



Ticagrelor-based antiplatelet regimens in patients with atherosclerotic artery disease— A meta-analysis of randomized clinical trials

Salvatore Cassese, MD PhD,^a Gjin Ndrepepa, MD,^a Robert A. Byrne, MB BCh PhD,^{a,b}
Karl-Ludwig Laugwitz, MD,^{b,c} Heribert Schunkert, MD,^{a,b} Massimiliano Fusaro, MD,^a
Fernando Alfonso, MD PhD,^d and Adnan Kastrati, MD^{a,b}

Background Randomized trials did not consistently support superiority of ticagrelor, as monotherapy or in combination with aspirin, in terms of efficacy or safety, in patients with atherosclerotic artery disease.

Methods Medline, EMBASE, the Cochrane Central Register of Controlled Trials, and scientific session abstracts were searched for trials of patients with coronary or peripheral artery disease (with >1,000 participants and a follow-up ≥ 3 months) randomly assigned to ticagrelor-based or conventional antiplatelet therapies. Trial-level hazard ratios (HRs) were pooled using a fixed- or random-effect model (in case of significant heterogeneity) with the inverse variance weighting. The primary outcome was all-cause mortality. Other outcomes were myocardial infarction (MI), stroke, and major bleeding.

Results Overall 77,489 patients received either ticagrelor-based ($n = 38,721$) or conventional antiplatelet regimens ($n = 38,768$) in 6 trials. The primary outcome occurred in 4.5% of patients treated with experimental therapy and 4.9% of patients treated with control therapy (HR = 0.91, 95% CI 0.81-1.01; $P = .07$). Overall, patients treated with ticagrelor-based versus conventional antiplatelet regimens showed no significant difference in terms of all-cause death, MI, stroke, or major bleeding after 20 months. However, in trials of patients with coronary artery disease as primary diagnosis, the risk for all-cause death (HR = 0.84 [0.77-0.91], $P < .001$) and MI (HR = 0.87 [0.80-0.94], $P = .007$) was significantly reduced by experimental therapy.

Conclusions In patients with atherosclerotic artery disease, the benefit of ticagrelor-based therapies was confined to patients treated for coronary artery disease. The drug significantly reduced the risk for all-cause death and MI without excess risk of bleeding in these patients. In consideration of limitations of subgroup analyses, these results need further validation. (Am Heart J 2020;219:109-16.)

Antiplatelet agents represent the cornerstone of pharmacological prevention of recurrent ischemic events in patients with vascular manifestations of atherosclerosis.¹ Indeed, in patients treated with a percutaneous intervention for stable coronary artery disease (CAD) or acute coronary syndrome (ACS) and not requiring an oral anticoagulation, guideline-writing authorities recommend a strategy of dual antiplatelet therapy (DAPT) for

a period of time ranging between 6 and 12 months followed by at least 1 antiplatelet agent lifelong.² Similarly, patients with clinically managed or revascularized symptomatic peripheral artery disease (PAD) receive at least 1 antiplatelet agent lifelong or 1-month DAPT as standard of care.³ The direct-acting, oral cyclopentyltriazolo-pyrimidine ticagrelor, which reversibly blocks the adenosine diphosphate receptor P2Y₁₂ on platelets, has become an essential component of anti-thrombotic therapy for patients with ACS or with stabilized heart attack because it improves clinical outcomes as compared to other thienopyridines (namely, clopidogrel) or aspirin alone.¹ The lower ischemic risk associated with a more potent and/or prolonged platelet inhibition may be offset by an increased risk of bleeding.⁴ In this regard, the search for alternative antiplatelet regimens ensuring intensified platelet inhibition while having a wide therapeutic window is a matter of broad clinical interest. Recent randomized clinical trials⁵⁻¹⁰ did not consistently support the superior efficacy and safety

From the ^aDeutsches Herzzentrum München, Technische Universität München, Munich, Germany, ^bDZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany, ^c1. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität München, Munich, Germany, and ^dCardiac Department, Hospital Universitario de La Princesa Madrid, Madrid, Spain.

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Reprint requests: Salvatore Cassese, MD PhD, Deutsches Herzzentrum München, Technische Universität München, Lazarettstrasse, 36-Munich, Germany.

E-mail: cassese@dzm.mhn.de

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of ticagrelor as monotherapy or in combination with aspirin compared with other antiplatelet regimens for secondary prevention of ischemic events in patients with CAD and/or PAD. Against this background, we performed this meta-analysis to investigate the clinical impact of ticagrelor-based versus conventional antiplatelet regimens in this setting.

