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ORIGINAL ARTICLE
Thrombosis and antithrombotic therapy

Antithrombotic therapy and major adverse limb events in patients with chronic lower extremity arterial disease: systematic review and meta-analysis from the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy in Collaboration with the European Society of Cardiology Working Group on Aorta and Peripheral Vascular Diseases

Gianluigi Savarese [1]*, Martin F. Reiner[2], Alicia Uijl[1,3], Domenico D'Amario[4], Stefan Agewall[5], Dan Atar [5], Iris Baumgartner[6], Claudio Borghi[7], Marco De Carlo[8], Heinz Drexel[9,10,11], Juan Carlos Kaski[12], Keld P. Kjeldsen[13,14], Nils Kucher[15], Lars H. Lund[1], Alexander Niessner[16], Anne Grete Semb[17], Thomas A. Schmidt[18], Patrick Sulzgruber [16], Juan Tamargo[19], Cristiana Vitale[20], Sven Wassmann[21,22], Victor Aboyans[23,24], and Basil S. Lewis[25]

[1]Division of Cardiology, Department of Medicine, Karolinska Institutet, S1:02, 171 76 Stockholm, Sweden; [2]Department of Medicine, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland; [3]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands; [4]Dipartimento di Scienze Cardiovascolari, Fondazione Policlinico A. Gemelli IRCCS, UNIVERSITÀ Cattolica del Sacro Cuore, Largo A.Gemelli 8, 00168 Rome, Italy; [5]Department of Cardiology, Ullevål, Oslo University Hospital, and Institute of Clinical Sciences, Søsterhjemmet, University of Oslo, Oslo, Norway; [6]Division of Angiology, Swiss Cardiovascular Center, Inselspital, Bern University Hospital, 3010 Bern, Switzerland; [7]Medicine and Surgery Science Department, University of Bologna, Via Massarenti 9, 40138, Bologna, Italy; [8]Cardiothoracic and Vascular Department, Azienda Ospedaliero-Universitaria Pisana, Via Paradisa, 2, 56100 Pisa, Italy; [9]Vorarlberg Institute for Vascular Investigation and Treatment, Feldkirch, Austria; [10]Division of Angiology, Swiss Cardiovascular Center, Bern, Switzerland; [11]Drexel University College of Medicine, Philadelphia, PA, USA; [12]Molecular and Clinical Sciences Research Institute, St George's, University of London, Cranmer Terrace, London SW17 0RE, UK; [13]Department of Cardiology, Copenhagen University Hospital (Amager-Hvidovre), Italiensvej 1, DK-2300 Copenhagen, Denmark; [14]Department of Health Science and Technology, The Faculty of Medicine, Aalborg University, Fredrik Bajers Plads 7 D2, DK-9220 Aalborg, Denmark; [15]Clinic for Angiology, University Hospital Zurich, Zurich, Switzerland; [16]Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria; [17]Department of Rheumatology, Preventive Cardio-Rheuma Clinic, Diakonhjemme Hospital, Oslo, Norway; [18]Emergency Department, Bispebjerg and Frederiksberg Hospital, Copenhagen University Hospital, Copenhagen, Denmark; [19]Department of Pharmacology and Toxicology, School of Medicine, Universidad Complutense, CIBERCV, 28040 Madrid, Spain; [20]Department of Medical Sciences, IRCCS San Raffaele, Rome, Italy; [21]Cardiology Pasing, Institutstr. 14, 81241 Munich, Germany; [22]Department of Cardiology, University of the Saarland, Kirrbergerstr. 100, 66421 Homburg/Saar, Germany; [23]Department of Cardiology, Dupuytren University Hospital, 2, Martin Luther King ave, 87000 Limoges, France; [24]Inserm 1094, Limoges School of Medicine, Limoges, France; and [25]Cardiovascular Clinical Research Institute, Lady Davis Carmel Medical Center and the Ruth and Bruce Rappaport School of Medicine, Technion-Israel-Institute of Technology, Haifa, Israel

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Aims The role and selection of antithrombotic therapy to improve limb outcomes in chronic lower extremity artery disease (LEAD) is still debated. We conducted a meta-analysis to examine the efficacy and safety of antithrombotic and more intense antithrombotic therapy on limb outcomes and limb salvage in patients with chronic LEAD.

