



Ischemic and bleeding outcomes of triple therapy in patients on chronic anticoagulation undergoing percutaneous coronary intervention: A meta-analysis of randomized trials



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Abstract

Background: Triple therapy (TT) that includes oral anticoagulation and dual antiplatelet therapy is recommended in patients who are on chronic anticoagulation and undergo percutaneous coronary intervention (PCI). The randomized clinical trials (RCTs) comparing the effectiveness and safety of TT compared to double therapy (DT), which consists of an oral anticoagulation and one of the P2Y₁₂ inhibitors, have shown increased risk of bleeding; however, none of the individual studies were powered to show a difference in ischemic outcomes. To compare the clinical outcomes of TT and DT, we performed this meta-analysis of RCTs.

Methods: Electronic search of PubMed, EMBASE and Cochrane CENTRAL databases was performed for RCTs comparing TT and DT in patients who were on oral anticoagulation (Vitamin K antagonist or non-vitamin K antagonist oral anticoagulant) who underwent PCI. All-cause and cardiovascular mortality, myocardial infarction (MI), stroke, stent thrombosis (ST) and TIMI major and minor bleeding were the major outcomes.

Results: An analysis of 5 trials including 10,592 total patients showed that TT, compared to DT, resulted in non-significant difference in risk of all-cause [odds ratio (OR); 1.14; 95% confidence interval (CI): (0.80–1.63); $P = 0.46$] and cardiovascular mortality [1.43 (0.58–3.36); $P = 0.44$], MI [0.88 (0.64–1.21); $P = 0.42$], stroke [1.10 (0.75–1.62); $P = 0.63$] and ST [0.82 (0.46–1.45); $P = 0.49$]. TT, compared to DT resulted in higher risk of TIMI major bleeding [1.61 (1.09–2.37); $P = 0.02$], TIMI minor bleeding [1.85 (1.23–2.79); $P = 0.003$] and TIMI major and minor bleeding [1.81 (1.38–2.38); $P < 0.0001$; $I^2 = 52\%$].

Conclusion: Compared to DT, the patients receiving TT are at a higher risk of major and minor bleeding with no survival benefit or impact on thrombotic outcomes.

Keywords

Triple therapy, double therapy, chronic anticoagulation, percutaneous coronary intervention, atrial fibrillation, meta-analysis

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Introduction

After percutaneous intervention (PCI), dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ inhibitor is recommended to prevent stent thrombosis.^{1,2} Many of these patients have coexisting atrial fibrillation (AF), mechanical heart valve in place or have venous thromboembolism that warrants concomitant use of uninterupted oral anticoagulation (OAC) with either vitamin

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K antagonist or non-vitamin K antagonist oral anticoagulant (NOAC) to prevent systemic thromboembolism.^{3–5} Therefore, taking the risk of stroke and stent thrombosis into account, guidelines suggest the use of “triple therapy” (TT) consisting of aspirin, P2Y₁₂ (clopidogrel) inhibitor and an OAC.⁶ Since this approach may result in considerable fatal and non-fatal bleeding risk,^{7–9} the shortest possible duration of TT followed by dual therapy (DT) comprising of single antiplatelet and OAC is usually recommended.⁶ On the other hand, some studies have suggested the use of DT instead by omitting aspirin and maintaining Clopidogrel and OAC¹⁰ to reduce bleeding complications.

Several randomized clinical trials (RCT) have studied the role of TT vs. DT in this patient population and the results have been conflicting or underpowered to assess ischemic outcomes.^{10–13} Therefore, to investigate the role of TT as opposed to DT on ischemic outcomes in patients who undergo PCI and have an indication for OAC use, we conducted this meta-analysis of available published RCTs.

