

Efficacy and Safety of Ticagrelor Monotherapy in Patients Undergoing Percutaneous Coronary Intervention: A Meta-Analysis

Georg Gelbenegger¹, Christian Schoergenhofer¹, Bernd Jilma¹, Gloria M. Gager^{1,2}, Al Medina Dizdarevic², Mamas A. Mamas^{3,4}, Biljana Parapid⁵, Poonam Velagapudi⁶ and Jolanta M. Siller-Matula^{2,7,*}

Dual antiplatelet therapy (DAPT) and subsequent P2Y₁₂ inhibitor monotherapy, particularly ticagrelor, is an emerging treatment strategy in patients undergoing percutaneous coronary intervention (PCI). This meta-analysis was designed to investigate whether short-term DAPT followed by ticagrelor monotherapy is associated with a favorable outcome as compared with standard DAPT (1–3 months of DAPT was termed “short-term” DAPT, 6–12 months DAPT was termed “standard” DAPT). The primary outcome was the composite of major adverse cardiovascular events (MACE) comprising myocardial infarction, stroke, and cardiovascular death. Secondary outcomes included all-cause mortality and net adverse clinical events (NACE; myocardial infarction, stroke, all-cause death, stent thrombosis, and major bleeding). The primary safety outcome was major bleeding. Three studies comprising 26,143 patients were included. The risk of MACE was similar between the two treatment groups (risk ratio (RR) 0.86, 95% confidence interval (CI), 0.72–1.02, $P = 0.08$, $I^2 = 22\%$). Short-term DAPT followed by ticagrelor monotherapy resulted in a 20% relative risk reduction of all-cause mortality (RR 0.80, 95% CI, 0.65–0.98, $P = 0.03$, $I^2 = 0\%$) and an 18% relative risk reduction of NACE (RR 0.82, 95% CI, 0.71–0.94, $P = 0.005$, $I^2 = 33\%$) as compared with standard DAPT. Short-term DAPT followed by ticagrelor monotherapy significantly decreased the risk of major bleeding (RR 0.67, 95% CI, 0.49–0.92, $P = 0.01$, $I^2 = 65\%$). In patients with acute coronary syndrome, short-term DAPT followed by ticagrelor monotherapy resulted in an unchanged ischemic risk but a significantly lower bleeding risk compared with standard DAPT. Short-term DAPT followed by ticagrelor monotherapy compared with standard DAPT resulted in a favorable safety and efficacy profile. Direct comparisons of aspirin vs. ticagrelor monotherapy following PCI are needed.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Dual antiplatelet therapy (DAPT) is effective in preventing thromboembolic complications following percutaneous coronary intervention (PCI) but is associated with an increased risk of bleeding. P2Y₁₂ inhibitor monotherapy, as opposed to aspirin monotherapy, has emerged as an up-and-coming treatment regimen following DAPT.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ This study sought to evaluate the efficacy and safety of ticagrelor monotherapy following PCI.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✓ Short-term DAPT (1–3 months) followed by ticagrelor monotherapy was associated with less all-cause mortality, net adverse clinical events, and major bleeding but an unchanged risk of ischemic events compared with standard DAPT (12 months).

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✓ Short-term DAPT followed by ticagrelor monotherapy is safe and effective and may present an attractive treatment regimen in patients with a high bleeding risk.

Dual antiplatelet therapy (DAPT), defined as a combination of aspirin plus a P2Y₁₂ inhibitor, has become the cornerstone treatment in patients with acute coronary syndrome (ACS) or undergoing

planned percutaneous coronary intervention (PCI).^{1,2} For patients with stable coronary artery disease undergoing PCI and no high bleeding risk, current guidelines, from both the European Society

¹Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria; ²Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria; ³Keele Cardiovascular Research Group, Keele University, Keele, UK; ⁴Royal Stoke University Hospital, Stoke-on-Trent, UK; ⁵Division of Cardiology, Faculty of Medicine, Clinical Center of Serbia, University of Belgrade, Belgrade, Serbia; ⁶Division of Cardiology, University of Nebraska Medical Center, Omaha, Nebraska, USA; ⁷Department of Experimental and Clinical Pharmacology, Centre for Preclinical Research and Technology, Medical University of Warsaw, Warsaw, Poland. *Correspondence: Jolanta M. Siller-Matula (Jolanta.siller-matula@meduniwien.ac.at)

Received December 16, 2020; accepted February 23, 2021. doi:10.1002/cpt.2226

of Cardiology (ESC) and the American College of Cardiology (ACC)/American Heart Association (AHA), recommend DAPT with clopidogrel for the duration of 6 months.^{1,2} For patients with ACS that are being treated with PCI, both guidelines suggest DAPT for a period of 12 months, with a class IIb recommendation to continue DAPT for an extended period over 1 year.