Methods and results Study inclusion criteria were: enrolment of patients with LEAD, randomized allocation to more vs. less intense antithrombotic therapy [more vs. less intense single-antiplatelet therapy (SAPT); dual-antiplatelet therapy vs. SAPT;

* Corresponding author. Tel: +46 8-517 792 68, Email: gianluigi.savarese@ki.se

dual antithrombotic therapy vs. SAPT or oral anticoagulant]; enrolment of ≥200 patients; reporting of at least one of following outcomes: limb amputation or revascularization. Seven randomized studies enrolling 30 447 patients were included. Over a median follow-up of 24 months, more vs. less intense antithrombotic therapy or placebo significantly reduced the risk of limb revascularization [relative risk (RR) 0.89, 95% confidence interval (CI) 0.83–0.94] and limb amputation (RR 0.63, 95% CI 0.46–0.86), as well as stroke (RR 0.82, 95% CI 0.70–0.97). There was no statistically significant effect on the risk of myocardial infarction (RR 0.98, 95% CI 0.87–1.11), all-cause (RR 0.93, 95% CI 0.86–1.01), and cardiovascular death (RR 0.97, 95% CI 0.86–1.08). Risk of major bleeding increased (RR 1.23, 95% CI 1.04–1.44).

Conclusion In patients with LEAD, more intense antithrombotic therapy reduces the risk of limb amputation and revascularization as well as stroke with an increase in the risk of bleeding events.

Keywords Peripheral artery disease • Cardiovascular disease • Lower extremity artery disease • Anticoagulation • Antiplatelet therapy • Antithrombotic therapy • Bleeding • Meta-analysis

Introduction

Lower extremity artery disease (LEAD) is a disabling disease which affects 40 million people in Europe and 202 million people globally.[1] It is a manifestation of systemic atherosclerosis and is associated with an increased risk of cardiovascular (CV)- and cerebrovascular disease. In Western Europe, annual mortality rate is 3.5 per 100 000 individuals.[1] The rate of lower extremity amputation, a major complication of LEAD, ranges between 120 and 500 per million and is associated with significant morbidity, mortality, and healthcare costs.[1–3]

Arterial thrombosis following atherosclerotic plaque rupture, and subsequent activation of platelets and coagulation,[3,4] is a key event in the pathogenesis of acute and chronic limb-threatening ischaemia, potentially leading to the clinical cascade which results in need for endovascular or surgical revascularization or, when this is unsuccessful, to limb amputation.[5] Current guidelines of the European Society of Cardiology/European Society of Vascular Surgery guidelines (ESC/ESVS) and American Heart Association/American College of Cardiology (AHA/ACC) recommend the use of single-antiplatelet therapy (SAPT) to reduce the risk of myocardial infarction (MI), stroke, and vascular death in patients with symptomatic LEAD (IA recommendation).[1,5] However, there is no recommendation for antithrombotic therapy to reduce major adverse limb events (MALE) in LEAD patients. Indeed, previous trials in LEAD populations were undertaken and powered only for major adverse CV or cerebrovascular events (MACE).[6] Little attention was paid to limb outcomes, a limited number of MALE were reported, and most studies were underpowered to detect the effect of antithrombotic therapies on limb outcomes. The role of more intense antithrombotic therapy in preventing MALE in LEAD patients is currently of major interest, especially in view of the recent Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) and Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trials which support a more intense antithrombotic approach over SAPT.[7,8]

The aim of this study was to evaluate the efficacy and safety of antithrombotic and, especially, more intense antithrombotic therapy in reducing need for acute limb revascularization and amputation in patients with chronic LEAD by a meta-analysis of randomized controlled trials.

Methods

Data sources and search strategy

The meta-analysis was designed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. PubMed and ISI Web of Science databases were searched for articles published until January 2019 combining the following terms [('peripheral artery disease' OR 'peripheral arterial disease' OR 'intermittent claudication') AND ('randomized' OR 'randomised')]. No language restrictions were applied.

Study selection

Study inclusion criteria were: enrolment of patients with LEAD (studies not reporting separately outcomes for patients with LEAD and carotid artery disease were not considered) defined as in Supplementary material online, *Table S1*, randomized allocation to more vs. less intense chronic antithrombotic therapy [more vs. less intense SAPT; dual-antiplatelet therapy (DAPT) vs. SAPT; dual antithrombotic therapy vs. SAPT or oral anticoagulant]; enrolment of more than 200 patients; reporting of at least one of following outcomes: limb amputation or lower limb revascularization. Studies assessing the use of antithrombotic drugs following an acute limb intervention (percutaneous or surgical revascularization) were not considered eligible.

