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 & Peripheral Vascular Diseases

Savarese, Gianluigi; Reiner, Martin F; Uijl, Alicia; D´Amario, Domenico; Agewall, Stefan; Atar, Dan; Baumgartner, Iris; Borghi, Claudio; De Carlo, Marco; Drexel, Heinz; Kaski, Juan Carlos; Kjeldsen, Keld P; Kucher, Nils; Lund, Lars H; Niessner, Alexander; Semb, Anne Grete; Schmidt, Thomas A; Sulzgruber, Patrick; Tamargo, Juan; Vitale, Cristiana; Wassmann, Sven; Aboyans, Victor; Lewis, Basil S

Published in:
European Heart Journal - Cardiovascular Pharmacotherapy

DOI (link to publication from Publisher):
10.1093/ehjcvp/pvz036

Publication date:
2020

Document Version
Accepted author manuscript, peer reviewed version

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 & 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]; Juan Carlos Kaski[10]; Keld P Kjeldsen[11]; Nils Kucher[12]; Lars H Lund[1]; Alexander Niessner[13]; Anne Grete Semb[14]; Thomas A Schmidt[15]; Patrick Sulzgruber[13]; Juan Tamargo[16]; Cristiana Vitale[17]; Sven Wassmann[18]; Victor Aboyans[19]; Basil S Lewis[20]

1. Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden
2. Institute for Intensive Care Medicine, University Hospital Zurich, Zurich, Switzerland
3. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, the Netherlands
4. Fondazione Policlinico A. Gemelli IRCCS - Università Cattolica Sacro Cuore, Rome, Italy
5. Oslo University Hospital Ullevål and Institute of Clinical Sciences, University of Oslo, Oslo, Norway.
6. Division of Angiology, Swiss Cardiovascular Center, Inselspital, Bern University Hospital, Bern, Switzerland.
7. Medicine and Surgery Science Department, University of Bologna, Bologna , Italy.
8. Cardiothoracic and Vascular Department, Azienda Ospedaliero-Universitaria Pisana, Italy.
9. Vorarlberg Institute for Vascular Investigation and Treatment, Feldkirch, Austria & Division of Angiology, Swiss Cardiovascular Center, Bern, Bern, Switzerland & Drexel University College of Medicine, Philadelphia, PA, USA.
10. Molecular and Clinical Sciences Research Institute, St. George's, University of London, London, United Kingdom.

11. Department of Cardiology, Copenhagen University Hospital (Hvidovre-Amager), Copenhagen and Department of Health Science and Technology, The Faculty of Medicine, Aalborg University, Aalborg, Denmark
12. Clinic for Angiology, University Hospital Zurich, Switzerland
13. Department of Medicine II, Division of Cardiology, Medical University of Vienna, Austria.
14. Preventive Cardio-Rheuma clinic, Department of Rheumatology, Diakonhjemme Hospital, Oslo, Norway.
15. Emergency Department, Bispebjerg and Frederiksberg Hospital, Copenhagen University Hospital, Copenhagen, Denmark
16. Department of Pharmacology and Toxicology, School of Medicine , Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense, CIBERCV , Madrid , Spain.
17. Department of Medical Sciences, IRCCS San Raffaele, Rome, Italy
18. Cardiology Pasing, Munich, Germany and University of the Saarland, Homburg, Saar, Germany
19. Department of Cardiology, Dupuytren University Hospital, Limoges, France; Inserm 1094, Limoges School of Medicine, Limoges, France.
20. 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

Running head: Antithrombotic therapy in PAD

Word count: 4´986

Correspondence:

Gianluigi Savarese, MD PhD
Department of Medicine, Cardiology Unit
Karolinska Institutet
S1:02, 171 76
Stockholm, Sweden
mail. gianluigi.savarese@ki.se

Abstract

Introduction. 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 anti-thrombotic and more intense antithrombotic therapy on limb outcomes and limb salvage in patients with chronic LEAD.

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

Results. 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% confidence interval [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 risk of limb amputation and revascularization as well as stroke, with an increase in the risk of bleeding events.

Key words: peripheral artery disease, cardiovascular disease, lower extremity artery disease, anticoagulation, antiplatelet therapy, anti-thrombotic therapy, bleeding, meta-analysis.