Methods

Data sources and searches

We searched Medline, EMBASE, the Cochrane Central Register of Controlled Trials, scientific session abstracts, and relevant Web sites (www.cardiosource.com, www.clinicaltrialresults.org, www.escardio.org, www.tctmd.com, www.theheart.org) without restricting language or publication status. The references listed in all eligible studies were checked to identify further citations. The last search was performed on 6 January 2019. Search terms included the keywords and the corresponding Medical Subject Headings for “ticagrelor,” “clopidogrel,” “aspirin,” “antiplatelet,” “secondary prevention,” “trial,” and “randomized trial.” Inclusion criteria were (1) randomized design, (2) total number of participants >1,000, and (3) follow-up duration ≥ 3 months. Comparisons of ticagrelor- versus prasugrel-based antiplatelet regimens¹¹ and trials of ticagrelor-based versus conventional antiplatelet regimens after routine administration of thrombolytic agents¹² were ineligible.

Study selection and quality assessment

Two investigators (S. C. and G. N.) independently assessed publications for eligibility at title and/or abstract level, with divergences resolved by a third investigator (A. K.). Studies that met inclusion criteria were selected for further analysis. Freedom from bias was independently evaluated for each study by the same investigators in accordance with The Cochrane Collaboration method.¹³ Composite quality scores were not assigned.¹⁴

Data extraction and outcome variables

The primary outcome was all-cause mortality. Main secondary outcome was myocardial infarction (MI). Other secondary outcomes were stroke and major bleeding. All end points were evaluated in the intention-to-treat population up to the maximum follow-up duration in accordance to definitions reported in the original protocols.

Data synthesis and analysis

We used hazard ratios (HRs) and 95% CIs to compare the outcomes of interest associated with ticagrelor-based therapy (experimental group) versus conventional antiplatelet regimens (control group). Trial-level logHRs and corresponding SEs were pooled using a fixed- or random-effect model (in case of significant heterogeneity) with

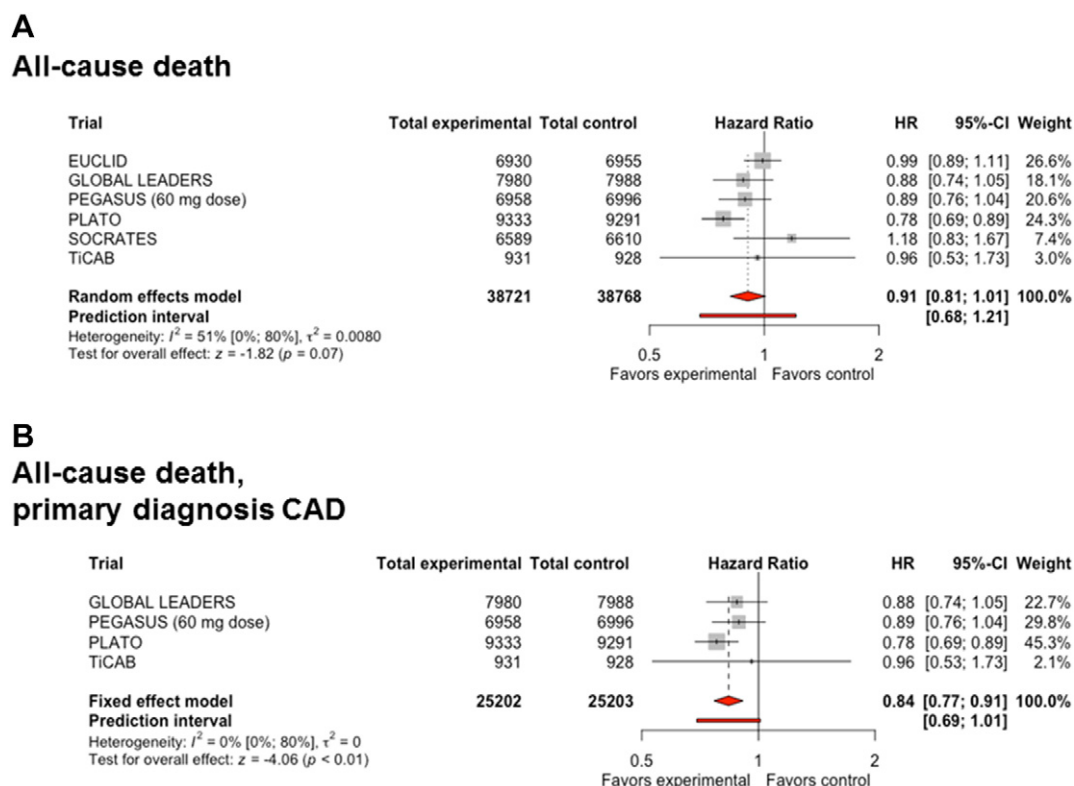
the inverse variance weighting. Heterogeneity between the trials was quantified using the I^2 statistic: I^2 values around 25%, 50%, and 75% were considered to indicate low, moderate, or high heterogeneity, respectively.¹³ In addition, we estimated the between-study variance (τ^2) according to DerSimonian-Laird and derived the 95% prediction interval of pooled estimates.¹⁵ An influence analysis, in which meta-analysis estimates are computed omitting one study at a time, was performed for the primary and main secondary outcomes. We performed a linear regression test for funnel plot asymmetry for main outcomes. We used a χ^2 test for treatment-by-subgroup interaction to investigate whether the treatment effect was dependent on the primary diagnosis of enrolled patients in the original trials (CAD or PAD). By means of random-effects meta-regression analysis, we assessed the impact of therapy adherence and duration in the experimental arm with respect to primary and main secondary outcomes. Finally, we determined the power of our random-effects meta-analysis to detect a prespecified 20% relative risk reduction (RRR) for primary and main secondary outcomes with the experimental therapy conditional on the observed precision of the pooled estimate.¹⁶ The 20% RRR threshold was chosen because it was the average risk reduction threshold (range 13.5%–22.5%) selected to power the individual study designs of randomized trials included in this meta-analysis. This study was reported in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (Supplemental Table D).¹⁷ All analyses were performed in R (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria). No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Results