Data extraction and quality assessment

Articles were screened for fulfilment of inclusion criteria by two independent reviewers (G.S. and D.D.A.). The reviewers compared selected trials and discrepancies were resolved by agreement. Corresponding authors were asked to provide full-text articles, if they were not publicly available. From each study, information about methods, year of publication, number of patients in treatment and control arms, duration of follow-up, age, gender, data on prevalence of hypertension, diabetes, coronary artery disease (CAD), hyperlipidaemia, smoking, use of aspirin, and lipid-lowering agents were collected and entered into STATA (version 14.2, StataCorps, College Station, TX, USA) by one author (D.D.A.) and checked by another author (G.S.). The outcomes abstracted were limb amputation and lower limb revascularization, major bleeding, all-cause death, CV death, MI, and stroke. The definition of amputation and

bleeding for the different trials included is reported in Supplementary material online, *Table S2*.

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) method was used to summarize the findings and score the overall quality of evidence.

Data synthesis and analysis

Relative risks (RRs) of the effect of randomized treatments were calculated using the metan routine (STATA Statacorp, version 14.2) to account the probability of events occurring in treatment group vs. control group. Relative risks and 95% confidence intervals (CIs) for each outcome were calculated separately for each trial, with grouped data using the intention-to-treat principle (when applicable). Overall estimates of effect were calculated with a fixed effect model (Mantel–Haenszel method) or a random effects (DerSimonian and Laird) model in presence of non-explainable significant heterogeneity.

The assumption of homogeneity between the treatment effects in different trials was tested by Q statistic and further quantified by I^2 statistic. A significant heterogeneity was defined by a $P < 0.10$ at Q statistic; I^2 ranging from 0% to 40% might indicate not important heterogeneity, from 30% to 60% might represent moderate heterogeneity, from 50% to 90% might indicate substantial heterogeneity, and from 75% to 100% might represent considerable heterogeneity. The significance level for all outcome analyses was set at $P < 0.05$.

Sensitivity analysis

To assess the consistency of outcome meta-analysis results, the influence of each individual study on the summary effect estimate was assessed by the one-study removed sensitivity analysis using the 'metaninf' command (STATA).

To explore the influence of potential effect modifiers on outcomes, random effects meta-regression analyses weighted for the inverse of studies' variances were performed with the 'metareg' command (STATA) to test demographic characteristics of the study population, CV risk factors, and concomitant medications.

Publication bias

To evaluate potential publication bias, Peter's test was performed. The significance level for the publication bias analysis was set at $P < 0.05$.

Results

Characteristics of included trials

The characteristics of included trials are reported in *Table 1* and Supplementary material online, *Table S1*. Of 6273 manuscripts identified in the initial search, 4383 were retrieved for more detailed evaluation after the removal of duplicates. Thereafter, seven randomized controlled trials were finally included, which enrolled 30 447 patients, of which 16 445 randomized to a more intense vs. 14 002 randomized to a less intense antithrombotic therapy regimen or placebo. One trial, COMPASS, evaluated a dual anticoagulant–antiplatelet approach (rivaroxaban + aspirin vs. rivaroxaban or aspirin alone), whereas six trials (24 056 patients) compared different antiplatelet therapy approaches. Median age was 66 (range 64–68) years, 32% were women. Median follow-up was 24 (range 16.5–36) months.

Outcome analysis

Limb amputation and limb revascularization occurred in 0.8% and 9.9% of patients randomized to more intense vs. 1.3% and 11.9% of those enrolled to less intense antithrombotic therapy, respectively. Thus, more intense antithrombotic treatment reduced the risk of limb amputation by 37% (RR 0.63, 95% CI 0.46–0.86) and the risk of limb revascularization by 11% (RR 0.89, 95% CI 0.83–0.94) with no statistical heterogeneity ($pQ = 0.96$ and 0.37; $I^2 = 0.0\%$ and 8.1%, respectively) (*Figure 1*).

Myocardial infarction and stroke occurred in 4.5% and 2.2% of patients allocated to a more intense antithrombotic treatment vs. 4.6% and 2.6% of those randomized to a less intense approach. Thus, although the treatment did not significantly reduce the risk of MI (RR 0.98, 95% CI 0.87–1.11), a significant 18% reduction of risk of stroke was observed in patients treated with a more vs. less intense antithrombotic approach (RR 0.82, 95% CI 0.70–0.97), with no statistical heterogeneity ($pQ = 0.14$ and 0.47; $I^2 = 45.6\%$ and 0.0%, respectively) (*Figure 2*).

