ORIGINAL ARTICLE

Safety and efficacy of dual versus triple antithrombotic therapy in Patients with atrial fibrillation undergoing percutaneous coronary intervention: a meta-analysis

Abdelmoniem Moustafa, Mohammad Saud Khan, Abdalla Marei[1], Mohd Amer Alsamman, Muhammad Baig, Marwan Saad[2]

Department of Internal Medicine, The Miriam Hospital, Warren Alpert School of Medicine at Brown University, Providence, Rhode Island, USA, [1]Department of Cardiac Surgery, Duesseldorf University Hospital, Düsseldorf, Germany, [2]Department of Cardiology, Warren Alpert School of Medicine at Brown University, Providence, Rhode Island, USA

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ABSTRACT

Background: Patients with atrial fibrillation undergoing percutaneous coronary intervention have indications for oral anticoagulation and dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor. The concurrent use of all three agents, termed triple oral antithrombotic therapy (TAT), increases the risk of bleeding. A number of prospective trials showed that the omission of aspirin mitigates the risk of bleeding without affecting major adverse cardiovascular event (MACE). **Materials and Methods:** The databases of PubMed, Embase, and Cochrane Central databases were searched from inception to October 2019. Relevant randomized control trials comparing dual antithrombotic therapy (DAT) versus TAT were identified and a metanalysis was performed using random-effect model. The safety endpoints of interest were thrombolysis in myocardial infarction criteria (TIMI) major and minor bleeding, TIMI major bleeding, and intracranial bleeding. The efficacy endpoints of interest were MACE and individual components of MACE. **Results:** Six trials with 11,722 patients were included. For safety endpoint, DAT was associated with significantly lower incidence of TIMI major and minor bleeding [RR: 0.58, 95% CI 0.44–0.77, $P = 0.0001$], TIMI major bleeding [RR: 0.55, 95% CI 0.42–0.73, $P < 0.0001$] as well as intracranial bleeding [RR: 0.35, 95% CI 0.16–0.73, $P = 0.006$] compared with TAT. No significant difference was observed for MACE [RR: 0.96 (0.79–1.17) $P = 0.71$] or any of the individual components of MACE between the two groups. **Conclusion:** Omission of aspirin from TAT in patients with Atrial Fibrillation (AF) after percutaneous coronary intervention is associated with lower risk of bleeding without compromising the efficacy in terms of mortality and cardiovascular thrombotic events.

Key words: Atrial fibrillation, CAD, coronary artery disease, dual antithrombotic therapy, stent, triple antithrombotic therapy

INTRODUCTION

Coronary artery disease (CAD) occurs in 20%–30% of patients with atrial fibrillation (AF), and 5.3%–28% of hospitalized patients with the acute coronary syndrome (ACS) develop new-onset AF during their hospitalization.[1-3] AF

Address for correspondence: Dr. Abdelmoniem Moustafa, Department of Internal Medicine, The Miriam Hospital, Warren Alpert School of Medicine at Brown University, 164 Summit Ave, Providence, Rhode Island 02906, USA.
E-mail: mon3melshimi@gmail.com

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patients with CHADS2 VASc score of 2 or more who undergo percutaneous coronary intervention (PCI) are candidates for triple antithrombotic therapy (TAT).[4] A combination of an anticoagulant and dual antiplatelet therapy (DAPT) is associated with a high risk of major bleeding 4.7%–12% over 12 months.[5-8] The WOEST trial was the first to omit aspirin and compare vitamin K antagonist (VKA)-based dual antithrombotic therapy (DAT) with clopidogrel versus TAT (VKA, clopidogrel, and aspirin). Results showed statistically significant lower bleeding events without increase in thrombotic events in DAT versus TAT. This opened the gate for further randomized controlled trials (RCT) to compare VKA and non-VKA-based DAT versus TAT.[9] The results were consistently in favor of DAT in terms of lower bleeding events with no difference in efficacy outcome between the two groups. Nevertheless, these studies were not powered to detect the difference in major adverse cardiovascular events (MACE). Although several studies addressed this subject, our meta-analysis included all RCTs that compared VKA and direct oral anticoagulant (DOAC) as part of DAT versus TAT including the recently published ENTRUST AF-PCI trial for edoxaban-based DAT.[10]

MATERIALS AND METHODS

Data sources and search strategy

This meta-analysis was performed in accordance with the guidelines of the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis). PubMed, Embase, and Cochrane Central databases were searched from inception through October 2019. The following search terms were used: "atrial fibrillation, PCI, percutaneous coronary intervention, dual antithrombotic therapy, and triple antithrombotic therapy." We also manually searched reference lists of retrieved articles to identify any relevant studies. All results were imported into EndNote x8.2 (Clarivate Analytics) and duplicate results were identified and removed.