Eligible studies

The flow diagram for the trial selection process is shown in Supplemental Figure 1. After application of inclusion/exclusion criteria, 6 trials were included in meta-analysis: 5 trials published as full-length manuscripts^{5–9} and 1 trial as meeting presentation¹⁰. In these trials, a total of 84,477 patients were randomly allocated and received at least 1 dose of either experimental ($n = 45,709$) or control therapy ($n = 38,768$). In 1 trial,⁶ patients received either ticagrelor 60 mg twice daily ($n = 6,958$) or ticagrelor 90 mg twice daily ($n = 6,988$): for the main analysis, we obtained from this study only the treatment arm prescribing ticagrelor 60 mg twice daily because the latter dose regimen is actually recommended from guideline-writing authorities for long-term secondary prevention after MI.² In addition, we explored the treatment effect for all outcomes of

Figure 1



Risk estimates of primary outcome for ticagrelor-based versus conventional antiplatelet regimens. Plot of HR for all-cause death associated with ticagrelor-based (experimental) versus conventional antiplatelet regimens (control) in the overall population (**A**) and in trials which enrolled patients with CAD as primary diagnosis (**B**). The diamonds indicate the point estimate and the left and the right ends of the lines the 95% CI. Trial acronyms are as in the [Table](#).

interest by pooling outcomes data from treatment arms prescribing either ticagrelor 60 mg or 90 mg twice daily to derive summary risk estimates. Thus, a total of 77,489 participants were available for final analyses allocated to experimental ($n = 38,721$) or control ($n = 38,768$) therapy. All trials had a multicenter design. The main characteristics of the trials included are shown in Supplemental Table II. Briefly, patients with obstructive chronic/stable or unstable CAD and/or PAD were randomized to experimental or control therapy. Patients assigned to experimental therapy received ticagrelor 60 or 90 mg twice daily as monotherapy or in combination with aspirin 75-150 mg once daily for a period of time ranging between 3 and 33 months. Patients assigned to control therapy received clopidogrel 75 mg once daily as monotherapy or in combination with aspirin 75-150 mg once daily. The GLOBAL LEADERS trial⁹ had a peculiar 3-arm design: in this study, the experimental treatment consisted of ticagrelor 90 mg twice daily in combination with aspirin 75-150 mg once daily for 1 month followed by ticagrelor monotherapy for 23 months, whereas the control arms consisted of clopidogrel 75 mg once daily or

ticagrelor 90 mg twice daily in combination with aspirin 75-150 mg once daily for 12 months followed by aspirin 75-150 mg once daily for further 12 months. For the current study, data belonging to these 2 latter groups were pooled in the control therapy in the main analysis. Additionally, 2 separate analyses explored the treatment effect for main outcomes associated with either ticagrelor (experimental therapy) or aspirin (control therapy) beyond 1 year and with either ticagrelor (experimental therapy) or clopidogrel (control therapy) up to 2 years. In 4 trials^{5,6,9,10} the predominant diagnosis was CAD including patients with ACS or stabilized MI. The Ticagrelor in Coronary Artery Bypass Graft (TICAB) trial¹⁰ allocated patients after surgical coronary revascularization to either ticagrelor or aspirin. One trial⁷ enrolled patients with nonsevere ischemic stroke or high-risk transient ischemic attack not due to a cardioembolic cause. In the experimental group, the adherence to assigned antiplatelet therapy at the longest available follow-up ranged between 69.9% and 86.2%. All patients received ancillary therapies for acute or chronic manifestations of CAD and/or PAD in accordance with

Table. Main characteristics of patients enrolled among trials included in the study