As many as 8.4% and 4.9% of patients receiving a more intense treatment vs. 9.0% and 5.0% of those allocated to a less intense antithrombotic approach died from any or CV cause, respectively. Thus, the 7% reduction in risk of all-cause death (RR 0.93, 95% CI 0.86–1.01) induced by a more vs. less intense antithrombotic therapy did not reach statistical significance, and no reduction in risk of CV death was observed (RR 0.97, 95% CI 0.86–1.08), with no statistically significant heterogeneity for both outcomes ($pQ = 0.13$ and 0.11; $I^2 = 44.4\%$ and 46.6%, respectively) (*Figure 3*).

The occurrence of major bleeding was observed in 2.0% of patients treated with more intense vs. 1.6% of those receiving less intense antithrombotic therapy. Thus, a more intense antithrombotic treatment regimen was significantly associated with a 23% increase in risk of major bleeding (RR 1.23, 95% CI 1.04–1.44), with no statistically significant heterogeneity ($pQ = 0.12$; $I^2 = 40.5\%$) (*Figure 4*).

Methodology quality

The assessment of the overall quality of evidence according to the GRADE method is shown in Supplementary material online, *Table S3*. Most reported outcomes were scored with a high level of evidence. We downgraded limb amputation with one point due to moderate risk of imprecision; the total number of events was small which lead to a larger CI compared to the other outcomes. We also downgraded CV death and all-cause death with one point due to publication bias. No publication bias was reported for any of the other outcomes ($P > 0.05$ at Peters' test).

Sensitivity analysis

One-study removed analysis confirmed mostly all the results (Supplementary material online, *Figures S1–S7*). After the removal of the Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) and PEGASUS-TIMI 54 trials, the reduction in risk of stroke induced by a more intense antithrombotic treatment only approximated statistical significance. Additionally, after the removal of EUCLID a more vs. less intense antithrombotic treatment significantly removed the risk of all-cause and CV death. After the removal

Table 1 **Baseline characteristics of studies included in the meta-analysis**

Trials	Treatment arms	Follow-up (months)	Treatment (n)	Control (n)	Age (years)	Females (%)	CAD (%)	Stroke (%)	Revascularization (%)	Smokers (%)	Diabetes (%)	HYLD (%)	HYPT (%)	LLA (%)	Aspirin (%)
CHARISMA[9,10]	Clopidogrel plus low-dose aspirin vs. placebo plus low-dose aspirin	26	1545	1551	66	30	25	9	51	85[a]	36	70	72	85	100
COMPASS[7,11]	Rivaroxaban (2.5 mg b.i.d.) plus aspirin; rivaroxaban (5 mg b.i.d. with aspirin placebo q.d.); aspirin (100 mg o.d. and rivaroxaban placebo b.i.d.)	21	4268	2123	68	28	65	—	32	75[a]	45	—	79	82	100
DAVID[12]	Picotamide vs. aspirin	24	603	606	64	27	19	10	—	71[a]	100	38	57	15	50
EUCLID[13]	Ticagrelor vs. clopidogrel	30	6930	6955	66	28	29	8	57	78[a]	39	76	78	73	67
PEGASUS-TIMI 54[8,14]	Ticagrelor vs. placebo on a background of aspirin	33	739	404	66	22	100	3	34	30[b]	42	81	85	93	100
TRA 2P-TIMI 50[15,16]	Vorapaxar vs. placebo	36	1892	1895	66	29	57	14	62	31[b]	36	87	83	82	88
TRACER[17,18]	Vorapaxar vs. placebo	16.5	468	468	66	26	44	10	—	77[a]	46	78	85	87	96

CAD, coronary artery disease; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management, and Avoidance; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; DAVID, Drug evaluation in Atherosclerotic Vascular disease In Diabetics; EUCLID, Examining Use of Ticagrelor in Peripheral Artery Disease; HYLD, hyperlipidaemia; HYPT, hypertension; LLA, lipid-lowering agents; PEGASUS-TIMI 54, Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54; TRACER, Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome; TRA 2P-TIMI 50, Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischaemic Events (TRA 2P)–Thrombolysis in Myocardial Infarction (TIMI) 50.

[a]Current or former smoker.

[b]Current smoker.