Study selection/quality assessment

Two reviewers (Moustafa A and Khan MS) independently assessed the eligibility of identified studies. A study was considered eligible for inclusion in the analysis if it (1) was a RCT and (2) reported safety and efficacy outcomes comparing DAT and TAT. Only articles published in peer review journals were included. Published abstracts and meeting presentations were excluded. Quality of included studies by assessed by Cochrane risk of bias tool for RCTs. Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool was then used to assess quality of evidence at each outcome level as recommended by the Cochrane Handbook for Systematic Reviews of Interventions. This tool specifies four levels of quality (high, moderate, low, and very low) depending on the type of studies included in the assessment of each outcome.[11]

Data extraction and outcomes definition

Two authors (Moustafa A and Khan MS) independently extracted data on age, gender, body mass index (BMI), history of hypertension, diabetes mellitus, myocardial infarction, and stroke. The safety endpoints of interest were thrombolysis in myocardial infarction criteria (TIMI) major and minor bleeding, TIMI major bleeding, and intracranial bleeding. The efficacy endpoints of interest were trial defined MACE, all-cause mortality, cardiac mortality, myocardial infarction, ischemic stroke, and stent thrombosis.

Data synthesis and statistical analysis

Statistical analysis was performed using Review Manager, version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We performed meta-analysis on safety and efficacy outcomes separately. A random-effect model was used to pool data. Subgroup analysis was performed for safety and efficacy outcomes for DOAC-based DAT and TAT. I^2 statistic was used to assess heterogeneity among studies. A value of between 25% and 50% was considered low heterogeneity, between 50% and 75% moderate heterogeneity, and more than 75% was considered high heterogeneity. Any disagreement among reviewers about study selection, data extraction, or quality assessment was discussed with a third reviewer (Alsamman MA) and resolved with consensus.

RESULTS

Search results and study population

PRSIMA flow chart highlights the search strategy [Figure 1 Supplemental Material]. Our initial search strategy yielded 1405 studies; of which six trials were included [Appendix 1 Supplemental Material]. Six randomized control trials with a total of 11,722 patients were included. The trials were conducted in the United States and Europe between 2013 and 2019. Two trials included VKA-based DAT versus TAT.[9,11] The other four trials included DOAC-based DAT versus VKA-based TAT.[10,12-14] History of intracranial bleeding was a common exclusion criterion across the trials. Four trials (DOAC based) excluded patients with mechanical prosthetic valve. Three trials (DOAC based with an exception of ENTRUST AF PCI trial) excluded patients with renal impairment (GFR <30). In Pioneer-AF PCI, patients with history of ischemic stroke or transient ischemic attack (TIA) were excluded. The majority of population were males (75%), with age between 69.5 and 73.9 years, with 53% assigned to DAT and 47% were included in TAT groups. Patient characteristics are summarized in Table 1, and studies characteristics are shown in Table 2.

Safety endpoint

Major bleeding events as per TIMI criteria occurred in 1.7% of DAT group and 3.2% of TAT group. DAT group showed significantly lower TIMI minor and major bleeding [7.6% versus 13.7%, RR 0.58, 95% CI 0.44–0.77, $P = 0.0001$], TIMI major bleeding [1.7% versus 3.2% RR 0.55 (0.42–0.73) $P < 0.0001$], and Intracranial bleeding [0.25% versus 0.73% RR 0.35, 95% CI 0.16–0.73, $P = 0.006$] compared with TAT [Figure 1].

Efficacy endpoint

No significant difference was observed between DAT and TAT groups for endpoints of MACE [8.8% versus 8.1%, RR 0.96, 95% CI 0.79–1.17, $P = 0.71$]. Similarly, no difference was identified for other efficacy endpoints including all-cause mortality [4.% versus 4.2%, RR 0.96 95% CI 0.71–1.30, $P = 0.78$], cardiac mortality [2.5% versus 2.4%, RR 0.98, 95% CI 0.70–1.37, $P = 0.92$], MI [3.3% versus 2.8%, RR 1.14, 95% CI 0.90–1.45, $P = 0.27$], Ischemic stroke [0.97%