Trial	Patients, n	Age, y	Females, %	Diabetes, %	Current smoker, %	Previous MI, %	Previous CVA, %
EUCLID	13,885	66.0	3888 (28.0)	5345 (38.5)	4289 (30.8)	2522 (18.1)	1650 (11.8)
GLOBAL LEADERS	15,968	64.5	3714 (23.2)	4038 (25.2)	4169 (26.1)	3710 (23.2)	421 (2.6)
PEGASUS TIMI 54	14,112 (21,162)*	65.3	3378 (23.9)	4565 (32.3)	2349 (16.6)	2356 (16.6)†	N/A
PLATO	19,624	62.0	5288 (26.9)	4662 (23.7)	6678 (34.0)	3824 (19.4)	722 (3.6)
SOCRATES	13,199	65.8	2759 (20.9)	3212 (24.3)	N/R	548 (4.1)	2449 (18.5)
TiCAB	1859	66.7	280 (15.1)	668 (35.9)	387 (20.8)	422 (22.7)	108 (5.8)

Overall numbers (proportions) and means are reported. CVA, cerebrovascular accident; N/A, not applicable; N/R, not reported.

Official titles and acronyms: EUCLID: A Randomized, Double-blind, Parallel Group, Multicentre Phase IIIb Study to Compare Ticagrelor With Clopidogrel Treatment on the Risk of Cardiovascular Death, Myocardial Infarction and Ischemic Stroke in Patients With Established Peripheral Artery Disease (Examining Use of ticagrelor In PAD); GLOBAL LEADERS: Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-day Intensive Dual Antiplatelet Therapy in All-comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-eluting Stent Use; PEGASUS TIMI 54: Prevention of Cardiovascular Events (eg, Death From Heart or Vascular Disease, Heart Attack, or Stroke) in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin; PLATO: A Randomised, Double-blind, Parallel Group, Phase 3, Efficacy and Safety Study of Ticagrelor Compared With Clopidogrel for Prevention of Vascular Events in Patients With Non-ST or ST Elevation Acute Coronary Syndromes (ACS) [a Study of PLATelet Inhibition and Patient Outcomes]; SOCRATES: Acute Stroke Or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes; TiCAB: A Randomized, Parallel Group, Double-Blind Study of Ticagrelor Compared With Aspirin for Prevention of Vascular Events in Patients Undergoing Coronary Artery Bypass Graft Operation TiCAB—Ticagrelor in CABG.

* Without (with) the treatment arm receiving ticagrelor 90 mg twice daily.

† Refers to previous MI other than the one qualifying the inclusion in the trial.

standard of care. All trials had sufficient statistical power for composite clinical end points, which included overall mortality and MI in most of them. Three trials^{6,8,9} reported outcome data beyond 12 months. The definitions of outcomes are reported in Supplemental Table III, and the risk of bias among studies is reported in Supplemental Table IV.

Baseline characteristics are shown in the Table. Patients were more often male and had a median age of 65.5 years (interquartile range, 64.5-66.0), nearly a third of them had diabetes, and one fourth of them were active smokers at the time of inclusion in the primary trials. A previous MI was reported in 18.7% of patients and 5.8% of the patients have had cerebrovascular accidents before enrolment. The weighted median follow-up available for the assessment of outcomes of interest was 20 months (mean 19.0 ± 11.8).