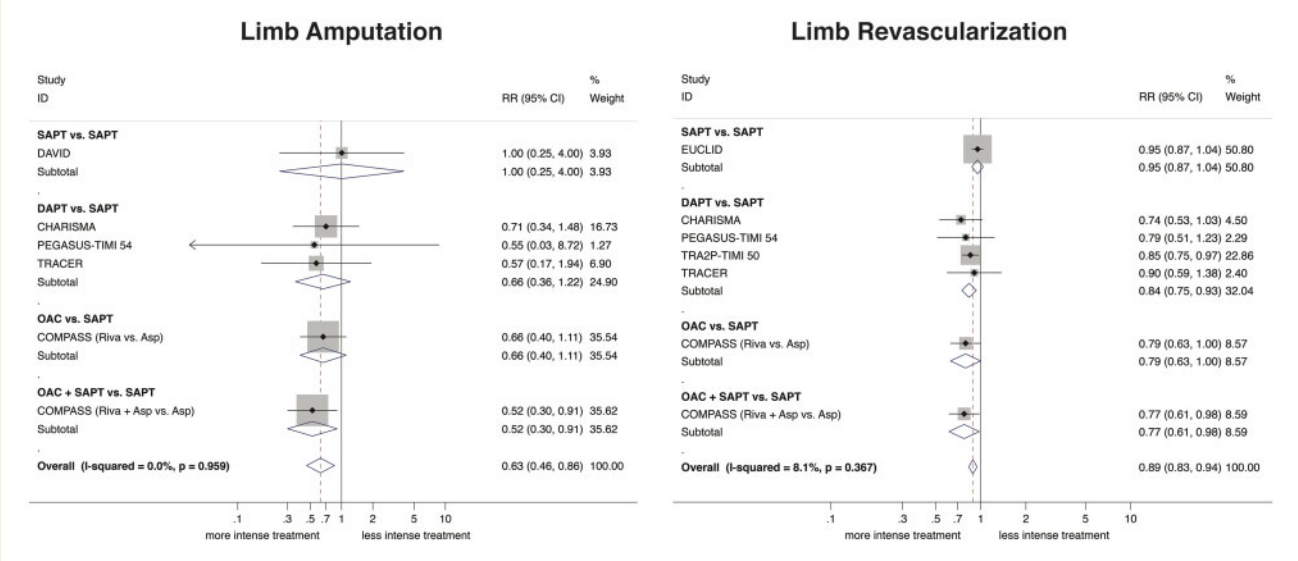

Figure 1 Risk of limb amputation and limb revascularization. Grey squares represent relative risks in trials. The 95% confidence intervals for individual trials are denoted by lines and those for the pooled relative risks by open diamonds. Meta-analysis is performed by fixed effects model. CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management, and Avoidance; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; DAPT, dual-antiplatelet therapy; DAVID, Drug evaluation in Atherosclerotic Vascular disease In Diabetics; EUCLID, Examining Use of Ticagrelor in Peripheral Artery Disease; OAC, oral anticoagulant; PEGASUS-TIMI 54, Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54; SAPT, single-antiplatelet therapy; TRACER, Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome; TRA 2P-TIMI 50, Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischaemic Events (TRA 2P) - Thrombolysis in Myocardial Infarction (TIMI) 50.

of the COMPASS trial, treated and control patients showed similar risk of major bleeding.

Meta-regression analyses showed a potential role for age as effect modifier for risk of major bleeding ($P = 0.049$) (Supplementary material online, *Table S4*).

Discussion

In this meta-analysis, we found that a more intense antithrombotic therapy, including a more vs. less intense SAPT, DAPT vs. SAPT, or a combination of antiplatelet and anticoagulant therapy, significantly reduced the risk of limb revascularization compared to a less intense control group by 11%, and importantly, limb amputation, by 37%, over a median follow-up of 24 months. Stroke was also statistically significantly lower in patients treated with a more intense antithrombotic approach. The 7% reduction in risk of all-cause death observed in patients treated with more vs. less intense antithrombotic treatment did not reach statistically significance. The more intense therapies (moving from single antiplatelet to dual antiplatelet to antiplatelet–anticoagulant combination) were more effective but also caused more bleeding. The data regarding MALE (particularly limb salvage) are compelling and provide evidence on the limb-specific benefits of antithrombotic therapy which should be considered in clinical patient management.

Current guideline recommendations

The current ESC/ESVS guidelines recommend in chronic LEAD patients (i.e. not following revascularization): (i) no antiplatelet therapy if asymptomatic (IIIA recommendation); and (ii) long-term SAPT, preferentially the more efficient $P2Y_{12}$ receptor antagonist clopidogrel over aspirin, if symptomatic (IA).[1] Yet, anticoagulation is only recommended in patients with comorbidities that require anticoagulant therapy independent of the LEAD.[1] The guidelines of the AHA/ACC recommend antiplatelet therapy also in asymptomatic LEAD patients with an ankle–brachial index ≤0.9 (IIaC recommendation), and they suggest SAPT with aspirin or clopidogrel without preferences in symptomatic LEAD patients (IA recommendation).[5] Furthermore, they add that the overall benefit of vorapaxar in addition to antiplatelet therapy in symptomatic LEAD patients is uncertain (IIbB recommendation), and they recommend against the use of anticoagulants (IIIA recommendation).[5] This meta-analysis does not provide enough granularity to specifically address asymptomatic vs. symptomatic patients.