Abbreviations

ABI	Ankle-brachial index
ADEP	Atherosclerotic Disease Evolution by Picotamide
BID	Twice a day
CAD	Coronary artery disease
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CI	Confidence intervals
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
CV	Cardiovascular
DAPT	Dual antiplatelet therapy
DAVID	Drug evaluation in Atherosclerotic Vascular disease In Diabetics
EUCLID	Examining Use of Ticagrelor in Peripheral Artery Disease
GRADE	Grading of recommendations assessment, Development and Evaluation
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
HYLD	Hyperlipidemia
HYPT	Hypertension
ISTH	International Society of Thrombosis and Hemostasis
LDL	Low-density lipoprotein
LEAD	Lower extremity artery disease
LLA	Lipid lowering agents
MACCE	Major adverse cardio- and cerebrovascular events
MALE	Major adverse limb events

MI	Myocardial infarction
QD	Once a day
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
POPADAD	prevention of progression of arterial disease and diabetes
RR	Relative risk
SAPT	Single antiplatelet therapy
STIMS	Swedish Ticlopidine Multicentre Study
TIMI	Thrombolysis in myocardial infarction
TID	three times a day
TRA 2P–TIMI 50	Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P) – Thrombolysis in Myocardial Infarction (TIMI) 50
TRACER	Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome

Introduction

Lower extremity peripheral 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 health-care 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 ischemia, 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: enrollment of patients with LEAD (studies not reporting separately outcomes for patients with LEAD and carotid artery disease were not considered) defined as in Supplemental Material Table 1, 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 fulfillment of inclusion criteria by two independent reviewers (GS, DDA). 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), hyperlipidemia, smoking, use of aspirin and lipid-lowering agents were collected and entered into STATA (version 14.2, StataCorps, College Station, Texas) by one author (DDA) and checked by another author (GS). 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 Supplemental Material Table 2.

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 (RR) 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 versus control group. Relative risks (RRs) 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 and heterogeneity 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 1-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 Supplemental Material Table 1. Of 6'273 manuscripts identified in the initial search, 4'383 were retrieved for more detailed evaluation after the removal of duplicates. Thereafter, 7 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 6 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).

MI and stroke occurred in 4.5% and 1.6% of patients allocated to a more intense antithrombotic treatment vs. 4.6% and 2.1% of those randomized to a less intense approach. Thus, although the treatment did not significantly reduce the risk of myocardial infarction (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 anti-thrombotic therapy. Thus, a more intense anti-thrombotic 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 Supplemental Material Table 3. 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 confidence interval 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>0.10 at Peters' test).

Sensitivity analysis

One-study removed analysis confirmed mostly all the results (Supplemental Figures 1-7). 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 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) (Supplemental Material Table 4).

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) 1) no antiplatelet therapy if asymptomatic (III A recommendation); and 2) long-term SAPT, preferentially the more efficient $P2Y_{12}$ receptor antagonist clopidogrel over aspirin, if symptomatic (I A).[1] Yet, anticoagulation is only recommended in patients with co-morbidities 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 (IIa C recommendation), and they suggest SAPT with aspirin or clopidogrel without preferences in symptomatic LEAD patients (I A recommendation).[5] Furthermore, they add that the overall benefit of vorapaxar in addition to antiplatelet therapy in

symptomatic LEAD patients is uncertain (IIb B recommendation), and they recommend against the use of anticoagulants (III A recommendation).[5] This meta-analysis does not provide enough granularity to specifically address asymptomatic versus 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.[9, 10] However, the newer $P2Y_{12}$ receptor antagonist ticagrelor, which exhibits somewhat greater inhibition of adenosine diphosphate-induced platelet aggregation than clopidogrel,[11] was not more effective when evaluated in chronic LEAD patients.[12-15] Indeed, the EUCLID trial compared these single antiplatelet drug regimens - ticagrelor vs. clopidogrel - as antiplatelet mono-therapy in 13'885 patients with symptomatic LEAD and found no differences in MACE or hospitalizations for MALE or major bleeding events.[12] In contrast, a post-hoc analysis of PEGASUS-TIMI 54, which included 1'143 LEAD patients with a prior MI, showed that DAPT, using ticagrelor (60 mg or 90 mg twice daily) plus aspirin (pooled analysis), compared with aspirin alone, did reduce MACE and MALE without increasing major bleeding events.[13] 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 twice daily.[13] 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[16]. 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 LEAD