Methods

Data sources and search strategy

We conducted this meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).¹⁴ We searched electronic databases of PubMed, EMBASE and Cochrane Central Register of Clinical Trials with no language restriction from inception through June 2019 using the search terms: “triple therapy” OR “triple antithrombotic therapy” AND “percutaneous coronary intervention” OR “PCI” AND “atrial fibrillation” OR “AF”. Two investigators (KD and NA) independently performed the database search and agreed on final study selection. In addition, a manual search was performed for relevant references from the selected articles and published reviews.

Study selection

Randomized clinical trials comparing the outcomes of triple therapy (defined as DAPT plus an OAC) and double therapy (defined as one of the P2Y₁₂ inhibitors antiplatelet agent plus an OAC) in adult patients (≥ 18 years) who were taking chronic anticoagulation and underwent percutaneous coronary intervention (PCI) were selected for meta-analysis if they reported on major bleeding and ischemic outcomes as crude events. Studies, which were meeting abstracts and non-randomized were excluded. Additionally, studies studying triple therapy in different patient population were also excluded.

Data extraction

Two investigators (NA and HB) extracted data from the selected studies in duplicate using standardized data-extraction form, which were confirmed by a third investigator (KD). We obtained data on study characteristics (study design, patient selection, inclusion and exclusion criteria, follow-up duration, number of patients, double and triple therapy regimen and endpoints), patient characteristics (age, sex, race, co-morbidities, indication of chronic anticoagulation and PCI and medication use), and crude events on mortality, myocardial infarction, stroke, stent thrombosis and different types of bleeding at follow-up.

Outcomes

All-cause and cardiovascular mortality, myocardial infarction (MI), stroke, stent thrombosis (ST) and major and minor bleeding were the major outcomes. For uniformity among the studies, TIMI bleeding classification was used.

Statistical analysis

We performed statistical analyses with Review Manager (RevMan 5.3, Cochrane Collaboration, Nordic Cochrane Center, Copenhagen, Denmark). We calculated odds ratio (OR) with 95% confidence interval (CI) using random-effects model from the individual studies using the total number of events and patients. The studies were assessed with Cochrane Collaboration’s Bias Assessment Tools.¹⁵ Study heterogeneity was evaluated with Cochran’s Q and I² index with a plan to explore significant heterogeneity (I² >50%) with sensitivity analyses. We planned pre-specified subgroup analyses based on type of OAC (warfarin-based vs. NOAC-based) and sensitivity analyses based on study design and type of antithrombotic therapy.

Results

Description of included studies

The flow diagram of study selection is shown in e-Figure 1. Electronic search of three databases (PubMed, EMBASE and CENTRAL) and manual search retrieved a total of 297 publications. After removal of duplicates, we screened 242 citations for eligibility and extracted 22 publications for full text review. Finally, we had a total of five publications^{10–13,16} for qualitative and quantitative analysis after excluding 17 citations for reasons as specified in the PRISMA diagram.

Table 1. Study characteristics of included studies.

	ISAR-TRIPLE, 2015	PIONEER AF-PCI, 2017	RE-DUAL PCI, 2017	WOEST, 2013	AUGUSTUS, 2019
Study Design	Randomized, open-label, multicenter	Randomized, open-label, multicenter	Randomized controlled, open label, multicenter	Randomized controlled, open-label, multi-center	Randomized controlled, multicenter
Indication for OAC	TT-AF/AFL: 261 (85%); MV: 28 (9.1%); VTE: 11 (3.6%); Other 7 (2.3%) and DT- AF/AFL:254 (82.7%); MV:17 (5.5%); VTE:23 (7.5%); Others: 13 (4.2%)	Non-valvular AF	Non-valvular AF	TT-AF/AFL: 162 (69%); MV: 25 (11%); Other (PE, apical aneurysm, PAD, EF <30%): 47 (20%) and DT-AF/AFL:164 (69%); MV:24 (10%); others 48 (20%)	AF
Total Participants, N	614	2124	2725	573	4556
TT, N	307	1415 (Group 2: 709 with rivaroxaban + DAPT) and Group 3: 706 with warfarin + DAPT)	981	284	2277
DT, N	307	709 (Low dose rivaroxaban + P2Y ₁₂ inhibitor)	1744 (981 on 110mg of dabigatran and 763 on 150mg dabigatran)	279	2279
Triple therapy regimen	Aspirin + Clopidogrel + Warfarin/Phenprocoumon	Warfarin/Rivaroxaban + P2Y ₁₂ inhibitor + low dose aspirin	warfarin + P2Y ₁₂ inhibitor + low dose aspirin	Aspirin + Warfarin + Clopidogrel	Aspirin + Apixaban or VKA + P2Y ₁₂ inhibitor
Double therapy regimen	Aspirin + Warfarin/Phenprocoumon	Rivaroxaban 15 mg daily + P2Y ₁₂	Dabigatran 110/150 mg + P2Y ₁₂ inhibitor	Warfarin + Clopidogrel	Apixaban or VKA + P2Y ₁₂ inhibitor
Follow-up, in months	9	12	14	12	6