Platelet inhibition in LEAD

Platelets play a pivotal role in arterial thrombosis,[3] and thus, stronger inhibition of platelet aggregation seems reasonable in order to prevent thrombus formation and its consequences on clinical outcome. In chronic (not requiring revascularization) patients, SAPT vs. placebo reduced need for acute limb interventions.[15,19] However, the newer $P2Y_{12}$ receptor antagonist ticagrelor, which exhibits somewhat greater inhibition of adenosine diphosphate-induced platelet aggregation than clopidogrel,[20] was not more effective when evaluated in chronic LEAD patients.[11,13,14,21] Indeed, the EUCLID trial compared these single antiplatelet drug regimens—ticagrelor vs. clopidogrel—

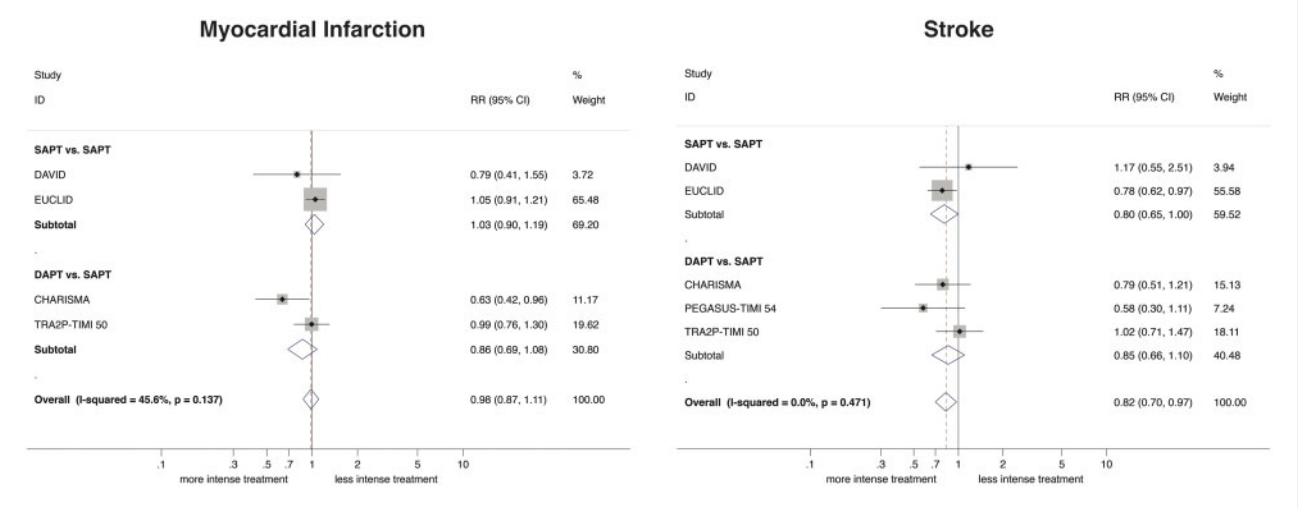

Figure 2 Risk of myocardial infarction and stroke. Explanation of the graph and other abbreviations as in *Figure 1*.