However, due to the increased risk of bleeding complications accompanying DAPT and associated compliance/adherence problems, shortening of DAPT or switching to single antiplatelet therapy have become options in patients undergoing PCI.³ In contrast to primary prevention,⁴ aspirin's efficacy in secondary prevention of cardiovascular disease is well-established,⁵ but its status as cornerstone treatment in antithrombotic therapy is being challenged due to the (i) increased bleeding events (especially with concomitant P2Y₁₂ inhibitor use or anticoagulation and in the elderly population),⁶ (ii) reduction of cardiovascular events by other cardiovascular drug classes, and (iii) and the introduction of other potent antiplatelet agents.⁷ Furthermore, the development of newer-technology drug-eluting stents with ultra-thin struts and bioresorbable polymers warrants stratified approaches toward duration of DAPT.^{8–12}

These changes have prompted studies investigating P2Y₁₂ inhibitor monotherapy with ticagrelor. This meta-analysis summarizes studies on P2Y₁₂ inhibitor monotherapy with ticagrelor after PCI and discusses their clinical implications.

METHODS

Data sources

Our trial was registered with PROSPERO under the ID CRD42020211516. We conducted a systematic search in the PubMed, Cochrane, Embase, and Web of Science from database inception through the final search date of June 30, 2020. We used the subsequent predefined search terms: ticagrelor monotherapy AND dual antiplatelet therapy AND duration AND bleeding. No language, publication date, or publication status restrictions were applied. References of retrieved articles and prior meta-analyses were checked for additional studies.

Trial eligibility and data extraction

This study was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table S1) and performed according to established methods, as described previously.^{13,14} Only full-text articles were included. Trials that (i) compared any different DAPT durations after PCI and used ticagrelor monotherapy, (ii) were randomized controlled trials, and (iii) reported on at least one of the outcomes of interest (major adverse cardiovascular events (MACE), myocardial infarction (MI), stroke, stent thrombosis (ST), all-cause death, cardiovascular death, and major bleeding) were included. Eligible reports were assessed for methodological quality using the Cochrane Risk of Bias Tool (Table S2). Studies were excluded if one could determine, from the title, or abstract, or both, that the study was not suitable for inclusion. Full text of the study was obtained and evaluated if an article could not be excluded with certainty. Two reviewers (authors G.G. and J.M.S.M.) independently and in duplicate applied the selection criteria. Any discrepancy was resolved by author consensus.

Outcomes and subgroup analysis

The primary efficacy outcome was the composite of MACE (the composite of MI, stroke, and cardiovascular death). The secondary efficacy outcomes included all-cause death, cardiovascular death, MI, ST, and stroke.

We also calculated the composite of net adverse clinical events (NACE; composite of MI, stroke, all-cause death, ST, and major bleeding). Major bleeding was defined as the primary safety outcome. Two different bleeding definitions, Thrombolysis in Myocardial Infarction (TIMI)¹⁵ and Bleeding Academic Research Consortium (BARC),¹⁶ were used in the trials included in this meta-analysis.

All outcomes were analyzed by an intention-to-treat analysis. We performed subgroup analyses for the primary efficacy outcome and the primary safety outcome, including only patients presenting with ACS and patients undergoing complex or noncomplex PCI. The definitions of complex PCI differed in the GLOBAL LEADERS and the TWILIGHT trial. Details about the differences between the definitions of complex PCI are shown in Table S3.

Due to the heterogeneous definitions of MACE and NACE used, we performed sensitivity analyses using the MACE/NACE definitions from each individual study.

Data synthesis and statistical analysis

DAPT durations were categorized into short-term DAPT (1–3 months) and standard DAPT (6–12 months). Variables were reported as number or percentages, as appropriate. Risk ratios (RRs) were computed from individual studies and pooled according to the inverse variance random effect method with 95% confidence intervals (CIs) using Review Manager (version 5.4; The Cochrane Collaboration, 2020). Unadjusted *P* values were reported throughout, with hypothesis testing set at the 2-tailed significance level of 0.05. We assessed studies for clinical and statistical heterogeneity. To assess statistical heterogeneity, we calculated the *I*² index and a *P* value. Percentages < 25% (*I*² = 25), 25–50% (*I*² = 50), and 50–75% (*I*² = 75) correlate to low, medium, and high heterogeneities, respectively.¹⁷ Due to the high clinical heterogeneity, we used the random-effect model.

RESULTS

Our search yielded 74 references. The flow diagram depicting our search algorithm is shown in Figure S1. Three studies, including a total of 26,143 patients, met our inclusion criteria.^{18–20} The TWILIGHT¹⁹ and the TICO trials¹⁸ both had a follow-up of 12 months. The GLOBAL LEADERS trial²⁰ provided a 2-year follow-up, yet for consistency of data, we chose to include data from the 1-year follow-up. Further, the GLOBAL LEADERS trial²⁰ did not report on the outcome of cardiovascular mortality, so all-cause mortality was used for the composite end point MACE.

Specific data for the ACS subgroup of the GLOBAL LEADERS was taken from a *post hoc* analysis.²¹ In the same manner, data for the complex/noncomplex PCI subgroups were taken from *post hoc* analyses from the GLOBAL LEADERS²² and the TWILIGHT trials.²³ Data from the GLOBAL LEADERS trial for the sensitivity analysis of NACE was taken from another *post hoc* analysis.²⁴

All studies^{18–20} exclusively included patients who underwent PCI with placement of a drug-eluting stent. The TWILIGHT trial included patients with high ischemic or bleeding risk but excluded patients presenting with ST-elevation MI.¹⁹ The TICO trial only included patients presenting with ACS but excluded patients with an increased risk of bleeding.¹⁸ Detailed information on the studies included can be found in Table 1 and Table S4.