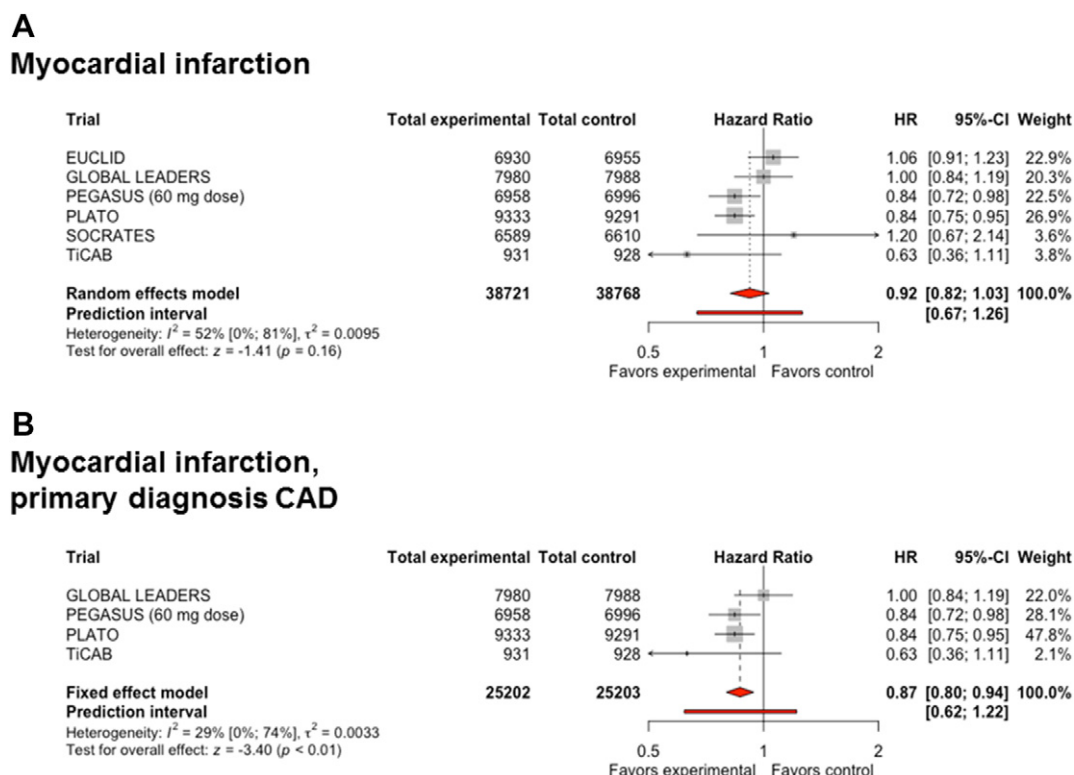
Clinical outcomes

Primary outcome. Overall, all-cause deaths occurred in 3,607 patients (4.6%; Figure 1, A). The primary outcome occurred in 4.5% of patients treated with experimental therapy and 4.9% of patients treated with control therapy (HR = 0.91, 95% CI 0.81-1.01; $P = .07$). The random-effects meta-analysis had 98.4% power to detect a 20% RRR of all-cause death associated with the experimental therapy. Of note, the 95% prediction interval for this outcome contained the null (0.68-1.21), and there was evidence of significant heterogeneity. However, the risk for all-cause death was significantly reduced with the experimental therapy in trials that enrolled only patients with CAD as primary diagnosis

(4.0% vs 4.8%; HR = 0.84 [0.77-0.91]; $P < .001$; Figure 1, B) compared with trials with PAD as primary diagnosis (5.1% vs 5.1%; 1.01 [0.91-1.12], $P = .91$; P for interaction [P_{int}] = .008). The number needed to treat to avoid 1 case of all-cause death with the experimental therapy in trials that enrolled patients with CAD as primary diagnosis was 130 patients (90-231). Cardiac death occurred in 1,985 patients (3.2%; data available for 61,521 participants; Supplemental Figure 2). Patients treated with experimental versus control therapy showed a comparable risk of cardiac death (3.1% vs 3.4%; HR = 0.92 [0.77-1.09], $P = .32$). Of note, the risk for cardiac death was significantly reduced with experimental therapy in trials that enrolled patients having CAD as primary diagnosis (HR = 0.80 [0.72-0.90], $P < .001$) compared with trials with PAD as primary diagnosis (HR = 1.08 [0.94-1.24], $P = .28$; $P_{int} = .001$).

Secondary outcomes. The secondary outcome of MI occurred in 2,996 patients (3.9%; Figure 2, A). Patients treated with experimental or control therapy had a similar risk of MI (3.7% vs 4.0%; HR = 0.92 [0.82-1.03], $P = .24$). The random-effects meta-analysis had 96.3% power to detect a 20% RRR of MI associated with the experimental therapy. However, the 95% prediction interval for this outcome contained the null (0.67-1.26), and there was evidence of significant heterogeneity. We found that the risk of MI was significantly reduced with experimental therapy in trials that enrolled patients having CAD as primary diagnosis (4.3% vs 4.8%; HR = 0.87 [0.80-0.94], $P = .007$; Figure 2, B) but not in trials of patients with PAD as primary diagnosis (2.8% vs 2.6%; HR = 1.07 [0.92-1.24], $P = .37$; $P_{int} = .025$). The number

Figure 2



Risk estimates of main secondary outcome for ticagrelor-based versus conventional antiplatelet regimens. Plot of HR for MI associated with ticagrelor-based (experimental) versus conventional antiplatelet regimens (control) in the overall population (**A**) and in trials which enrolled patients with CAD as primary diagnosis (**B**). The diamonds indicate the point estimate and the left and the right ends of the lines the 95% CI.

needed to treat to avoid 1 case of MI with the experimental therapy in trials that enrolled patients with CAD as primary diagnosis was 160 patients (104-347).

Stroke occurred in 1,799 patients (2.3%, Supplemental Figure 3). Patients treated with experimental as compared to control therapy showed a comparable risk of stroke (2.2% vs 2.5%; HR = 0.90 [0.79-1.04], $P = .15$). Despite the evidence of a lower risk of stroke with experimental therapy across trials, which enrolled patients having PAD as primary diagnosis (HR = 0.84 [0.74-0.94], $P = .003$), we found no treatment-by-subgroup interaction ($P_{\text{int}} = .22$).

