE: HR: 0.88 (0.76-1.04), p = 0.13 Major bleeding: HR: 0.99, (0.66-1.50), p = 0.98
Katsanos et al. <sup>26</sup>	34518 (49 RCTs)	Various antiplatelet agents as monotherapy or plus aspirin vs placebo	MACE: Clopidogrel: RR: 0.72, (0.58-0.91), NNT = 80, Ticlopidine: RR: 0.75, (0.58-0.96), NNT = 87, Clopidogrel and aspirin: RR: 0.78, (0.61-0.99), NNT = 98, Ticagrelor and aspirin: RR: 0.67, (0.46-0.96), NNT = 66 MALE: Clopidogrel and aspirin RR: 0.68, (0.46-0.99) compared to aspirin, NNT = 94 Major bleeding: Ticlopidine: RR: 5.03, (1.23-39.6), NNH = 25, Vorapaxar: RR: 1.80, (1.22-2.69), NNH = 130, Clopidogrel and aspirin: RR: 1.48, (1.05-2.10), NNH = 215
Navarese et al. <sup>27</sup>	65675 (10 RCTs)	DAPT vs aspirin (DAPT: Clopidogrel+aspirin 36353/60794 patients, ticagrelor+aspirin 1 trial, vorapaxar+aspirin 1 trial)	MACE: Mortality: RR: 0.89, (0.86-0.92), p <0.001 MALE: Peripheral revascularization: RR: 0.80, (0.69-0.92), p = 0.002 Major bleeding: RR: 1.21, (0.87-1.68) p = 0.26
Savarese et al. <sup>28</sup> *	30447 (7 RCTs)	SAPT or DAPT or anticoagulant vs SAPT/placebo	MACE: myocardial infarction: RR: 0.98, (0.87-1.11), pQ = 0.137, Stroke: RR: 0.82, (0.70-0.97), pQ = 0.471, Cardiovascular death: RR: 0.97, (0.86-1.08), pQ = 0.112, Overall mortality: RR: 0.93, (0.86-1, 01), pQ = 0.126 MALE: Limb revascularization: RR: 0.89, (0.83-0.94), pQ = 0.367, Limb amputation: RR: 0.63, (0.46-0.86), pQ = 0.959 Major bleeding: RR: 1.23, (1.04-1.44), pQ = 0.121

**Table 2:** The above table summarizes key data from the meta-analyses in patients with LEAD.

Values in parentheses are 95% confidence interval

ATC: Antithrombotic trialists'collaboration, SE: standard error, NNT: Number-needed-to-treat, NNH: Number-needed-to-harm.

\* Savarese et al. meta-analysis uses p-value at Q statistic (pQ) to test heterogeneity between the treatment effects of different trials (a significant heterogeneity was defined by  $p < 0.10$  at Q statistic).

A large meta-analysis of RCTs conducted in 2002, ATC, examined the efficacy of various antiplatelet agents in symptomatic LEAD patients at high risk for vascular thrombotic events and it showed that MACE was reduced with antiplatelets in comparison with placebo.<sup>20</sup> In a 2009 meta-analysis, Berger et al. examined the efficacy of aspirin with or without dipyridamole versus placebo in cardiovascular events in patients with LEAD with the majority of studies including patients with symptomatic LEAD. Aspirin was found to reduce the risk of non-fatal stroke by 34% without reducing overall cardiovascular mortality.<sup>21</sup> The use of antiplatelet therapy in LEAD patients was investigated in a recent network meta-analysis of Katsanos et al.<sup>26</sup> Data analysis showed that a significant reduction in the risk MACE was observed with monotherapy with clopidogrel,

ticlopidine, DAPT with clopidogrel and aspirin and DAPT with ticagrelor and aspirin, while MALE were reduced with the use of DAPT with clopidogrel and aspirin. Severe bleeding was significantly higher with ticlopidine, vorapaxar and DAPT with clopidogrel and aspirin. Based on the above, clopidogrel monotherapy presented the most favorable benefit-loss profile as it was the safest and most effective antithrombotic agent for LEAD patients and it should be the treatment of choice.<sup>26</sup> Another recent meta-analysis of Navarese et al. examined the benefits of DAPT versus SAPT with aspirin in patients with symptomatic LEAD and showed reduction in MACE and MALE without increase in major bleeding. This meta-analysis supports DAPT in patients with symptomatic PAD but it relies more on observational studies and does not specify the optimal duration of dual platelet therapy.<sup>27</sup> Finally, a meta-analysis of Savarese et al. examined the efficacy and safety of more or less intense antithrombotic therapy in patients with chronic LEAD and it showed that more intensive antithrombotic therapy reduces MALE and stroke with no effect on mortality but with an increased the risk of hemorrhagic episodes.<sup>28</sup>