AF: atrial fibrillation; AFL: atrial flutter; DAPT: dual-antiplatelet therapy; DT: dual therapy; EF: ejection fraction; MV: mechanical valve; N: number; OAC: oral anticoagulation, PAD: peripheral artery disease; TT: triple therapy; VTE: venous thromboembolism.

The individual study and patient characteristics of the included studies are shown, respectively, in Tables 1 and 2. There were 10,592 total patients (5,264 in TT arm and 5,328 in DT arm). Follow-up duration was 6–14 months. All the studies were multicenter international studies.

Major outcomes excluding bleeding

TT, compared to DT resulted in similar risk of all-cause mortality [1.14 (0.80–1.63); $P=0.46$; $I^2=46\%$] (e-Figure 2), cardiovascular mortality [1.43(0.58–3.36); $P=0.44$; $I^2=44\%$], MI [0.88 (0.64–1.21); $P=0.42$, $I^2=0\%$] (Figure 1), stroke [1.10 (0.75–1.62); $P=0.63$, $I^2=0\%$] and ST [0.82 (0.46–1.45); $P=0.49$; $I^2=35\%$].

Bleeding outcomes

TT, compared to DT significantly increased the risk of TIMI major bleeding [1.61 (1.09–2.37); $P=0.02$; $I^2=20\%$] (Figure 2), TIMI minor bleeding [1.85 (1.23–2.79); $P=0.003$; $I^2=39\%$] and combined TIMI major and minor bleeding [1.81 (1.38–2.38); $P<0.0001$; $I^2=52\%$].

Sensitivity and subgroup analyses

Since we included the results of the landmark analysis from ISAR-TRIPLE in our primary analysis, we performed a sensitivity analysis by excluding it. There was no change in the overall direction of results. In addition, we performed analysis by excluding rivaroxaban-based triple therapy outcomes in PIONEER-AF trial as that was the only trial with such comparison. There was no change in the overall results.

Additional subgroup analyses (figures presented as online supplement) were performed for warfarin-based DT vs. NOAC-based DT. There was no significant difference in TIMI major bleeding [1.43 (0.74–2.75); $P=0.29$; $I^2=0\%$] (e-Figure 3), TIMI minor bleeding [2.04 (0.85–4.85); $P=0.11$; $I^2=61\%$] (e-Figure 4) or combined TIMI major and minor [1.82 (0.71–4.68); $P=0.21$; $I^2=80\%$] between warfarin-based TT and warfarin-based DT (e-Figure 5). Compared to NOAC-based DT, warfarin-based TT resulted in significantly higher risk of TIMI major bleeding [1.93 (1.28–2.90); $P=0.002$; $I^2=5\%$], TIMI minor bleeding [2.15 (1.40–3.32); $P=0.0005$; $I^2=0\%$] and combined TIMI major and minor bleeding [1.83 (1.36–2.45); $P<0.0001$; $I^2=0\%$]. On the other hand, comparison of warfarin-based TT vs. warfarin-based DT showed higher all-cause mortality [2.01 (1.06–3.79); $P=0.03$; $I^2=0\%$] (e-Figure 6) in the warfarin-based TT group but no difference was noted in cardiovascular mortality [2.51 (0.97–6.51); $P=0.06$; $I^2=0\%$] (e-Figure 7)

Table 2. Patient characteristics in the included studies.