Major bleeding occurred in 2,745 patients (3.5%; data available for 77,243 participants; Figure 3). Patients treated with either experimental or control therapy had a comparable risk of major bleeding (3.7% vs 3.4%; HR = 1.16 [0.93-1.46], $P = .19$). Despite the significant heterogeneity observed, we found no treatment-by-subgroup interaction for this outcome ($P_{\text{int}} = .31$). The risk for major bleeding with either experimental or control therapy was also calculated after excluding coronary artery bypass graft-related bleeding reported in the

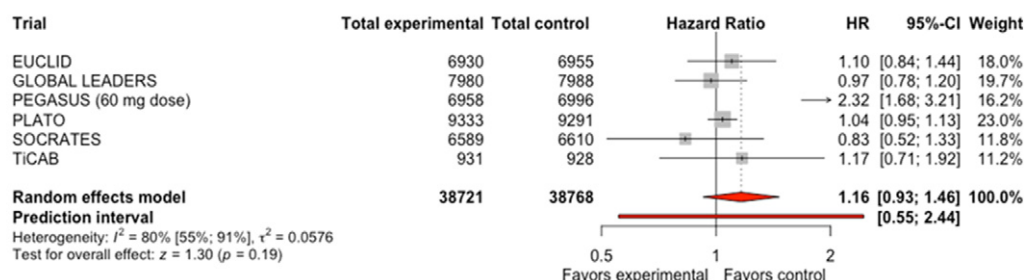
TiCAB trial,¹⁰ without significant changes in the direction of the summary estimation (HR = 1.17 [0.92-1.49], $P = .21$). Of note, patients treated with experimental as compared to control therapy had a higher risk of minor bleeding (HR = 1.32 [1.02-1.72], $P = .03$) without evidence of a treatment-by-subgroup interaction for this outcome ($P_{\text{int}} = .44$).

Sensitivity and influence analyses

Two sensitivity analyses for all-cause death and MI accounted for the peculiar design of the GLOBAL LEADERS trial.⁹ In the first analysis, the HRs between 1 and 2 years associated with either ticagrelor (experimental therapy) or aspirin (control therapy) in this trial were plotted with the HRs from other trials to derive summary risk estimates. In the second analysis, the HRs associated with either ticagrelor (experimental therapy) or clopidogrel (control therapy) up to 2 years in the GLOBAL LEADERS trial were plotted with the HRs from other trials to derive summary risk estimates. Both analyses provided no evidence in support of a significant change in the direction of the point estimations for primary and main secondary outcomes (Supplemental Table V).

Figure 3

Major bleeding



Risk estimates of major bleeding for ticagrelor-based versus conventional antiplatelet regimens. Plot of HR for major bleeding associated with ticagrelor-based (experimental) versus conventional antiplatelet regimens (control) in the overall population. The diamonds indicate the point estimate and the left and the right ends of the lines the 95% CI.

One additional sensitivity analysis accounted for the impact of outcome data from the treatment arm prescribing ticagrelor 90 mg twice daily in the PEGASUS TIMI 54 trial⁶ on the overall calculations: this analysis provided no evidence in support of a significant change in the direction of the point estimations, although patients receiving ticagrelor-based as compared to control antiplatelet regimens had higher, albeit statistically nonsignificant, risk of major bleeding (HR = 1.32 [0.98-1.75], $P = .06$) (Supplemental Table VI).

The influence analysis demonstrated that no single study significantly altered the direction of the summary HRs for primary and main secondary outcomes (Supplemental Figure 4, A and B). The linear regression test discarded a funnel plot asymmetry for all-cause death ($P = .66$) and MI ($P = .90$), respectively (Supplemental Figure 5, A and B). The meta-regression analysis found that the treatment effect for all-cause death ($P = .38$ and 0.88) and MI ($P = .20$ and 0.69) was not affected by the therapy adherence or duration in the experimental arm.

Discussion

This meta-analysis investigated the outcomes of patients with coronary or peripheral manifestation of obstructive atherosclerotic disease randomly assigned to either ticagrelor-based or conventional antiplatelet regimens for secondary prevention of ischemic events. After a median follow-up of 20 months, the experimental therapy was associated with a lower risk of death, including death due to cardiac causes in patients with chronic/stable or unstable CAD. The lower risk of cardiac death with ticagrelor-based antiplatelet regimens is at least in part attributable to a lower risk of MI. As recently reported, occurrence of MI was associated with almost 7-fold higher risk of all-cause death and 8-fold higher risk of cardiovascular death after percutaneous coronary inter-

vention.¹⁸ Interestingly, the magnitude of the treatment effect for death and MI did not depend on therapy adherence or duration in the experimental arm.