## PAD Guidelines

### International guidelines

Guidelines on Antithrombotic treatment in stable LEAD			
	ESC/ESVS 2017	AHA/ACC 2016	SVS 2015
Asymptomatic LEAD	Antiplatelet therapy is not recommended (III, A)	Antiplatelet therapy is reasonable in patients with ABI $\leq 0.90$ (IIa, C-EO) The use of SAPT is uncertain in patients with ABI 0.91-0.99 (borderline ABI) (IIb, B-R)	No reported recommendation
Symptomatic LEAD	Long-term SAPT is recommended (Aspirin or Clopidogrel) (I, A) Clopidogrel may be preferred over Aspirin (IIb, B)	SAPT with aspirin (75-325 mg daily) or clopidogrel (75 mg daily) to reduce cardiovascular ischemic risk (I, A)  The usefulness of DAPT (aspirin and clopidogrel) to decrease cardiovascular ischemic events is not well established (IIb, B-R)  Anticoagulation should not be used to decrease cardiovascular ischemic events in patients with LEAD. (III, A)	SAPT with aspirin 75-325 mg (I, A) Clopidogrel 75 mg is recommended as an effective alternative to aspirin (I, B) Warfarin should not be used to decrease the risk of cardiovascular events (I, C)
(A)symptomatic LEAD requiring oral anticoagulant	In patients with LEAD and AF, the use of OAC monotherapy is recommended when the CHA2DS2-VASc score is $> 2$ (I,A) In patients with LEAD and AF the use of OAC should be considered in all other patients. (IIa,B)B In patients with LEAD who have an indication for OAC, such as patients with AF or mechanical prosthetic valve, OACs alone should be considered.(IIa,B)	No reported recommendation	No reported recommendation

**Table 3:** AHA/ACC, ESC and SVS published guidelines regarding antithrombotic therapy in LEAD patients with several similarities and differences.<sup>2,3,29</sup>

Values in parentheses are Class, Level of Evidence

AHA/ACC: American Heart Association/American College of Cardiology, ABI: ankle-brachial index, B-R: level B randomized, C-LD: level C limited data, ESC: European Society for Cardiology, ESVS: European Society for Vascular Surgery, SVS: Society for Vascular Surgery.

All three guidelines provide a category IA recommendation for SAPT with either aspirin or clopidogrel in symptomatic LEAD.<sup>2,3,29</sup> However, there are no well-established data from RCTs regarding the effectiveness of aspirin monotherapy in

symptomatic LEAD and some authors have suggested that the recommendation for aspirin monotherapy should be supported by a lower level of recommendation.<sup>30</sup> The recently updated ESC / ESVS 2017 guidelines indicate that clopidogrel may

be preferred to aspirin based on level B documentation.<sup>2</sup>

The guidelines generally do not recommend full-dose anti-coagulant therapy to reduce ischemic attacks in patients with stable LEAD without any other indication for anticoagulant therapy. For the first time, ESC guidelines recommend OAC monotherapy in symptomatic or asymptomatic LEAD when there is an indication for OAC.<sup>2</sup> Each of these guidelines was published prior to the publication of the COMPASS study.<sup>31,32</sup> Therefore, the role of aspirin and very low-dose rivaroxaban

in patients with symptomatic LEAD was not considered during their preparation.

**IMETHA**

In March 2016, IMETHA which stands for Institute for the Study and Education in Thrombosis and Antithrombotic Treatment published the Greek guidelines regarding antithrombotic therapy in LEAD based on international guidelines over the past 5 years.<sup>1</sup>

Greek Guidelines for Lower Extremity Artery Disease (LEAD) - IMETHA			
Asymptomatic LEAD (ABI >0.90 or <1.0)	Antiplatelet therapy is uncertain ( <i>level of evidence low</i> )	It is not recommended the use of DAPT with clopidogrel+aspirin	It is not recommended adding coumadin anticoagulants to antiplatelet therapy ( <i>level of evidence high</i> )
Asymptomatic LEAD (ABI ≤ 0.90)	Antiplatelet therapy with aspirin(75-150mg) or clopidogrel 75mg daily is reasonable ( <i>level of evidence medium</i> )	DAPT is not superior to SAPT regarding MACE ( <i>level of evidence low</i> ) and it increases bleeding risk ( <i>level of evidence high</i> )	
Symptomatic LEAD	1) Lifelong SAPT ( <i>level of evidence high</i> ) with clopidogrel 75mg daily or low-dose aspirin (75-150mg daily) ( <i>level of evidence medium</i> ) 2) Cilostazol 100 mg twice daily on top of antiplatelet therapy increases the walking distance ( <i>level of evidence medium</i> )		