Study	Age, in years		Male, N (%)		HTN, N (%)		DM, N (%)		HLD, N (%)		Current smoking, N (%)		Indication for PCI		
	TT	DT	TT	DT	TT	DT	TT	DT	TT	DT	TT	DT	TT	DT	
ISAR-TRIPLE, 2015	73.3±8.7	73.9±7.7	242 (78.8%)	229 (74.5%)	72 (23.5%)	85 (27.7%)	232 (75.6%)	236 (76.9%)	230 (74.9%)	227 (73.9%)	32 (10.4%)	28 (9.1%)	STEMI: 2 (0.7%); NSTEMI: 41 (13.4%); UA: 52 (16.9%); Stable Angina: 212 (69.1%)	STEMI:3 (1%); NSTEMI: 50 (16.3%); UA: 49 (16%); Stable Angina: 205 (66.8%)	
PIONEER AF-PCI, 2017	Group 2: 70.4±9.1 Group 3: 70.0±9.1	70.4±9.1	1053 (75%)	528 (75%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
RE-DUAL PCI, 2017	71.7±8.9	71.5±8.9-Dabi 110 mg group, 68.6±7.7-Dabi 150 mg group	750 (76.5%)	Dabi 110 mg: 728 (74.2%), Dabi 150 mg: 592 (77.6%)	NR	NR	371 (37.9%)	Dabi 110 mg: 362 (36.9%), Dabi 150 mg: 260 (34.1%)	NR	NR	NR	NR	NR	Stable Angina, ACS, Staged PCI	Stable Angina, ACS, Staged PCI
WOEST, 2013	69.5±8	70.3±7	234 (82%)	214 (77%)	72 (25%)	68 (24%)	193 (68%)	193 (69%)	205 (72%)	191 (68%)	42 (15%)	60 (22%)	NR	NR	
AUGUSTUS, 2019	70.8	70.6	1611 (69.8%)	1666 (72.2%)	2031 (88%)	2042 (88.5%)	842 (36.5%)	836 (36.2%)	NR	NR	NR	NR	ACS, Elective PCI	ACS, Elective PCI	

TT: triple therapy; DT: dual therapy; HTN: hypertension; DM: diabetes mellitus; HLD: hyperlipidemia; PCI: percutaneous coronary intervention; ACS: acute coronary syndrome; Dabi: Dabigatran; NR: not reported.