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 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.[15] In the COMPASS study, a dual anti-thrombotic regimen of low-dose rivaroxaban (2.5 mg twice a day) 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 6'391 LEAD patients, low-dose rivaroxaban plus aspirin, compared with aspirin alone, reduced MALE as well as major amputation but increased major bleeding events.[14] Rivaroxaban alone (5 mg twice daily), compared with aspirin, did not reduce MALE or major amputations but did increase major bleeding events.[14] 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. single antiplatelet therapy, dual antiplatelet therapy, 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.

References

1. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Rother J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I, Group ESCSD. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;**39**(9):763-816.

2. Peacock JM, Keo HH, Duval S, Baumgartner I, Oldenburg NC, Jaff MR, Henry TD, Yu X, Hirsch AT. The incidence and health economic burden of ischemic amputation in Minnesota, 2005-2008. Preventing chronic disease 2011;**8**(6):A141.

3. Versteeg HH, Heemskerk JW, Levi M, Reitsma PH. New fundamentals in hemostasis. Physiological reviews 2013;**93**(1):327-58.

4. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature 2011;**473**(7347):317-25.

5. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FG, Hamburg NM, Kinlay S, Lookstein R, Misra S, Mureebe L, Olin JW, Patel RA, Regensteiner JG, Schanzer A, Shishehbor MH, Stewart KJ, Treat-Jacobson D, Walsh ME. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;**69**(11):1465-1508.

6. Antoniou GA, Fisher RK, Georgiadis GS, Antoniou SA, Torella F. Statin therapy in lower limb peripheral arterial disease: Systematic review and meta-analysis. Vascul Pharmacol 2014;**63**(2):79-87.

7. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar AK, Fox KAA, Parkhomenko AN, Ertl G, Stork S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusoff K, Steg PG, Metsarinne KP, Cook Bruns N, Misselwitz F, Chen E, Leong D, Yusuf S, Investigators C. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 2017;**377**(14):1319-1330.

8. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS, Committee P-TS, Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;**372**(19):1791-800.

9. Bergqvist D, Almgren B, Dickinson JP. Reduction of requirement for leg vascular surgery during long-term treatment of claudicant patients with ticlopidine: results from the Swedish Ticlopidine Multicentre Study (STIMS). Eur J Vasc Endovasc Surg 1995;**10**(1):69-76.

10. Bonaca MP, Scirica BM, Creager MA, Olin J, Bounameaux H, Dellborg M, Lamp JM, Murphy SA, Braunwald E, Morrow DA. Vorapaxar in patients with peripheral artery disease: results from TRA2{degrees}P-TIMI 50. Circulation 2013;**127**(14):1522-9, 1529e1-6.

11. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, Kereiakes DJ, Parris C, Purdy D, Wilson V, Ledley GS, Storey RF. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation 2009;**120**(25):2577-85.

12. Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, Katona BG, Mahaffey KW, Norgren L, Jones WS, Blomster J, Millegard M, Reist C, Patel MR, Committee ETS, Investigators. Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. N Engl J Med 2017;**376**(1):32-40.

13. Bonaca MP, Bhatt DL, Storey RF, Steg PG, Cohen M, Kuder J, Goodrich E, Nicolau JC, Parkhomenko A, Lopez-Sendon J, Dellborg M, Dalby A, Spinar J, Aylward P, Corbalan R, Abola MTB, Jensen EC, Held P, Braunwald E, Sabatine MS. Ticagrelor for Prevention of Ischemic Events After Myocardial Infarction in Patients With Peripheral Artery Disease. J Am Coll Cardiol 2016;**67**(23):2719-2728.

14. Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, Abola MT, Branch KRH, Keltai K, Bhatt DL, Verhamme P, Fox KAA, Cook-Bruns N, Lanius V, Connolly SJ, Yusuf S. Major Adverse Limb Events and Mortality in Patients With Peripheral Artery Disease: The COMPASS Trial. J Am Coll Cardiol 2018;**71**(20):2306-2315.