Patients with a diagnosis of atherosclerotic disease affecting the coronary and/or peripheral vascular beds are at high risk for recurrent ischemic events even with contemporary, highly effective antiplatelet therapies.¹ Here, we investigated the clinical impact of ticagrelor-based versus conventional antiplatelet regimens for secondary prevention of ischemic events by means of a meta-analysis of aggregate data from large-scale randomized trials including $\approx 80,000$ patients with CAD and/or PAD. The results of this study need a careful discussion.

First, in the present analysis, patients treated with experimental versus control therapy showed nonsignificantly lower overall mortality. However, patients with CAD as primary diagnosis had 16% relative reduction in the risk of all-cause death by receiving the experimental therapy. Consistently, we observed a 20% relative reduction in the risk of cardiac death associated with the experimental therapy in this subset of patients. The improved survival rate with the experimental therapy in patients with CAD as primary diagnosis is likely due, among others, to a decreased risk of MI. Indeed, this analysis showed a 13% relative reduction in the risk of MI in this group of patients. The present meta-analysis has sufficient statistical power to ascertain any clinically relevant benefit in terms of mortality and MI associated with the experimental therapy and is expected to remain the best evidence base for ticagrelor-based regimens for the foreseeable future.

Second, a comparative analysis of PLATO trial⁵ which included patients with CAD as primary diagnosis and EUCLID trial⁸ which predominantly included patients with PAD shows that ticagrelor (as compared with clopidogrel) reduces the risk for mortality in patients with CAD but not

in those with PAD, and current meta-analysis seems to support this finding. Although the reasons for this differential efficacy in these 2 vascular beds remain unclear, it has been suggested that patients with CAD and PAD have important biological and physiological differences that are poorly understood. It is plausible that platelet-independent mechanisms leading to adverse vascular events are more frequent among patients with PAD than those with CAD. Moreover, patients with PAD may have unique risk factors (diabetes, smoking) and clinical drivers that may lead to increased mortality due to noncardiovascular events. If PAD is complicated by acute limb ischemia, central thromboembolic events unrelated to an atherosclerotic artery disease may occur.¹⁹ This fact could explain the beneficial cardiovascular effect of drugs modulating thrombotic pathways other than platelet aggregation observed in recent investigations of patients with PAD.²⁰ Interestingly, although the superior antithrombotic efficacy of ticagrelor-based regimens is predictable because of a more intense antiplatelet inhibition as compared to antiplatelet regimens based on clopidogrel and/or aspirin, the superior efficacy of ticagrelor monotherapy as compared to ticagrelor plus aspirin might be less intuitive. In this regard, previous data suggest that aspirin may diminish the potent platelet inhibition of ticagrelor²¹ by inhibiting the endothelial release of prostacyclin, which reduces platelet reactivity²² and thus contributes synergistically to the antiplatelet effects of ticagrelor *in vivo*.

Third, the experimental therapy was associated with a 16% RRR of stroke in trials that enrolled patients with PAD as primary diagnosis. However, we found no evidence of interaction between the treatment effect and the predominant diagnosis qualifying the inclusion of patients in the original trials. The lower risk for recurrent stroke with more intense antiplatelet therapies does not represent a novel finding,²³ especially with ticagrelor-based regimens.²⁴ In contrast, the lack of significant reduction of cerebrovascular events among trials enrolling patients with CAD as primary diagnosis remains to be further elucidated.

Finally, patients treated with experimental versus control therapy showed a higher risk of minor bleeding, although the risk of major bleeding remained unaffected. Despite the large heterogeneity, these risk estimations were not dependent on whether the primary diagnosis of enrolled patients was CAD or not. The lower overall mortality observed in patients assigned to experimental therapy represents a reassuring signal. In fact, previous studies have shown that the intensification of antiplatelet therapies, either in terms of potency or duration, is associated with a trade-off between ischemic and bleeding risks.¹ In this regard, the use of a reversible agent as monotherapy is of certain value, and trials are under way to ascertain the potential role of ticagrelor monotherapy as compared to a combination of ticagrelor and aspirin (NCT03119012, NCT02494895).