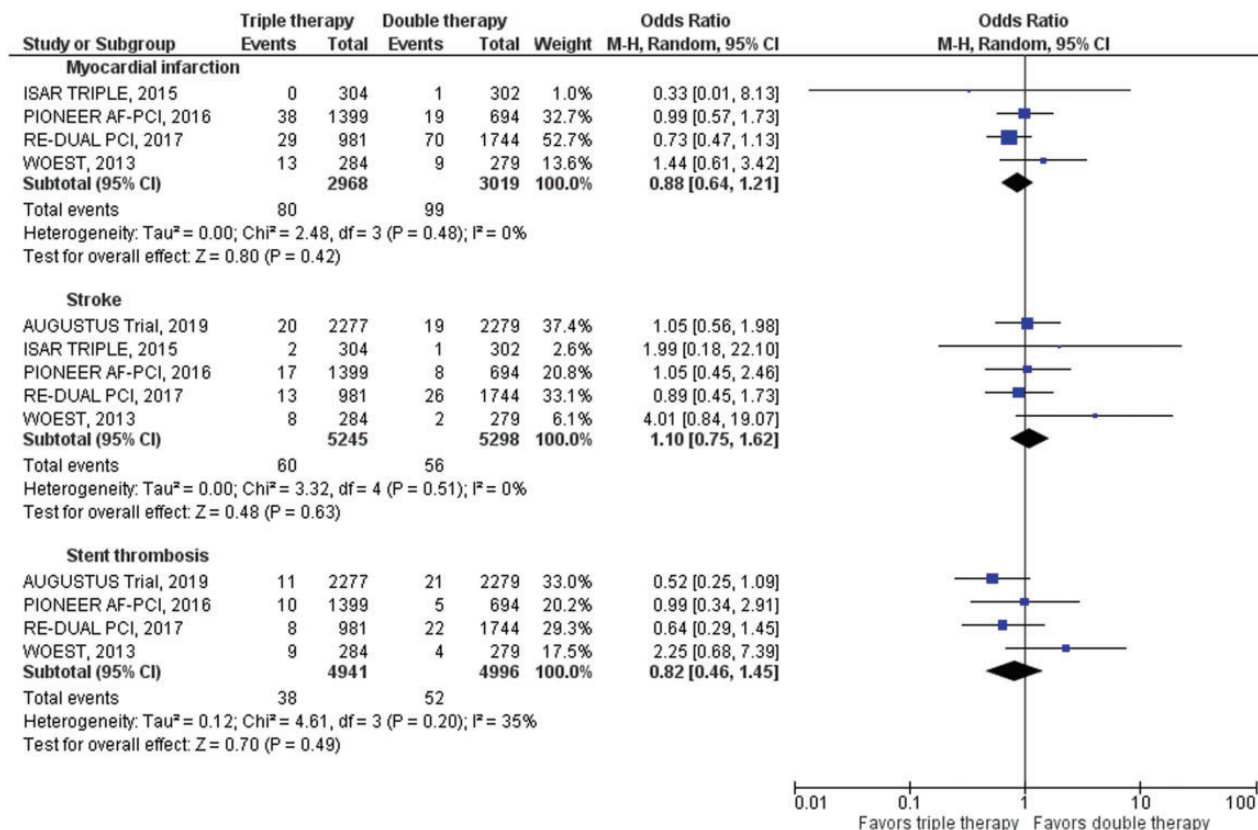


Figure 1. Forest plot for myocardial infarction, stroke and stent thrombosis.

between the two groups. No difference was noted in the outcomes of MI, ST and stroke in the subgroup analyses (e-Figures 8 to 10).

Study quality and publication bias

All the included studies showed bias for non-blinding of the participants and the outcomes per Cochrane collaboration’s bias tools. No bias was observed for randomization, allocation concealment, incomplete data and selective reporting. Publication bias was not tested due to small number of studies for meaningful assessment of publication bias.

Discussion

In this meta-analysis, we sought to compare “triple therapy” with “dual therapy” in patients undergoing PCI who had an indication for OAC use. We found no difference in all-cause and cardiovascular mortality, MI, stroke and ST between the groups, but the risk of bleeding was higher in patients on TT than on DT. The lack of benefits in ischemic outcomes and increase risk of bleeding were seen all four individual trials included in this analysis. Combining all randomized clinical trials potentially increased the analytical statistical power of

underpowered RCTs and therefore, this meta-analysis provides insight into the overall efficacy of TT vs. DT.

The findings of this meta-analysis are similar to the result of several observational studies¹⁷⁻¹⁹ and published meta-analyses of those studies.^{20,21} An important finding of our study is no difference in thrombotic and thromboembolic events between triple and dual therapy. One hypothesis of comparable ischemic outcomes between the groups could be direct or indirect thrombin inhibition by OAC,²² which can potentially provide cardio-protection against ischemic events/thromboembolism. Moreover, addition of OAC to antiplatelet therapy in patients with acute coronary syndrome who do not otherwise need OAC has shown to reduce ischemic events in RCTs,²³⁻²⁵ which can also explain possible benefit of OAC in patients with PCI when used as a part of DT. On the other hand, higher risk of bleeding with concomitant use of dual antiplatelet agents and OAC as TT has been reported in the past²⁶ and is well supported by our meta-analysis. It is important to note that bleeding events at follow-up in ISAR-TRIPLE were fewer in TT arm as compared to the rest of trials, which was because we only included landmark results in the analysis. However, our sensitivity analysis after excluding ISAR TRIPLE¹¹ showed