Table 1: Study characteristics

	Study population	Population no.	Study type	Inclusion criteria	Exclusion criteria	Analysis
WOEST 2013	Patient taking anticoagulant and undergoing PCI	573	Open label, multicenter RCT	Age 18–80 Long-term indication for oral anticoagulation treatment Severe coronary lesion with indication for PCI	History of intracranial bleeding Cardiogenic shock Contraindication to use of aspirin, clopidogrel, or both Peptic ulcer in the previous 6 months Thrombocytopenia (platelet concentration lower than 50×109/L) TIMI major bleeding in the past 12 months	ITT
ISAR TRIPLE 2015	Patient taking anticoagulation and undergoing PCI	614	Open label, multicenter RCT	Age ≥18 years Patients who have been receiving oral anticoagulant for at least 12 months and receiving a drug-eluting stent for stable angina or ACS	Previous stent thrombosis, drug-eluting stent implantation in the left main stem Active bleeding or bleeding diathesis History of intracranial bleeding	ITT
PIONEER 2016	AF patient undergoing PCI	2124	Open label, multicenter RCT	Age ≥ 18 years AF that occurred within last 1 year, or AF that occurred more than 1 year and the participant had been receiving oral anticoagulation for AF for the last 3 months	History of stroke or transient ischemic attack significant gastrointestinal bleeding within 12 months Calculated creatinine clearance of less than 30 ml per minute Anemia with a hemoglobin concentration of less than 10 g per deciliter	ITT and modified ITT
RE DUAL PCI 2017	Nonvalvular AF patient undergoing PCI	2725	Open label, multicenter RCT	Age ≥ 18 years Patients with nonvalvular AF who just underwent PCI with a bare-metal or drug-eluting stent for ACS or unstable angina Patients who have been receiving an oral anticoagulant or who were treatment-naïve prior to PCI	Presence of bioprosthetic Mechanical heart valves Creatinine clearance <30 ml per minute	ITT
AUGUSTUS 2019	Patient with AF and ACS and/ or PCI	4614	Open label, multicenter RCT	Age ≥ 18 years Patients with either active or a history of AF or flutter with planned or existing use of an oral anticoagulant for prophylaxis of thromboembolism Patients who have had an ACS and/or a PCI within the prior 14 days Planned use of an approved P2Y12 inhibitor for at least 6 months	Patients with other conditions that require anticoagulation (such as prosthetic valves or moderate or severe mitral stenosis) Severe renal insufficiency History of intracranial hemorrhage	ITT and modified ITT
ENTRUST AF PCI 2019	AF patient underwent successful PCI	1506	Open label, multicenter RCT	Age > 18 years	ESRD	ITT

RCT = randomized control trial, AF = atrial fibrillation, PCI = percutaneous intervention, CAD = coronary artery disease, MS = mitral stenosis, ACS = acute coronary syndrome, ITT = intention to treat, ESRD = end stage renal disease

Table 2: Study population characteristics

	WOEST	ISAR triple	REDUAL-combined	Pioneer	Augustus	Entrust
Treatment	DAT →TAT	DAT→TAT	DAT→TAT	DOAC+P2Y12- TAT	DOAC+P2Y12 versus TAT	DAT→TAT
Number	279 /284	307/307	3039/2278	709/706	1153/1154	751/755
Age	70.3(7)/69.5(8)	73.9(7.7)/73.3(8.7)	70.9/71.1	70.4(9.1)/69.9(8.7)	69.8(9.3)/70.5(9.07)	69/70
Male	214/234	229/242	2279/1754	528/518	840/815	557/563
BMI	27.5(4.3)/27.9(4.2)	27.5(4.2)/27.9(4.6)	27.9/28.2	28.6(25.7–32.4)/29(25.8–32.8)		
Current smoker%	22/15	9/10	10/9	5/7		
Dyslipidemia%	68/72	74/75	56/58	43/45		66/64
Diabetes%	24.3/25.4	27.7/23.5	32/32	29/31	35.9/35.9	34/34
Hypertension %	69/68	77/76	73/74	73/75	88.8/87.8	90/91
History of MI %	34/35	24/29	25/26	20/22		25/23
History of heart failure%	25.4/24.6			24/24.8	41.9/42.5	
History of stroke%	17.6/17.6		7.2/10.2		14.9/12.4	13/12
CHADS VASC						
<3		4.7/7.3	27.4/19.7	26.7/20.8	21.5/20.8	
=>3		95.3/92.7	72.6/80.3	73.3/79.2	78.5/79.2	
HAS BLED						
<3			36.4/29.4	27.6/29.5	51.7/50.9	
=>3			63.6/70.6	72.4/70.5	48.3/49.1	