Primary efficacy outcome: Major adverse cardiovascular events

Short-term DAPT followed by ticagrelor monotherapy was associated with a trend toward a decreased risk of MACE (RR

Table 1 Table depicting characteristics of included studies

Study	Design	Follow-up	P2Y ₁₂ inhibitor	Duration	N	Study population	DES type
Vranckx et al. GLOBAL LEADERS	Open-label, randomized superiority trial	12 months/730 days (24 months)	Ticagrelor	1 month vs. 12 months	15,968 7,980 vs. 7,988	ACS and stable CAD	Biolimus-eluting stent
Mehran et al. TWILIGHT	Randomized, placebo-controlled, double-blind, multicenter trial	12 months	Ticagrelor	3 months vs. 12 months	7,119 3,555 vs. 3,564	ACS and stable CAD	DES
Kim et al. TICO	Investigator-initiated, multicenter, randomized, unblinded trial	12 months	Ticagrelor	3 months vs. 12 months	3,056 1,527 vs. 1,529	ACS	Ultrathin bioresorbable polymer sirolimus-eluting stents

ACS, acute coronary syndrome; CAD, coronary artery disease; DES, drug-eluting stent.

0.86, 95% CI, 0.72–1.02, $P = 0.08$, $I^2 = 22\%$; **Figure 1a**) compared with standard DAPT. The absolute risk reduction, number needed to treat, and number of events reduced per 1,000 patients treated of the major outcomes of this study are shown in **Table 2**.

Secondary efficacy outcomes

Short-term DAPT followed by ticagrelor monotherapy resulted in a significant 18% relative risk reduction of the composite of NACE as compared with standard DAPT (RR 0.82, 95% CI, 0.71–0.94, $P = 0.005$, $I^2 = 33\%$; **Figure 1b**), resulting in a favorable net clinical benefit.

Short-term DAPT followed by ticagrelor monotherapy was associated with a significant 20% relative risk reduction of all-cause death (RR 0.80, 95% CI, 0.65–0.98, $P = 0.03$, $I^2 = 0\%$; **Figure 1c**), as compared with standard DAPT.

Two trials, the TWILIGHT¹⁹ and the TICO trials,¹⁸ reported on the outcome of cardiovascular death. Short-term DAPT was associated with a similar risk of cardiovascular death as compared with standard DAPT (RR 0.68, 95% CI, 0.44–1.05, $P = 0.08$, $I^2 = 0\%$; **Figure S2a**).

There were no statistically significant differences between short-term DAPT followed by ticagrelor monotherapy and standard DAPT regarding the relative risk of MI (RR 1.06, 95% CI, 0.88–1.27, $P = 0.57$, $I^2 = 11\%$; **Figure S2b**), ST (RR 1.14, 95% CI, 0.80–1.62, $P = 0.48$, $I^2 = 4\%$; **Figure S2c**), stroke (RR 1.13, 95% CI, 0.73–1.76, $P = 0.58$, $I^2 = 27\%$; **Figure S2d**) or target vessel revascularization (RR 0.87, 95% CI, 0.75–1.02, $P = 0.10$, $I^2 = 0\%$; **Figure S2e**).

Primary safety outcome: Major bleeding

One study¹⁸ reported on the major bleeding outcome according to the TIMI bleeding classification and all three studies^{18–20} according to the BARC bleeding classification.

Short-term DAPT followed by ticagrelor monotherapy significantly decreased the risk of major bleeding (according to the BARC bleeding classification) compared with standard DAPT (RR 0.67, 95% CI, 0.49–0.92, $P = 0.01$, $I^2 = 65\%$; **Figure 2**).

Subgroup analysis: Acute coronary syndrome

All three studies provided data on the ACS subgroup.^{18,19,21}

In patients presenting with ACS, standard DAPT was associated with an unchanged risk of MACE compared with short-term DAPT followed by ticagrelor monotherapy (RR 0.91, 95% CI, 0.74–1.12, $P = 0.38$, $I^2 = 15\%$; **Figure 3a**).

Patients with ACS receiving short-term DAPT followed by ticagrelor monotherapy had significantly lower risk of major bleeding compared with patients with ACS receiving standard DAPT (RR 0.50, 95% CI, 0.40–0.61, $P < 0.00001$, $I^2 = 0\%$; **Figure 3b**).

Subgroup analysis: Complex/noncomplex PCI

Post hoc analyses from two trials, GLOBAL LEADERS²² and TWILIGHT,²³ provided data on patients undergoing complex or noncomplex PCI.