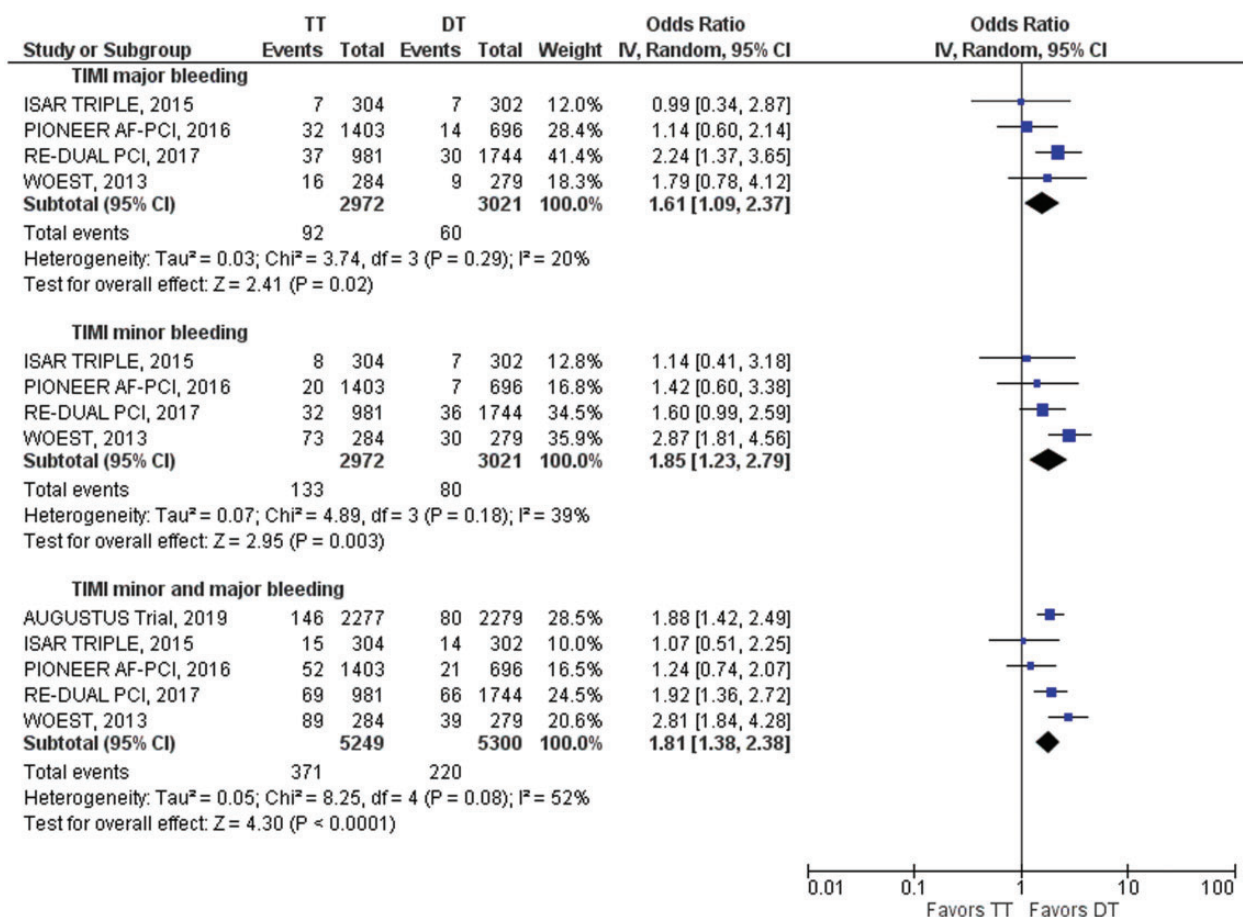


Figure 2. Forest plot for bleeding outcomes.