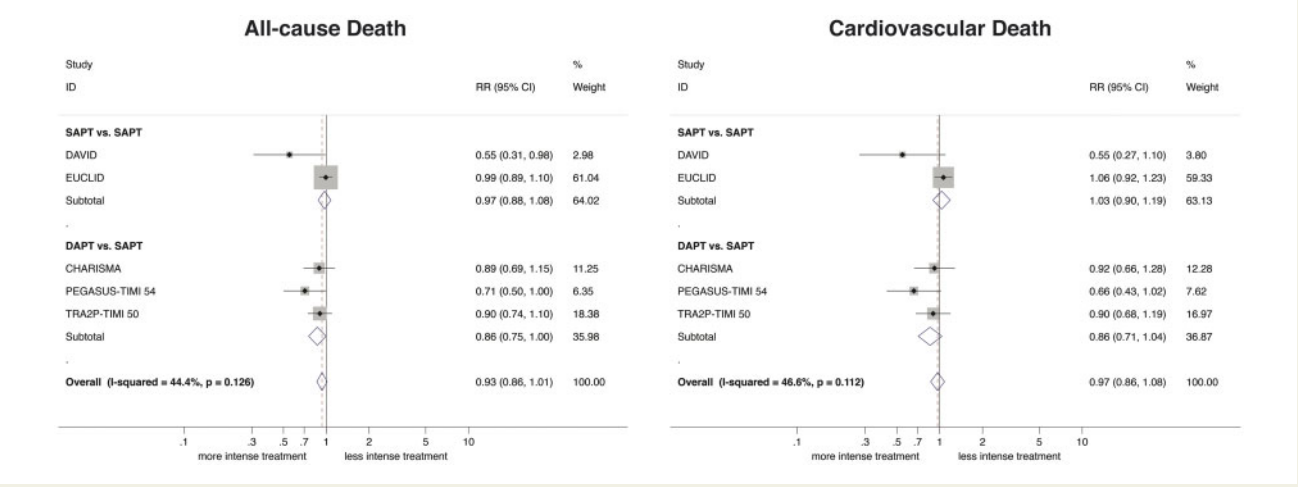

Figure 3 Risk of all-cause and cardiovascular death. Explanation of the graph and other abbreviations as in *Figures 1* and *2*.

as antiplatelet monotherapy in 13 885 patients with symptomatic LEAD and found no differences in MACE or hospitalizations for MALE or major bleeding events.[13] In contrast, a *post hoc* analysis of PEGASUS-TIMI 54, which included 1143 LEAD patients with a prior MI, showed that DAPT, using ticagrelor (60 mg or 90 mg b.i.d.) plus aspirin (pooled analysis), compared with aspirin alone, did reduce MACE and MALE without increasing major bleeding events.[14] The reduction in MACE and more importantly, the decrease in overall mortality, were driven by low-dose ticagrelor, whereas the reduction in MALE was driven by ticagrelor 90 mg b.i.d.[14] These results are in line with the overall findings in this meta-analysis, that increasing antithrombotic and, particularly, more intense antithrombotic therapy is beneficial in reducing limb revascularization and limb amputation, and supported by a previous meta-analysis showing greater benefit in terms of reduction of major amputations following leg revascularization in patients receiving a more intense antiplatelet approach (i.e. DAPT with clopidogrel plus aspirin vs. SAPT) but also a significantly increased risk of bleeding.[22] We also showed that a more intense antithrombotic approach was associated with increased risk of bleeding, but it was mostly driven by the inclusion of the COMPASS trial testing the direct factor Xa inhibitor rivaroxaban ± aspirin vs. aspirin alone. Indeed, after the removal of COMPASS trial, a more vs. less intense antiplatelet therapy still reduced the risk of limb revascularization without impacting on the risk of major bleeding.

Anticoagulation in lower extremity artery disease

In addition to platelets, the coagulation cascade is crucial for arterial thrombus formation. It not only enhances platelet activation via thrombin but also causes cross-linkage of platelets by fibrin leading to