**Table 5:** In summary, IMETHA’s guidelines are listed in the table above.<sup>1</sup>

IMETHA guidelines as well as global guidelines were published before COMPASS trial’s results. Therefore, the role of the combination treatment with very low-dose rivaroxaban

plus aspirin in symptomatic LEAD patients was not taken into consideration and there is no recommendation regarding DOACs.<sup>1</sup>

**Future perspectives**

Randomised Controlled Trials	Patients	Treatment	Results
<b>COMPASS PAD</b> <sup>32</sup> *	7470	1° part: Rivaroxaban 2.5mg x2 + Aspirin vs Aspirin + placebo	MACE: HR: 0.72 (0.57–0.90), p = 0.005
			MALE: HR: 0.54 (0.35–0.84), p = 0.005
		2° part: Rivaroxaban 5mg x2 vs Aspirin + placebo	Major bleeding: HR: 1.61 (1.12–2.31), p = 0.009
			MACE: HR: 0.86 (0.69–1.08), p = 0.19
<b>VOYAGER PAD</b> <sup>33</sup> **	6564	Rivaroxaban 2.5mg x2 + Aspirin vs Aspirin+placebo	MALE: HR: 0.63 (0.41–0.96), p = 0.03
			Major bleeding: HR: 1.68 (1.17–2.40), p = 0.004
			Primary efficacy outcome*** MACE, MALE: HR: 0.85 (0.76–0.96), p = 0.009
			Principal safety outcome: TIMI major bleeding: HR: 1.43 (0.97–2.10), p = 0.07

**Table 6:** The above table summarizes key data from all the clinical trials in patients with LEAD presented in the review. Values in parentheses are 95% confidence interval

COMPASS: Cardiovascular Events in Coronary or Peripheral Artery Disease, VOYAGER: Vascular Outcomes Study of ASA Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD

\* COMPASS PAD includes patients with stable LEAD and carotid artery disease

\*\* VOYAGER PAD includes patients with LEAD who underwent lower extremity revascularization

\*\*\* Primary efficacy outcome in VOYAGER PAD stands for MI, stroke, death from cardiovascular causes (MACE) and acute limb ischemia, major amputation for vascular causes (MALE)

Following the success in the treatment of venous thromboembolic disease (VTE), atrial fibrillation (AF) and acute coronary syndrome (ACS), Direct Oral Anticoagulants (DOACs), which target a single agent in the coagulation cataract, were tested in LEAD.<sup>34</sup> The rationale with dual inhibition pathway, which stands for the combination of antiplatelet and very low-dose

rivaroxaban, was first introduced in the ATLAS ACS 2-TIMI 51 in patients with ACS and resulted in a reduction of both CV and all-cause mortality.<sup>34</sup> COMPASS trial confirmed the role of dual inhibition pathway in patients with chronic stable PAD.<sup>32</sup> The overall trial as well as the predetermined subgroup of PAD patients showed that the combination of very low-dose rivar-



oxaban plus aspirin was superior to aspirin alone in decreasing MACE and MALE without increasing the life-threatening bleedings however with an increase in major ones. The net clinical benefit was in favor of the combination antithrombotic therapy (HR 0.72, CI 0.59–0.87,  $p = 0.008$ ) showing a reduction in both mortality and cardiovascular and lower extremity complications compared to aspirin.<sup>31,32,35,36,37</sup> A more recently published trial, which extends the observations of COMPASS in patients with symptomatic LEAD who had undergone lower-extremity revascularization, VOYAGER-PAD, shows that very low-dose rivaroxaban plus aspirin significantly reduces the primary efficacy outcome compared to aspirin alone with no increase in the principal safety outcome of TIMI major bleeding.<sup>33,38</sup> The results of VOYAGER PAD complement those of COMPASS and both trials provide new high quality evidence that this new dual inhibition treatment might be beneficial in the post-intervention lower-extremity revascularization period as well as for life-long use in patients with chronic stable LEAD.<sup>38,39</sup>