In patients undergoing complex PCI, short-term DAPT followed by ticagrelor monotherapy was associated with a significantly

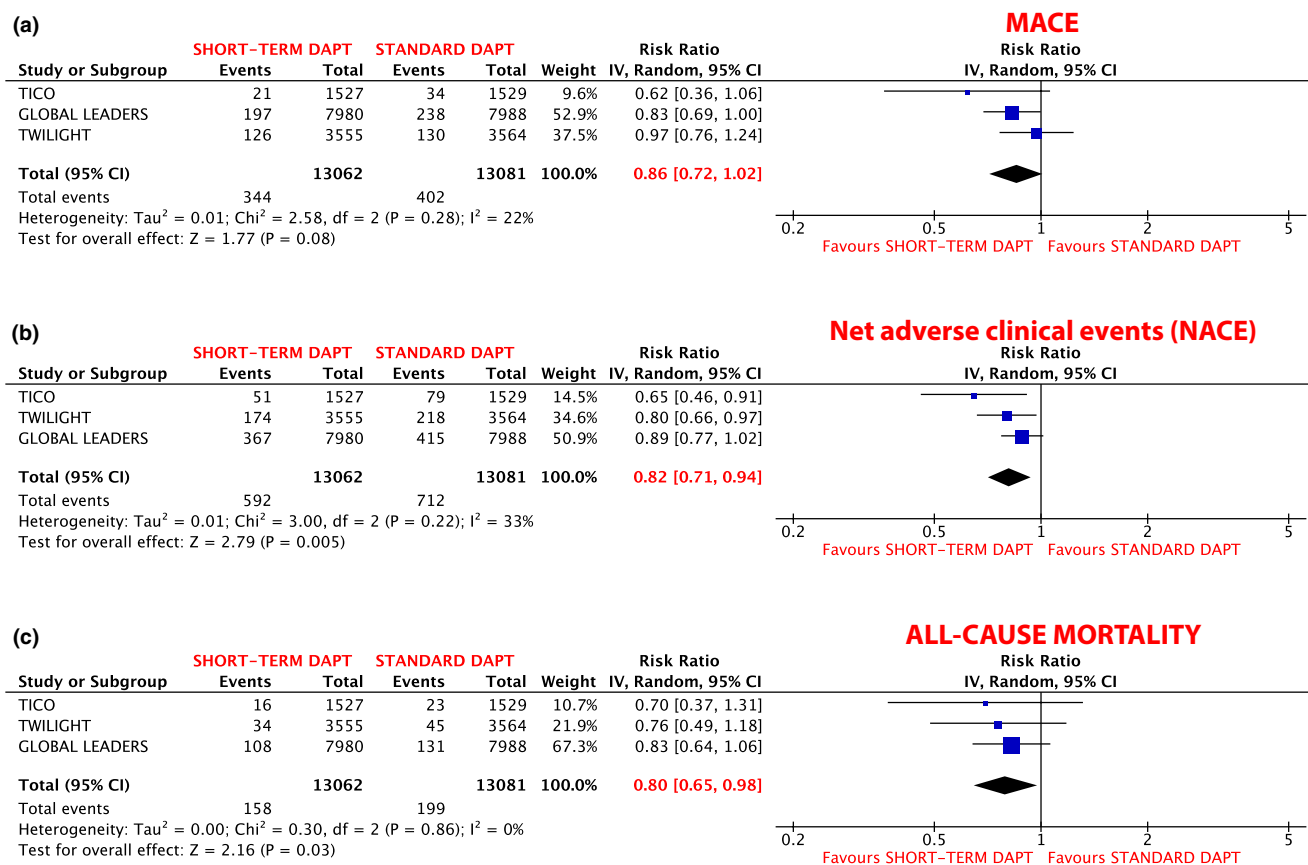


Figure 1 Forest plot showing the risk ratio of (a) major adverse cardiovascular events (MACE), (b) net adverse clinical events (NACE) and (c) all-cause mortality according to the two treatment regimens: short-term dual antiplatelet therapy (DAPT) followed by ticagrelor monotherapy vs. standard DAPT. CI, confidence interval.

Table 2 The RRR, ARR, the NNT, the number of events reduced per 1,000 patients treated, and the P value of the major outcomes of this study

	RRR, %	ARR, %	NNT	No. of events reduced per 1,000 treated patients	P value
MACE	14	0.4	250	4	0.08
NACE	18	0.9	111	9	0.005
All-cause mortality	20	0.3	333	3	0.03
Major bleeding	33	0.6	167	6	0.01

ARR, absolute risk reduction; MACE, major adverse cardiovascular event; NACE, net adverse clinical event; NNT, number needed to treat; RRR, relative risk reduction.

Bold indicates the values $P < 0.05$ are statistically significant.

lower risk of MACE compared with standard DAPT (RR 0.72, 95% CI, 0.56–0.93, $P = 0.01$, $I^2 = 0\%$; **Figure 3c**). There was no difference between treatment groups in patients undergoing non-complex PCI (RR 0.98, 95% CI, 0.78–1.23, $P = 0.84$, $I^2 = 33\%$; **Figure 3c**).

In patients undergoing complex or noncomplex PCI, there was no significant difference between treatment groups, however, both subgroups showed a trend toward a reduction of major bleeding in the short-term DAPT followed by ticagrelor monotherapy group (RR 0.62, 95% CI, 0.30–1.30, $P = 0.21$, $I^2 = 72\%$; **Figure 3d** and

RR 0.74, 95% CI, 0.48–1.14, $P = 0.17$, $I^2 = 54\%$, respectively; **Figure 3d**).

Sensitivity analysis: MACE (according to the individual studies' definition)

When the individual studies' definition of MACE was used, short-term DAPT followed by ticagrelor monotherapy significantly decreased the risk of MACE (RR 0.86, 95% CI, 0.74–0.99, $P = 0.04$, $I^2 = 10\%$; **Figure S3a**) compared with standard DAPT.