15. Anand SS, Yusuf S. Oral anticoagulants in patients with coronary artery disease. J Am Coll Cardiol 2003;**41**(4 Suppl S):62S-69S.

16. Katsanos K, Spiliopoulos S, Saha P, Diamantopoulos A, Karunanithy N, Krokidis M, Modarai B, Karnabatidis D. Comparative Efficacy and Safety of Different Antiplatelet Agents for Prevention of Major Cardiovascular Events and Leg Amputations in Patients with Peripheral Arterial Disease: A Systematic Review and Network Meta-Analysis. PLoS One 2015;**10**(8):e0135692.

17. Cacoub PP, Bhatt DL, Steg PG, Topol EJ, Creager MA, Investigators C. Patients with peripheral arterial disease in the CHARISMA trial. European heart journal 2009;**30**(2):192-201.

18. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. The New England journal of medicine 2006;**354**(16):1706-17.

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

20. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Ophuis TO, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS, Committee P-TS, Investigators. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. The New England journal of medicine 2015.

21. Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, Fox KA, Lipka LJ, Liu X, Nicolau JC, Ophuis AJ, Paolasso E, Scirica BM, Spinar J, Theroux P, Wiviott SD, Strony J, Murphy SA, Committee TPTS, Investigators. Vorapaxar in the secondary prevention of atherothrombotic events. The New England journal of medicine 2012;**366**(15):1404-13.

22. Tricoci P, Huang Z, Held C, Moliterno DJ, Armstrong PW, Van de Werf F, White HD, Aylward PE, Wallentin L, Chen E, Lokhnygina Y, Pei J, Leonardi S, Rorick TL, Kilian AM, Jennings LH, Ambrosio G, Bode C, Cequier A, Cornel JH, Diaz R, Erkan A, Huber K, Hudson MP, Jiang L, Jukema JW, Lewis BS, Lincoff AM, Montalescot G, Nicolau JC, Ogawa H, Pfisterer M, Prieto JC, Ruzyllo W, Sinnaeve PR, Storey RF, Valgimigli M, Whellan DJ, Widimsky P, Strony J, Harrington RA, Mahaffey KW, Investigators T. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. The New England journal of medicine 2012;**366**(1):20-33.

23. Jones WS, Tricoci P, Huang Z, Moliterno DJ, Harrington RA, Sinnaeve PR, Strony J, Van de Werf F, White HD, Held C, Armstrong PW, Aylward PE, Chen E, Patel MR, Mahaffey KW. Vorapaxar in patients with peripheral artery disease and acute coronary syndrome: insights from Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER). American heart journal 2014;**168**(4):588-96.

FIGURES LEGEND

Figure 1. Risk of limb amputation and limb revascularization. Gray squares represent relative risks (RRs) in trials. The 95% confidence intervals (CIs) for individual trials are denoted by lines and those for the pooled RRs by open diamonds. Meta-analysis is performed by fixed effects model. DAPT = dual antiplatelet therapy, CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance, COMPASS = Cardiovascular Outcomes for People Using Anticoagulation Strategies, DAVID = Drug evaluation in Atherosclerotic Vascular disease In Diabetics, 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.

Figure 2. Risk of myocardial infarction and stroke. EUCLID = Examining Use of Ticagrelor in Peripheral Artery Disease, TRA 2P–TIMI 50 = Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P) – Thrombolysis in Myocardial Infarction (TIMI) 50. 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 Figure 1 and 2.