## DISCUSSION

LEAD is a common manifestation of atherosclerosis associated with high morbidity and mortality.<sup>32,40</sup> Over the past 25 years, RCTs and meta-analyses have been performed on the best antithrombotic therapy for patients with LEAD. Guidelines recommend SAPT in symptomatic LEAD with mild preference or without preference for the use of clopidogrel in Europe and USA respectively.<sup>2,3</sup> For asymptomatic patients with LEAD, antiplatelet therapy is not recommended in accordance with European guidelines.<sup>2</sup> The indications for DAPT have no strong evidence of superiority<sup>2,3,15,16</sup> while treatment with coumadin and antiplatelet agent has been shown to be insufficient for patients with LEAD, increasing the bleeding risk.<sup>2,19</sup>

The recently published COMPASS and VOYAGER trials, which are not included in the above guidelines, showed a benefit with dual treatment with very low-dose rivaroxaban plus aspirin<sup>32,33,41,42</sup> as it represents the only antithrombotic option to date that has shown a reduction in both cardiovascular and lower extremity complications and overall mortality compared to aspirin.<sup>37,43,44</sup> It seems that the principle of using low-dose drugs targeting two separate pathophysiological 'pathways' may be used as a strategy to maximize the effectiveness of medication and minimize risks, as in the case of using a combination of antihypertensive drugs of different categories which act synergistically.<sup>43</sup> Specifically, dual inhibition pathway applies in patients with LEAD and multivascular disease, and other comorbidities, such as heart failure, chronic kidney disease and diabetes mellitus or previous revascularization or amputation surgery.<sup>45-49</sup>

Although COMPASS trial seems to be a promising regimen against CV death, several limitations of the study should be acknowledged. Firstly, when compared to aspirin, the dual antithrombotic treatment reduces the primary outcome by 1.3% but this comes with the cost of 1.2% increase in major bleeding, while fatal bleeding remains the same.<sup>31,32</sup> Another limitation is the comparison of dual antithrombotic therapy with aspirin and not clopidogrel which is preferred in PAD

patients. According to CAPRIE trial subgroup analysis in PAD patients, clopidogrel offered an absolute reduction of 1.15% against aspirin (RRR 23.8%)<sup>14</sup> similar to the 1.3% offered by the combo aspirin-rivaroxaban treatment.<sup>32</sup> Finally, COMPASS trial applies better to high thrombotic risk patients and it should be avoided in the group of patients with high bleeding risk. Indeed, a careful subgroup analysis might be necessary in order to find these subgroups that will benefit from this treatment.

New diabetes and cardiovascular guidelines from the ESC and EASD included COMPASS results for a combination of low-dose rivaroxaban 2.5mg twice daily and aspirin 100mg once daily in patients with chronic symptomatic lower extremity disease and diabetes when the bleeding risk is not high.<sup>50</sup> Following the COMPASS and VOYAGER trials and the benefits of the dual inhibition treatment, possible revision of the LEAD guidelines should be considered especially in high-risk multivascular patients with comorbidities<sup>46</sup> after further investigation.

A limitation of the review was the inclusion of the WAVE trial<sup>19</sup> in the RCTs regarding anticoagulation and stable LEAD as this RCT incorporates patients with LEAD and carotid artery disease (PAD patients). However the lack of RCTs in the literature regarding coumadins and patients with stable LEAD made the current results of the WAVE trial useful for evaluation. Similarly, another limitation of this review was the fact that COMPASS PAD trial<sup>32</sup> included patients with LEAD and carotid artery disease and that VOYAGER PAD trial<sup>33</sup> included patients with LEAD who had undergone lower-extremity revascularization. However these trials are an essential part of this review as they introduce the dual inhibition pathway and they are considered as two of the most important recent trials in patients with LEAD having probably a major impact on future treatment policies in patients with multivascular disease.

In summary, patients with LEAD are at high risk for MACE and MALE. For decades, antiplatelet monotherapy has been the antithrombotic option with the best evidence for reducing cardiovascular events. Recent data highlight the dual nature of LEAD as both atherosclerotic and thromboembolic disease.<sup>9,32,33</sup> It is necessary to further investigate and probably revise the guidelines for stable LEAD with the inclusion of new data. At the same time, new clinical studies on stable LEAD are needed, such as comparing the combination of low-dose rivaroxaban and aspirin with clopidogrel alone or with a combination of aspirin and clopidogrel or the use of FXI inhibitors as a new anticoagulant, possibly safer than FXa inhibitors with the same efficacy.<sup>51</sup> Ultimately, a better understanding of the mechanisms of action and complications of different combinations of antiplatelets and anticoagulants, as defined by clinical data, will enable the medical community to treat stable LEAD safely and effectively.

SAPT is effective in symptomatic LEAD, while the use of DAPT is not recommended at the moment. The combination of a very low-dose rivaroxaban with aspirin seems promising in the management of LEAD with possible application in patients with multivascular disease. Future guidelines should assess its role.

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