Study or Subgroup	SHORT-TERM DAPT		STANDARD DAPT		Weight	Risk Ratio	
	Events	Total	Events	Total		IV, Random, 95% CI	IV, Random, 95% CI
BARC 3-5							
TWILIGHT	34	3555	69	3564	27.9%	0.49	[0.33, 0.74]
TICO	53	1527	83	1529	32.7%	0.64	[0.46, 0.90]
GLOBAL LEADERS	117	7980	136	7988	39.4%	0.86	[0.67, 1.10]
Subtotal (95% CI)		13062		13081	100.0%	0.67	[0.49, 0.92]
Total events	204		288				
Heterogeneity: Tau ² = 0.05; Chi ² = 5.79, df = 2 (P = 0.06); I ² = 65%							
Test for overall effect: Z = 2.47 (P = 0.01)							

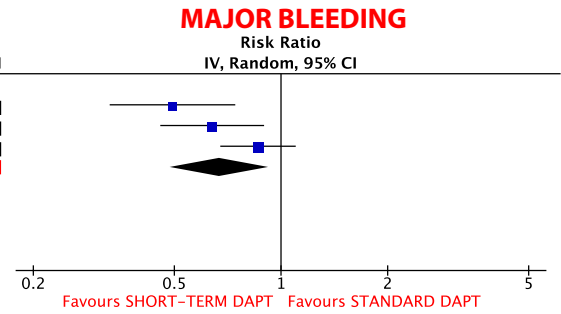


Figure 2 Forest plot showing the risk ratio of major bleeding (Bleeding Academic Research Consortium (BARC) 3–5) according to the bleeding academic research consortium in the two treatment regimens: short-term dual antiplatelet therapy (DAPT) followed by ticagrelor monotherapy vs. standard DAPT.

Sensitivity analysis: NACE (according to the individual studies’ definition)

The GLOBAL LEADERS trial²⁴ and the TICO trial¹⁸ reported on the incidence of NACE. When the individual studies’ definition of NACE was used, there was no statistically significant difference between short-term DAPT followed by ticagrelor monotherapy and standard DAPT regarding the relative risk of NACE (RR 0.81, 95% CI, 0.59–1.11, P = 0.19, I² = 73%; **Figure S3b**).

DISCUSSION

This systematic review and meta-analysis comprise three trials (> 26,000 patients) investigating the novel concept of ticagrelor monotherapy in patients undergoing PCI following a short-term treatment with DAPT. All included studies compared short-term DAPT (1–3 months) followed by P2Y₁₂ inhibitor monotherapy with ticagrelor to standard DAPT (12 months).

Our meta-analysis shows that short-term DAPT followed by ticagrelor monotherapy is safe and effective. In particular, we demonstrate that, compared with standard DAPT, short-term DAPT followed by ticagrelor monotherapy (i) is associated with a trend towards a reduced risk of MACE, (ii) significantly decreases all-cause mortality and the risk of NACE and major bleeding, and (iii) results in an unchanged risk of cardiovascular death, MI, ST, and stroke. See **Figure 4** for the summary of key outcomes.

The balance between ischemic and bleeding risks determines the overall benefit of antithrombotic treatments. Across all three included studies,^{18–20} short-term DAPT followed by ticagrelor monotherapy resulted in an unchanged risk of MACE compared with standard DAPT. Although the TICO¹⁸ and TWILIGHT trials¹⁹ found significant increases of major bleeding events with standard DAPT, the GLOBAL LEADERS trial²⁰ could not detect a significant difference between the treatment groups. This is rather unexpected, as the GLOBAL LEADERS trial²⁰ compared the shortest DAPT duration (1 month) to standard DAPT—the other two trials^{18,19} both compared 3-month DAPT to standard 12-month DAPT—which may have led to the assumption that it would show the greatest relative risk reduction of major bleeding. In contrast, the TWILIGHT trial¹⁹ included both high-risk bleeding and ischemic patients and therefore expectedly demonstrated a significantly increased risk of major bleeding events in

patients with standard DAPT. The TICO trial¹⁸ excluded patients at increased risk of bleeding, yet still showed a significant decrease of major bleeding events in the short-term DAPT followed by ticagrelor monotherapy group.

Interestingly, short-term DAPT followed by ticagrelor monotherapy significantly decreased all-cause mortality compared with standard DAPT, which may be due to the accompanying decreased risk of major bleeding. Further studies investigating the particular concept of P2Y₁₂ inhibitor/ticagrelor monotherapy are needed to underscore and confirm this result. Indeed, the reduction of major bleeding following PCI is an important clinical aim, due to its strong association with mortality.²⁵ All three trials^{18–20} in this analysis compared short-term DAPT followed by ticagrelor monotherapy to standard DAPT. Conceivably, it is easier to demonstrate less bleeding with a single antiplatelet therapy regimen than with a DAPT regimen, and our meta-analysis confirmed the significant reduction of major bleeding events with short-term DAPT followed by ticagrelor monotherapy compared with standard DAPT.