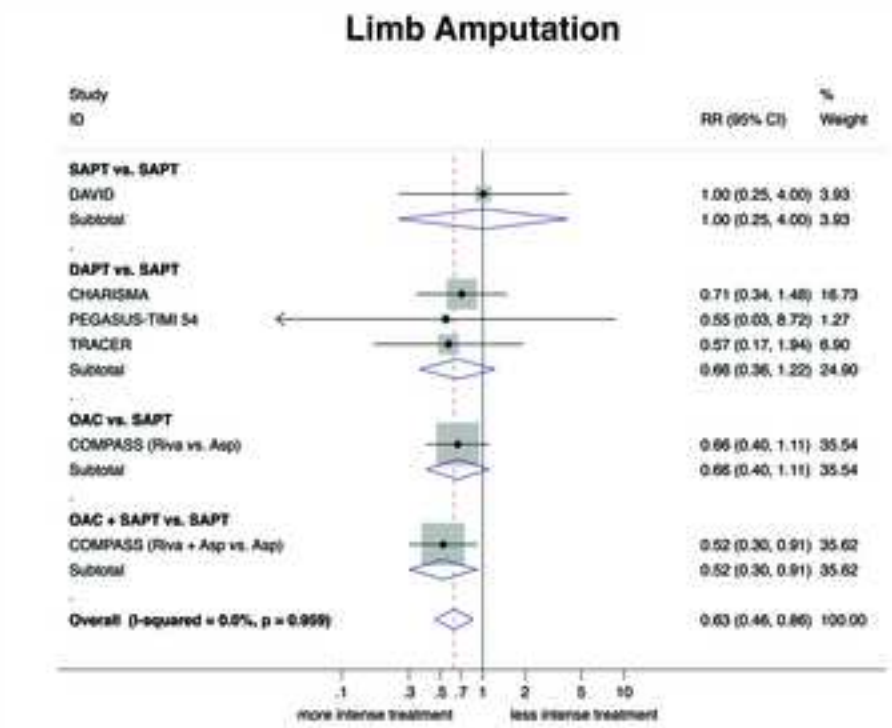
Figure 4. Risk of major bleeding. Explanation of the graph and other abbreviations as in Figure 1 and 2.

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[17, 18]	Clopidogrel plus low-dose aspirin vs. placebo plus low-dose aspirin	26	1545	1551	66	30	25	9	51	85*	36	70	72	85	100
COMPASS[7, 14]	Rivaroxaban (2·5 mg BID) plus aspirin; Rivaroxaban BID (5 mg with aspirin placebo QD); Aspirin OD (100 mg and rivaroxaban placebo BID)	21	4268	2123	68	28	65	-	32	75*	45	-	79	82	100
DAVID[19]	Picotamide vs. aspirin	24	603	606	64	27	19	10	-	71*	100	38	57	15	50
EUCLID[12]	Ticagrelor vs clopidogrel	30	6930	6955	66	28	29	8	57	78*	39	76	78	73	67
PEGASUS-TIMI 54[13, 20]	Ticagrelor vs placebo on a background of aspirin	33	739	404	66	22	100	3	34	30[#]	42	81	85	93	100
TRA 2P-TIMI 50[10, 21]	Vorapaxar vs placebo	36	1892	1895	66	29	57	14	62	31[#]	36	87	83	82	88
TRACER[22, 23]	Vorapaxar vs placebo	16.5	468	468	66	26	44	10	-	77*	46	78	85	87	96

*Current or former smoker, #Current smoker. CAD = coronary artery disease, HYLD = hyperlipidemia, HYPT = hypertension, LLA = lipid lowering agents. Other abbreviations as in Figure 1 and 2.