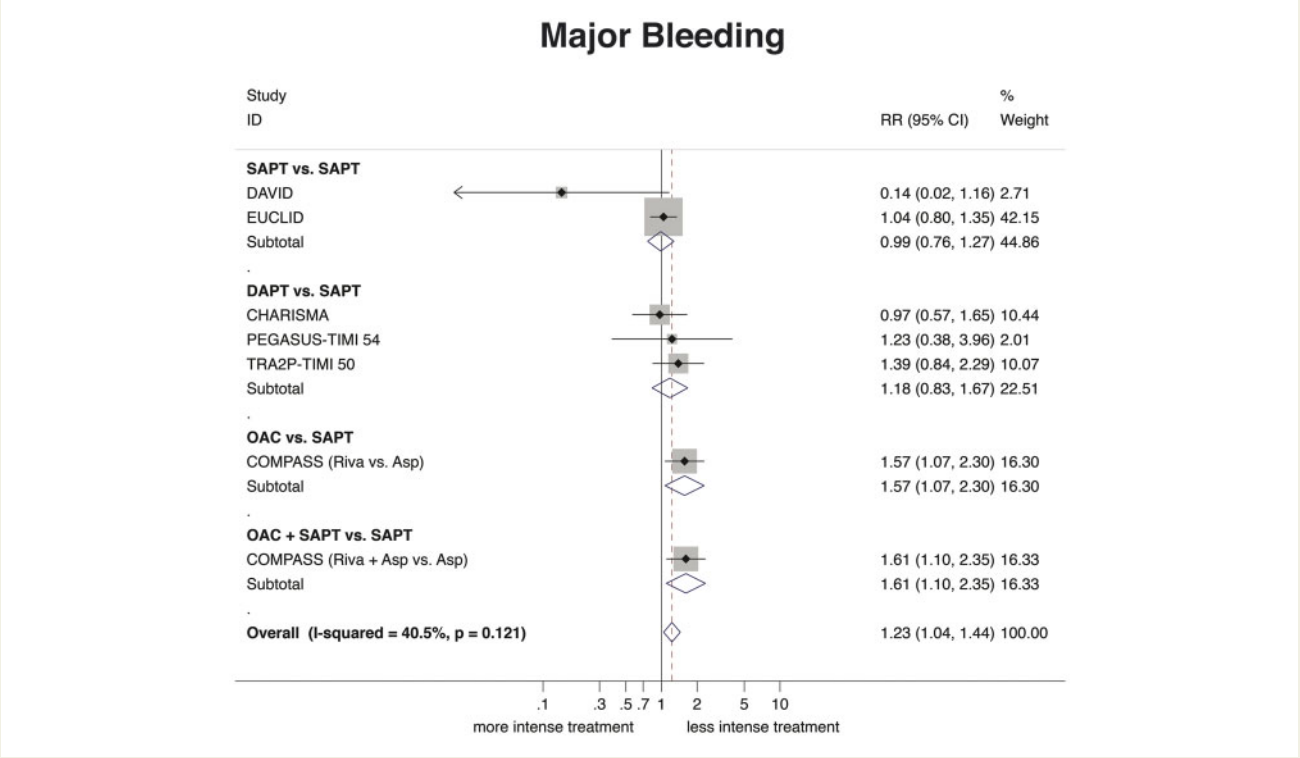

Figure 4 Risk of major bleeding. Explanation of the graph and other abbreviations as in *Figures 1* and *2*.

stable clot formation.[6] Indeed, anticoagulation with vitamin-K antagonists has been previously shown to reduce the risk for thrombotic events but to significantly increase the bleeding risk in CAD patients.[21] In the COMPASS study, a dual antithrombotic regimen of low-dose rivaroxaban (2.5 mg b.i.d.) plus aspirin, compared with aspirin alone, reduced the risk for stroke, MI, and CV death in 27 395 patients with stable CAD disease, LEAD, or carotid artery disease.[7] In a *post hoc* analysis of the COMPASS trial including the 6391 LEAD patients, low-dose rivaroxaban plus aspirin, compared with aspirin alone, reduced MALE as well as major amputation but increased major bleeding events.[11] Rivaroxaban alone (5 mg b.i.d.), compared with aspirin, did not reduce MALE or major amputations but did increase major bleeding events.[11] The benefits of a more intense antithrombotic approach in terms of reduction of major disabling clinical outcome events such as MALE (particularly limb salvage) and MACE outcomes may outweigh the increased risk of bleeding, with a net clinical benefit in LEAD patients.

Strengths and limitations of the study

Strength of our meta-analysis is the large sample size, which led to a powered analysis of outcomes such as limb amputation and revascularization. Limitations include (i) the fact that the analyses were based on aggregate trial-level data and not on patient-level data, which prevented time-to-event analyses and investigation of important subgroups of LEAD patients (i.e. symptomatic or asymptomatic LEAD). (ii) We pooled trials testing different pharmacological treatments (i.e. SAPT, DAPT, combination of anticoagulant and antiplatelets), which thus represent different mechanisms of action and may have different effects on outcomes. Moreover, the included trials investigated different patient populations, e.g. primarily LEAD patients in EUCLID vs. patients with CAD/MI and LEAD in PEGASUS, which may have led to different effects. Additionally, different levels of antithrombotic treatment intensity were tested in the different trials (less vs. more intense SAPT, DAPT, dual antithrombotic treatment), which makes it difficult for clinical specific clinical recommendations. (iii) LEAD was differently defined across the studies included in our meta-analysis, and there were also some differences in outcome definitions, and thus the effects of the treatments might have varied according to the definition used. However, the lack of significant heterogeneity for all the outcome analyses suggests consistency of treatment effect across the trials, which is also confirmed by the one-study removed meta-analysis. (iv) Finally, patients' characteristics varied across the trials, but except for a potential role for age on risk of major bleeding, we excluded the effect of any other known baseline characteristic on our results by a meta-regression analysis.

Conclusions

An antithrombotic and more intense antithrombotic therapeutic regimen reduces limb amputation and revascularization in chronic LEAD patients, as well as risk of stroke, but increases the risk of bleeding. These findings may foster changes in clinical practice, while encouraging future randomized trials powered specifically on MALE outcomes in chronic LEAD patients.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

Conflict of interest: none declared.

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