no impact on the results. In RE-DUAL PCI trial, the use of DT lowered bleeding incidence from one quarter to one half in a dose-dependent fashion when compared to TT.¹² Stopping one of the antiplatelet agents most likely aspirin, which could cause gastric irritation and cause gastrointestinal bleeding, could explain the lower incidence of bleeding with dual therapy approach. Moreover, clopidogrel has shown to be more effective than aspirin in preventing ischemic events²⁷ likely from inhibiting platelet activation.²⁸

Our findings are in line with a recently published meta-analysis²⁹ which shows similarly higher rate of bleeding with TT; however, we have performed multiple subgroup analyses (e-Figures) comparing bleeding and thrombotic outcomes from VKA vs. NOAC-based OAC which provides an important information of higher bleeding from warfarin-based TT, suggesting that NOAC should be preferred when bleeding risk is high. However, due to small number of studies in the subgroup analyses, the results should be interpreted cautiously and considered hypothesis-generating at best. Furthermore, to potentially balance the risk of bleeding (based on HAS-BLED score) with prevention

of thromboembolism (based on CHA₂DS₂VASc score), limiting the duration of TT to a shortest possible should be considered. For selected patients at high thrombotic and low bleeding risks, current guidelines recommend extending the use of TT beyond hospital discharge for up to one month followed by DT for up to 12 months.³⁰ In contrast, for those patients with low thrombotic and high bleeding risk, single antiplatelet agent can be discontinued after six months followed by full stroke prevention OAC dose.³⁰

Regardless of subgroup analyses, our meta-analysis suggests use of DT as an alternative to the TT in patients undergoing PCI who concurrently need OAC. While more randomized trials are necessary, we believe that with our findings, which are based on analysis of randomized trials, DT would be a suitable alternative to using triple therapy in this patient population.

Study limitations

The major limitation of the current meta-analysis is small number of randomized trials, which were underpowered to point a difference in thrombotic outcomes.

The use of different agents in the individual trials may limit generalizability of the results. However, no significant heterogeneity was observed in the overall analyses. Lack of patient level data is another potential limitation. Due to limited data, it was not possible to perform analyses on the outcomes of ischemic vs. hemorrhagic stroke. The results of subgroup analyses should be interpreted cautiously since only two studies were available for the subgroup analysis.

Conclusion

This meta-analysis shows that compared to double therapy, patients receiving triple therapy are at a higher risk of both TIMI major and minor bleeding with no evidence of benefits on the thrombotic outcomes. Future research should focus on the appropriate combination therapy of OAC and antiplatelet therapy in this patient group.

Authors' contributions

KD took part in the study concept and design; SPS, UM, NA, HB, HW, MH, GM, HW, MA, JL, PK and KM took part in acquisition, analysis, or interpretation of data; KD and UM drafted the manuscript; SPS, UM, NA, HB, HW, MH, GM, HW, MA, JL, PK and KM were involved in the critical revision of the manuscript for important intellectual content; KD took part in the statistical analysis; SPS, UM, NA, HB, HW, MH, MA, JL, GM, PK and KM were in charge of the study supervision.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

References

1. Valgimigli M, Byrne RA, Collet J-P, et al. ESC focused update on dual antiplatelet therapy in coronary artery

disease developed in collaboration with EACTS. *Eur Heart J* 2017; 39: 213–260.