Figure 1



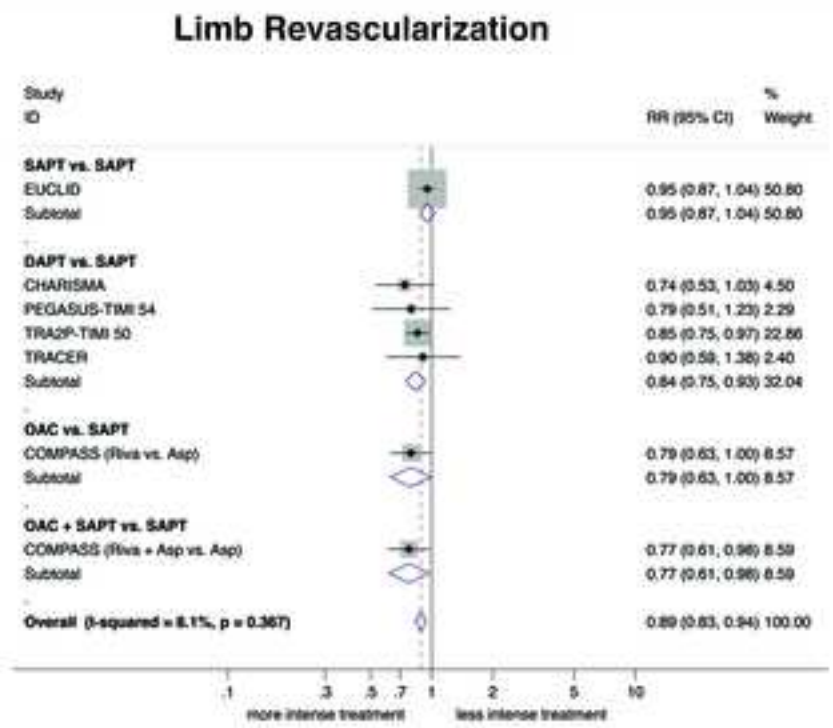
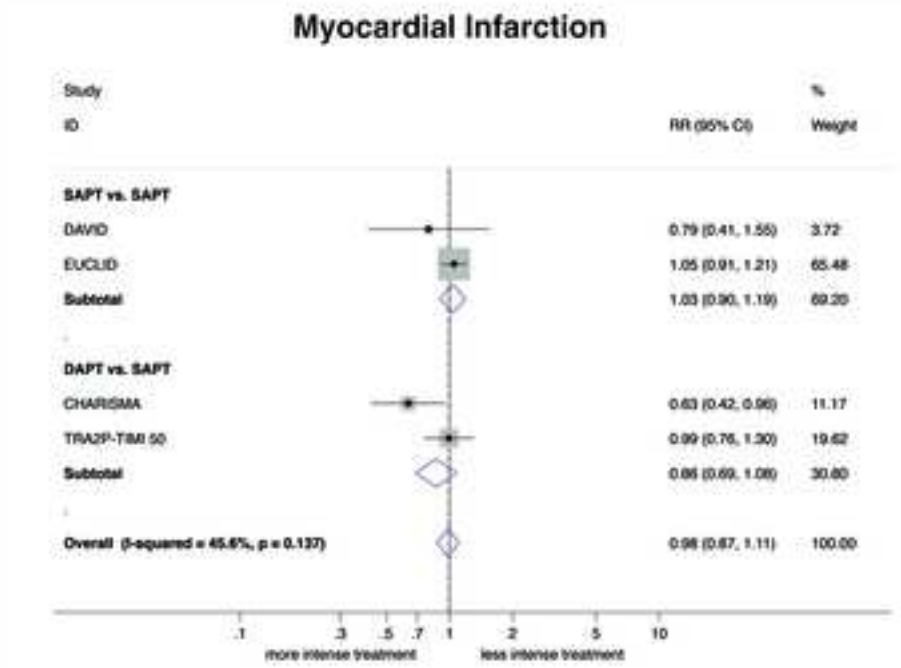