In contrast, short-term DAPT followed by ticagrelor monotherapy was associated with an unchanged relative risk of MACE compared with standard DAPT, even showing a trend toward fewer events in the ticagrelor monotherapy treatment group, which makes it an attractive and feasible treatment option in the future. This is further substantiated by the significant results in favor of short-term DAPT followed by ticagrelor monotherapy in our net clinical benefit analysis (**Figure 1b**).

Compared with ticagrelor monotherapy, aspirin monotherapy may have similar efficacy in reducing bleeding events, with potentially no increased risk of MACE. Each of the three clinical trials fall short of a duly needed third study arm, investigating the effects of short-term DAPT followed by aspirin monotherapy. The head-to-head comparison of short-term DAPT followed by aspirin vs. P2Y₁₂ inhibitor (ticagrelor in particular) monotherapy is, however, missing. Given the relatively inexpensive costs of aspirin compared with ticagrelor and increased risk of discontinuation due to side effects, such as dyspnea, a three-way study design would be of major interest. Two studies, the RESET²⁶ and the OPTIMIZE²⁷ trials, have investigated the concept of short-term DAPT (1–3 months) followed by aspirin monotherapy vs. standard DAPT (6–12 months). Both studies used zotarolimus-eluting stents only and found no change in ischemic and bleeding risk between groups.

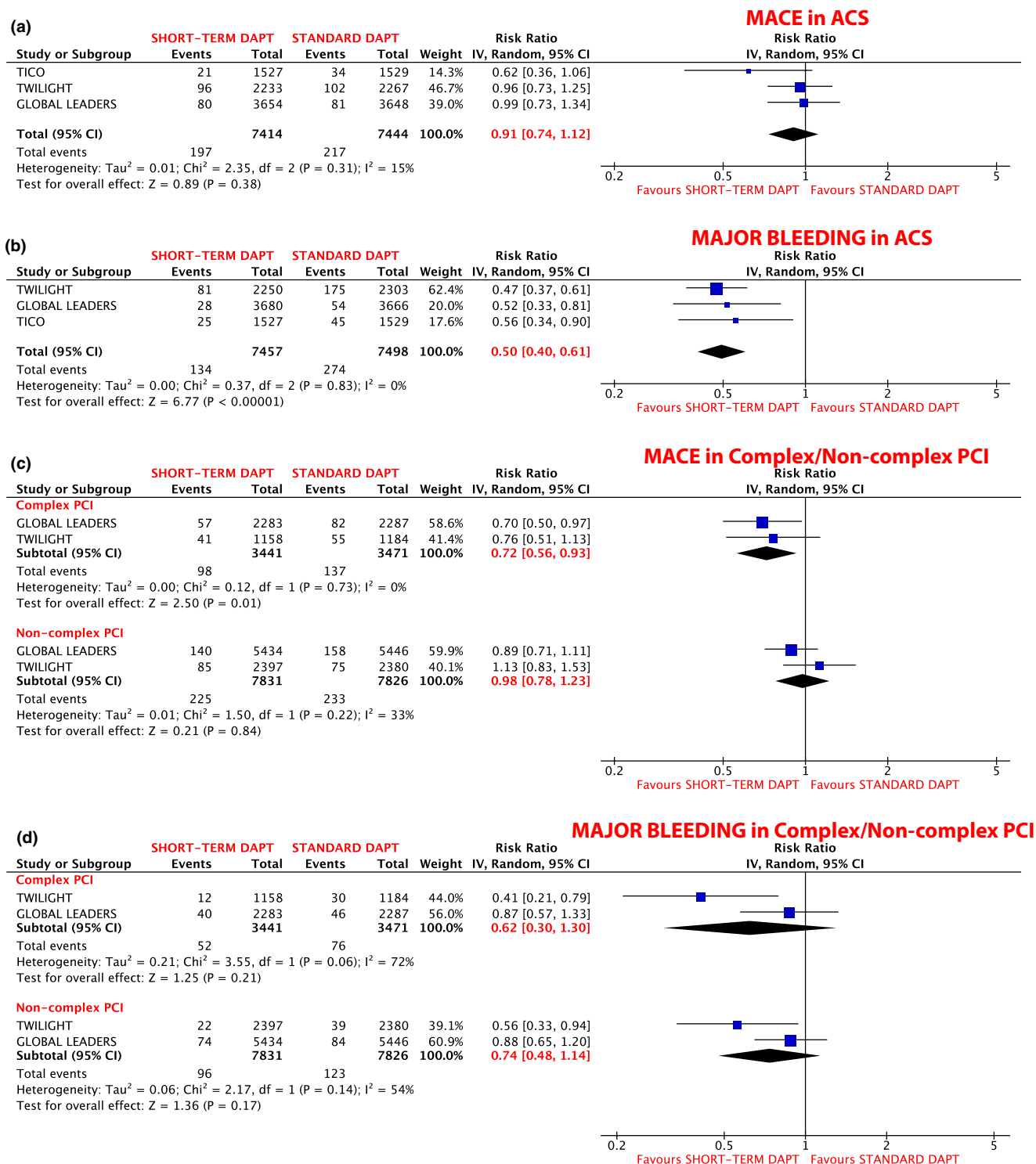


Figure 3 Subgroup analyses. Forest plot showing the risk ratio of (a) major adverse cardiovascular event (MACE) in patients presenting with acute coronary syndrome (ACS), (b) major bleeding in patients presenting with ACS, and (c) MACE in patients undergoing complex or noncomplex percutaneous coronary intervention (PCI), and (d) major bleeding in patients undergoing complex or noncomplex PCI according to the two treatment regimens: short-term dual antiplatelet therapy (DAPT) followed by ticagrelor monotherapy vs. standard DAPT.