2. Iakovou I, Schmidt T, Bonizzi E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005; 293: 2126–2130.
3. Connolly S, Pogue J and Hart R. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006; 367: 1903–1912.
4. Hart RG, Pearce LA and Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; 146: 857–867.
5. Leiria TLL, Lopes RD, Williams JB, et al. Antithrombotic therapies in patients with prosthetic heart valves: guidelines translated for the clinician. *J Thromb Thrombolysis* 2011; 31: 514–522.
6. Kirchhof P, Benussi S, Kotecha D, et al. [2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS]. *Kardiologia Polska* 2016; 74: 1359–1469.
7. Andrade JG, Deyell MW, Khoo C, et al. Risk of bleeding on triple antithrombotic therapy after percutaneous coronary intervention/stenting: a systematic review and meta-analysis. *Can J Cardiol* 2013; 29: 204–212.
8. Lamberts M, Olesen JB, Ruwald MH, et al. Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study. *Circulation* 2013; 126: 1185–1193.
9. Brtko M and Dusek J. Antithrombotic therapy in patients after valve surgery with special attention to the combination of anticoagulant and antiplatelet therapy. *Cor Vasa* 2013; 55: e164–e169.
10. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013; 381: 1107–1115.
11. Fiedler KA, Maeng M, Mehilli J, et al. Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation. *JACC* 2015; 65: 1619–1629.
12. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017; 377: 1513–1524.
13. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016; 375: 2423–2434.
14. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLOS Med* 2009; 6: e1000097
15. Higgins JPT, Thomas J, Chandler J, et al (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019).

- Cochrane, 2019. Available from www.training.cochrane.org/handbook.
16. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med* 2019; 380: 1509–1524.
 17. Kawai H, Watanabe E, Yamamoto M, et al. Major bleeding complications related to combined antithrombotic therapy in atrial fibrillation patients 12 months after coronary artery stenting. *J Cardiol* 2015; 65: 197–202.
 18. De Vecchis R, Cantatrione C and Mazzei D. Clinical relevance of anticoagulation and dual antiplatelet therapy to the outcomes of patients with atrial fibrillation and recent percutaneous coronary intervention with stent. *J Clin Med Res* 2016; 8: 153–161.
 19. Lamberts M, H, Gislason G, Bjerring Olesen J, et al. Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. *JACC* 2017; 62: 981–989.
 20. D'Ascenzo F, Taha S, Moretti C, et al. Meta-analysis of randomized controlled trials and adjusted observational results of use of clopidogrel, aspirin, and oral anticoagulants in patients undergoing percutaneous coronary intervention. *Am J Cardiol* 2015; 115: 1185–1193.
 21. Zhu W, Guo L, Liu F, et al. Efficacy and safety of triple versus dual antithrombotic therapy in atrial fibrillation and ischemic heart disease: a systematic review and meta-analysis. *Oncotarget* 2018; 8: 81154–81166.
 22. Walker CPR and Royston D. Thrombin generation and its inhibition: a review of the scientific basis and mechanism of action of anticoagulant therapies. *Br J Anaesthesia* 2002; 88: 848–863.
 23. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *NEJM* 2012; 366: 9–19, <http://dxdoiorg/101056/NEJMoa1112277>.
 24. Mega JL, Braunwald E, Mohanavelu S, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. *Lancet* 2009; 374: 29–38.
 25. Connolly SJ, Eikelboom JW, Bosch J, et al. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017; 391: 205–218.
 26. Dans AL, Connolly SJ, Wallentin L, et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. *Circulation* 2013; 127: 634–640.
 27. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE.). *Lancet* 1996; 348: 1329–1339.
 28. Moshfegh K, Redondo M, Julmy F, et al. Antiplatelet effects of clopidogrel compared with aspirin after myocardial infarction: enhanced inhibitory effects of combination therapy. *JACC* 2000; 36: 699–705.
 29. Golwala HB, Cannon CP, Steg PG, et al. Safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J* 2018; 39: 1726–1735a.
 30. Angiolillo DJ, Goodman SG, Bhatt DL, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American. *Circulation* 2018; 138: 527–536. DOI: 10.1161/CIRCULATIONAHA.118.034722.