Study limitations

The current study has some limitations. First, this meta-analysis was based on study-level data: although we believe that the questions under consideration can be reliably answered by a meta-analysis of aggregate data, a meta-analysis of individual participant data remains necessary to investigate a variation of treatment effect across different subgroups of patients. Thus, although we found no interaction between the treatment effect for main outcomes and the therapy adherence and duration in the experimental arm, the actual compliance to experimental therapy at specific time points cannot definitively be investigated in this context. Second, the median follow-up duration was 20 months and varied considerably among the trials: a more extended and homogeneous follow-up would have been desirable. As a consequence, we cannot exclude the possibility that significant differences may emerge at long term, especially for bleeding. Third, the results associated with experimental versus control therapy observed in this analysis do not apply to patients with clinical and anatomical features different from those represented here. Of note, the number needed to avoid 1 case of death or MI with the experimental therapy in patients with CAD as primary diagnosis remains relatively high due to the inclusion of low-risk patients with obstructive chronic/stable or unstable CAD. Fourth, the lack of a common experimental arm among those trials included precludes a firm recommendation concerning the ideal ticagrelor-based regimen for patients with CAD and/or PAD as a primary diagnosis. Finally, the ACS subgroup of the control arm of the GLOBAL LEADERS trial⁹ received also ticagrelor. The substantial difference in this subgroup consisted in the regimen of aspirin, with 24 months of treatment in the control arm and only 1 month in the experimental arm. However, the main outcomes did not differ after exclusion of patients assigned to ticagrelor in the control arm of this trial.

Conclusions

The present meta-analysis showed that in patients with atherosclerotic artery disease, the benefit of ticagrelor-based therapies was confined to patients treated for CAD. The drug significantly reduced the risk for all-cause death and MI without excess risk of bleeding in these patients. In consideration of limitations of subgroup analyses, these results need further validation.

Funding

None.

Conflict of interest

Robert A. Byrne reports lecture fees/honoraria from B. Braun Melsungen AG, Biotronik, Boston Scientific, and Micell Technologies and research grants to the institution

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Appendix. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ahj.2019.08.020>.

References

1. Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat Rev Cardiol* 2018;15(8):480-96.
2. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jørgensen A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease. *Eur Heart J* 2018;39(3):213-260.
3. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases. *Eur Heart J* 2018;39(9):763-816.
4. Udell JA, Bonaca MP, Collet JP, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. *Eur Heart J* 2016;37(4):390-9.
5. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361(11):1045-57.
6. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;372(19):1791-800.
7. Johnston SC, Amarenco P, Albers GW, et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. *N Engl J Med* 2016;375(1):35-43.
8. Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med* 2017;376(1):32-40.
9. Vranckx P, Valgimigli M, Juni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet* 2018;392(10151):940-9.
10. Schunkert H. The TiCAB Trial: Ticagrelor vs aspirin in patients undergoing coronary-artery bypass grafting. Oral presentation at American Heart Association Annual Scientific Sessions, Chicago, IL 2018;November 11.
11. Motovska Z, Hlinomaz O, Kala P, et al. 1-Year outcomes of patients undergoing primary angioplasty for myocardial infarction treated with prasugrel versus ticagrelor. *J Am Coll Cardiol* 2018;71(4):371-81.
12. Berwanger O, Nicolau JC, Carvalho AC, et al. Ticagrelor vs clopidogrel after fibrinolytic therapy in patients with ST-elevation myocardial infarction: a randomized clinical trial. *JAMA Cardiol* 2018;3(5):391-9.
13. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
14. Juni P, Witschi A, Bloch R, et al. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA* 1999;282(11):1054-60.
15. Int'Hout J, Ioannidis JP, Rovers MM, et al. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open* 2016;6(7), e010247.
16. Turner RM, Bird SM, Higgins JP. The impact of study size on meta-analyses: examination of underpowered studies in Cochrane reviews. *PLoS one* 2013;8(3), e59202.
17. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151(4):264-9 W64.
18. Brener SJ, Tarantini G, Leon MB, et al. Cardiovascular and noncardiovascular death after percutaneous coronary intervention: insights from 32 882 patients enrolled in 21 randomized trials. *Circ Cardiovasc Interv* 2018;11(7), e006488.
19. Ward R, Long C, Patel MR, et al. Antiplatelet therapy in peripheral artery disease: a review of the EUCLID trial results and current ongoing trials. *Clin Cardiol* 2018;41(1):137-43.
20. Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2018;391(10117):219-29.
21. Mahaffey KW, Wojdyla DM, Carroll K, et al. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation* 2011;124(5):544-54.
22. Cattaneo M, Lecchi A. Inhibition of the platelet P2Y12 receptor for adenosine diphosphate potentiates the antiplatelet effect of prostacyclin. *J Thromb Haemost* 2007;5(3):577-82.
23. Lee M, Saver JL, Hong KS, et al. Antiplatelet regimen for patients with breakthrough strokes while on aspirin: a systematic review and meta-analysis. *Stroke* 2017;48(9):2610-3.
24. Malhotra K, Goyal N, Kasunich AS, et al. Ticagrelor for stroke prevention in patients with vascular risk factors: a systematic review and meta-analysis. *J Neurol Sci* 2018;390:212-8.