Results from a meta-analysis comparing monotherapy with a P2Y₁₂ inhibitor vs. aspirin for secondary prevention of cardiovascular disease show that P2Y₁₂ inhibitor monotherapy was associated with a relative risk reduction of myocardial infarction but an

unchanged risk of stroke, all-cause death, cardiovascular death, and major bleeding.²⁸ The benefit of P2Y₁₂ inhibitor monotherapy is, however, questionable due to the high number needed to treat to prevent myocardial infarction and the lack of effect on mortality.

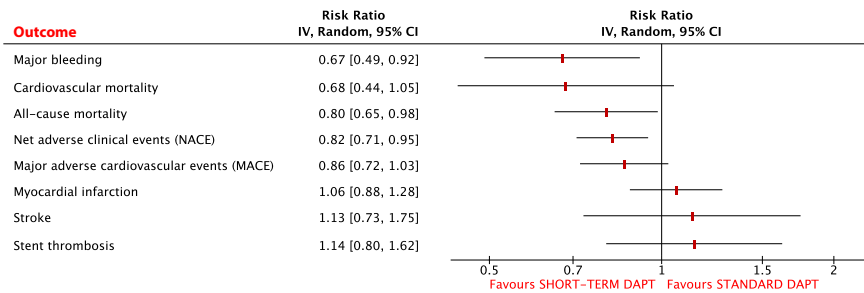


Figure 4 Forest plot showing the risk ratio of the key outcomes across the two treatment regimens: short-term dual antiplatelet therapy (DAPT) followed by ticagrelor monotherapy vs. standard DAPT.

Clinical implications

The available evidence shows that ticagrelor monotherapy might be effective and safe after an initial phase of DAPT. This might be of particular interest in patients with high bleeding risk. Importantly, a comparison of aspirin vs. ticagrelor monotherapy would be of great interest. Whether patients with high bleeding risk might benefit in terms of the net outcome from short-term DAPT with subsequent P2Y₁₂ inhibitor monotherapy compared with standard DAPT, is now additionally investigated in upcoming trials (A-CLOSE trial: NCT03947229 and SMART-CHOICEII trial: NCT03119012). For bleeding risk assessment, the PRECISE-DAPT score may be used.²⁹ The management of patients with both high ischemic and bleeding risk remains challenging and may necessitate an individualized antiplatelet approach.

Our meta-analysis further supports the use of short-term DAPT followed by ticagrelor monotherapy compared with standard DAPT in patients presenting with ACS, as it was associated with an unchanged ischemic risk and a significant reduction of bleeding events. Current ESC guidelines on the management of patients presenting without persistent ST-segment elevation MI have already incorporated the possibility of an aspirin-free treatment strategy, depending on the balance between the ischemic and bleeding risk (class IIa, level A recommendation).³⁰ This recommendation may be extended to patients presenting with ST-segment MI and patients with chronic coronary syndrome in the future.

The use of ticagrelor monotherapy following short-term DAPT may also be warranted in patients undergoing complex PCI, as it was associated with a lower ischemic and an unchanged bleeding risk compared with standard DAPT.

Limitations

Our meta-analysis has several limitations. First, its limited sample size, including only three trials and comprising a total of just 26,143 patients, precludes universal statements. Second, the patient population included was heterogenous and included patients at different ischemic and bleeding risks. One study only included patients presenting with ACS.¹⁸ Third, this meta-analysis lacks patient-level data, which precludes the evaluation of relevant subgroups and renders the performance of an accurate time-to-event analysis impossible. Fourth, for the composite end point MACE in the GLOBAL LEADERS

trial, all-cause mortality had to be used instead of cardiovascular mortality due to the unavailability of data. Fifth, this study assigns equal footing to the various outcomes of NACE despite differently weighted risks in real life.

CONCLUSION

Compared with standard DAPT, short-term DAPT followed by P2Y₁₂ inhibitor monotherapy with ticagrelor resulted in an unchanged ischemic risk but decreased all-cause mortality, the relative risk of NACE, and major bleeding. Direct comparisons of aspirin vs. P2Y₁₂ inhibitor monotherapy (in particular ticagrelor) after coronary stent implantation are needed.

Supporting Information

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

FUNDING

G.G. is supported by grant SFB54-P04 from the Austrian Science Funds. The funding had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CONFLICTS OF INTEREST

M.A.M. receives lecture fees from Daiichi Sankyo unrelated to the present manuscript. J.M.S.-M. receives lecture fees from Daiichi Sankyo, Chiesi, Astra Zeneca, Bayer, and BMS; all unrelated to the present manuscript. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

G.G. and J.M.S.M. wrote the manuscript. G.G. and J.M.S.M. designed and performed the research. G.G., C.S., B.J., G.M.G., A.M.D., M.A.M., B.P., P.V., and J.M.S.M. analyzed the data. All authors approved the final version of the manuscript.