Figure 2



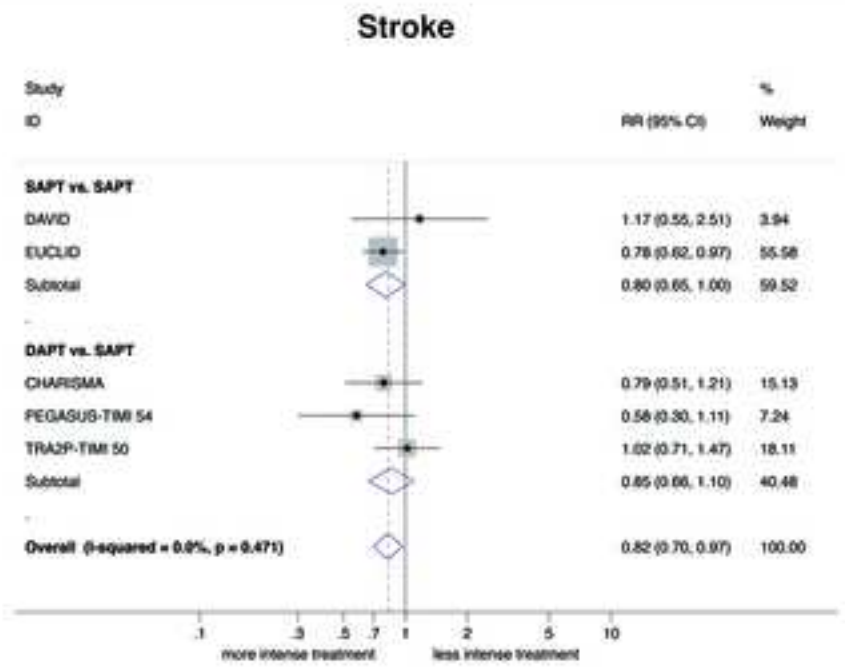
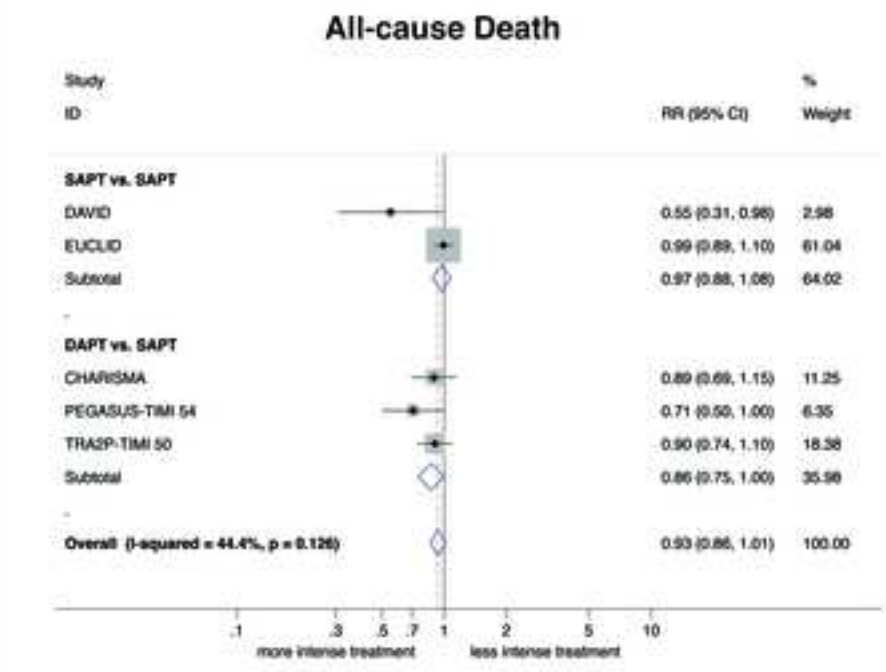


Figure 3



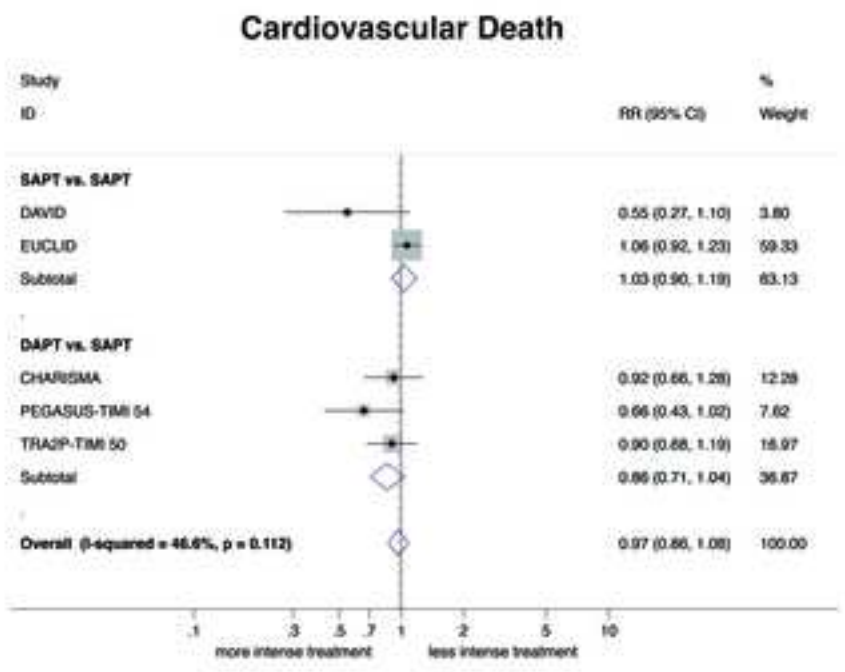


Figure 4