© 2021 The Authors. *Clinical Pharmacology & Therapeutics* published by Wiley Periodicals LLC on behalf of American Society for Clinical Pharmacology and Therapeutics.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

1. Levine, G.N. *et al.* 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for

- Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation* **134**, e123–e155 (2016).
2. Valgimigli, M. *et al.* 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur. Heart J.* **39**, 213–260 (2018).
 3. Alexopoulos, D., Mphahara, A. & Kassimis, G. Omitting aspirin in PCI patients: myth or reality? *Cardiovasc. Drugs Ther.* **33**, 711–724 (2019).
 4. Gelbenegger, G. *et al.* Aspirin for primary prevention of cardiovascular disease: a meta-analysis with a particular focus on subgroups. *BMC Med.* **17**, 198 (2019).
 5. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* **373**, 1849–1860 (2009).
 6. Eyleten, C. *et al.* Non-vitamin K oral anticoagulants (NOAC) versus vitamin K antagonists (VKA) for atrial fibrillation with elective or urgent percutaneous coronary intervention: a meta-analysis with a particular focus on combination type. *J. Clin. Med.* **9**, 1120 (2020).
 7. Capodanno, D. *et al.* Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat. Rev. Cardiol.* **15**, 480–496 (2018).
 8. Jezewski, M.P. *et al.* Bioresorbable vascular scaffolds-dead end or still a rough diamond? *J. Clin. Med.* **8**, 2167 (2019).
 9. Urban, P. *et al.* Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N. Engl. J. Med.* **373**, 2038–2047 (2015).
 10. Varenne, O. *et al.* Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. *Lancet* **391**, 41–50 (2018).
 11. Winter, M.P. *et al.* Advocating cardiovascular precision medicine with P2Y12 receptor inhibitors. *Eur. Heart J. Cardiovasc. Pharmacother.* **3**, 221–234 (2017).
 12. Winter, M.P. *et al.* Incidence, predictors, and prognosis of premature discontinuation or switch of prasugrel or ticagrelor: the ATLANTIS - SWITCH study. *Sci. Rep.* **9**, 8194 (2019).
 13. Gue, Y.X. *et al.* Impact of preadmission morphine on reinfarction in patients with ST-elevation myocardial infarction treated with percutaneous coronary intervention: a meta-analysis. *Clin. Pharmacol. Ther.* **108**, 54–62 (2020).
 14. Komosa, A. *et al.* Optimal timing of P2Y12 inhibitor loading in patients undergoing PCI: a meta-analysis. *Thromb. Haemost.* **119**, 1000–1020 (2019).
 15. Bovill, E.G. *et al.* Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI), Phase II Trial. *Ann. Intern. Med.* **115**, 256–265 (1991).
 16. Mehran, R. *et al.* Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* **123**, 2736–2747 (2011).
 17. Higgins, J.P. & Thompson, S.G. Quantifying heterogeneity in a meta-analysis. *Stat. Med.* **21**, 1539–1558 (2002).
 18. Kim, B.K. *et al.* Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO Randomized Clinical Trial. *JAMA* **323**, 2407–2416 (2020).
 19. Mehran, R. *et al.* Ticagrelor with or without aspirin in high-risk patients after PCI. *N. Engl. J. Med.* **381**, 2032–2042 (2019).
 20. Vranckx, 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* **392**, 940–949 (2018).
 21. Tomaniak, M. *et al.* Benefit and risks of aspirin in addition to ticagrelor in acute coronary syndromes: a post hoc analysis of the randomized GLOBAL LEADERS trial. *JAMA Cardiol.* **4**, 1092–1101 (2019).
 22. Serruys, P.W. *et al.* Impact of long-term ticagrelor monotherapy following 1-month dual antiplatelet therapy in patients who underwent complex percutaneous coronary intervention: insights from the Global Leaders trial. *Eur. Heart J.* **40**, 2595–2604 (2019).
 23. Dangas, G. *et al.* Ticagrelor with or without aspirin after complex PCI. *J. Am. Coll. Cardiol.* **75**, 2414–2424 (2020).
 24. Serruys, P.W. *et al.* Patient-oriented composite endpoints and net adverse clinical events with ticagrelor monotherapy following percutaneous coronary intervention: insights from the randomised GLOBAL LEADERS trial. *EuroIntervention* **15**, e1090–e1098 (2019).
 25. Luo, L. *et al.* The efficacy and safety of P2Y12 inhibitor monotherapy in patients after percutaneous coronary intervention. *Clin. Cardiol.* **43**, 235–241 (2020).
 26. Kim, B.K. *et al.* A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J. Am. Coll. Cardiol.* **60**, 1340–1348 (2012).
 27. Feres, F. *et al.* Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA* **310**, 2510–2522 (2013).
 28. Chiarito, M. *et al.* Monotherapy with a P2Y12 inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. *Lancet* **395**, 1487–1495 (2020).
 29. Costa, F. *et al.* Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* **389**, 1025–1034 (2017).
 30. Collet, J.P. *et al.* 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur. Heart. J.* <https://doi.org/10.1093/eurheartj/ehaa575>. [e-pub ahead of print].