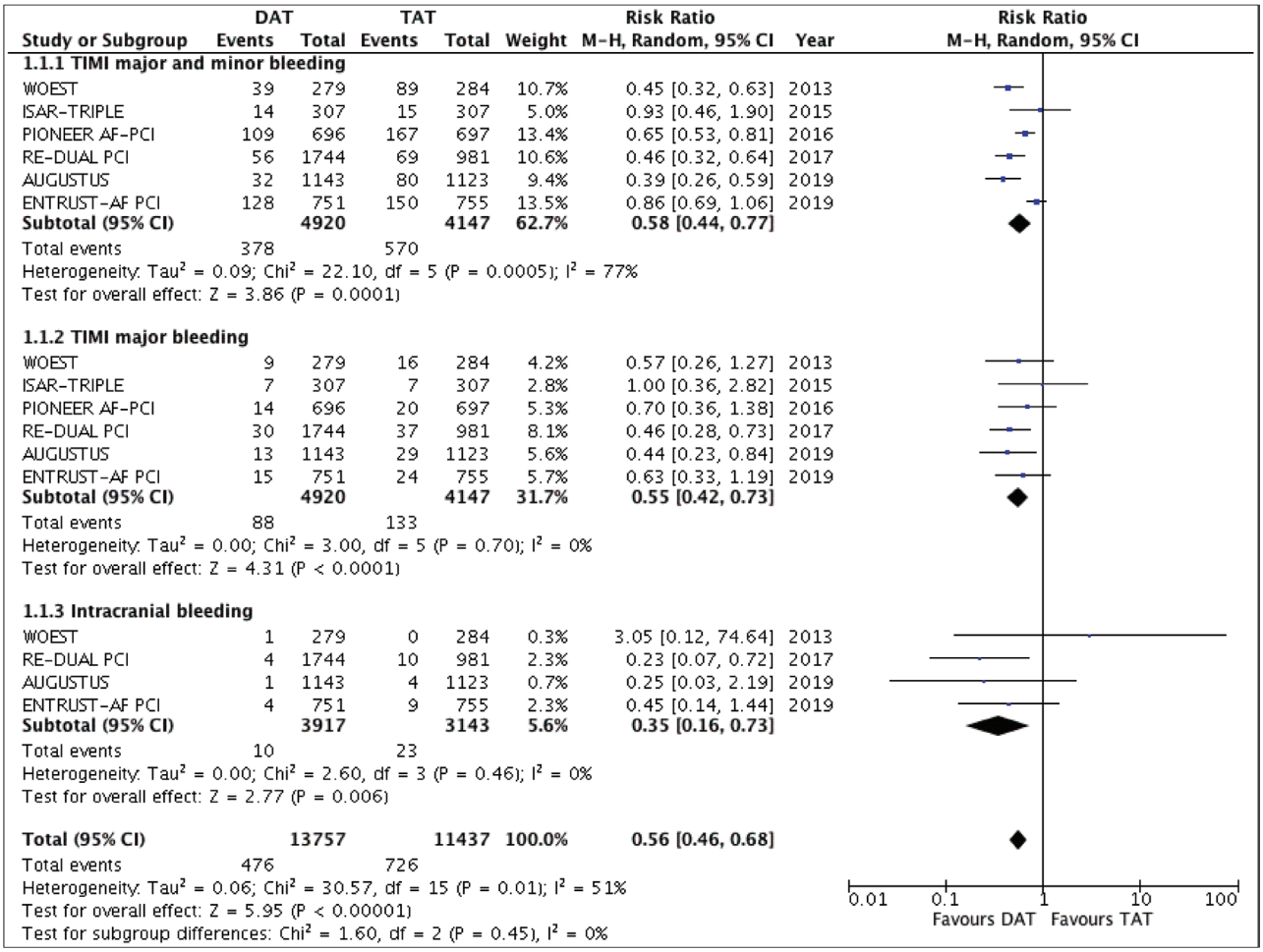

Figure 1: Summary forest plot of safety endpoint in DAT versus TAT groups

versus 1.1%, RR 0.80, 95% CI 0.51–1.26, $P = 0.34$], or stent thrombosis [1.4% versus 1.1. RR 1.32, 95% CI 0.88–1.96, $P = 0.18$] [Figure 2].

DOAC-based DAT versus TAT

Subgroup analysis was conducted by including only DOAC-based DAT versus TAT after excluding the

WOEST and ISAR TRIPLE trials. Compared with TAT, DOAC-based DAT remained associated with significantly lower TIMI major and minor bleeding [7.4% versus 13.1% RR 0.58 (0.42–0.81) $P = 0.001$], TIMI major bleeding [1.6% versus 3% RR 0.53 (0.39–0.71) $P < 0.0001$], and intracranial bleed [0.24% versus 0.8% RR 0.31 (0.14–0.66) $P = 0.003$] compared with TAT [Figure 3].

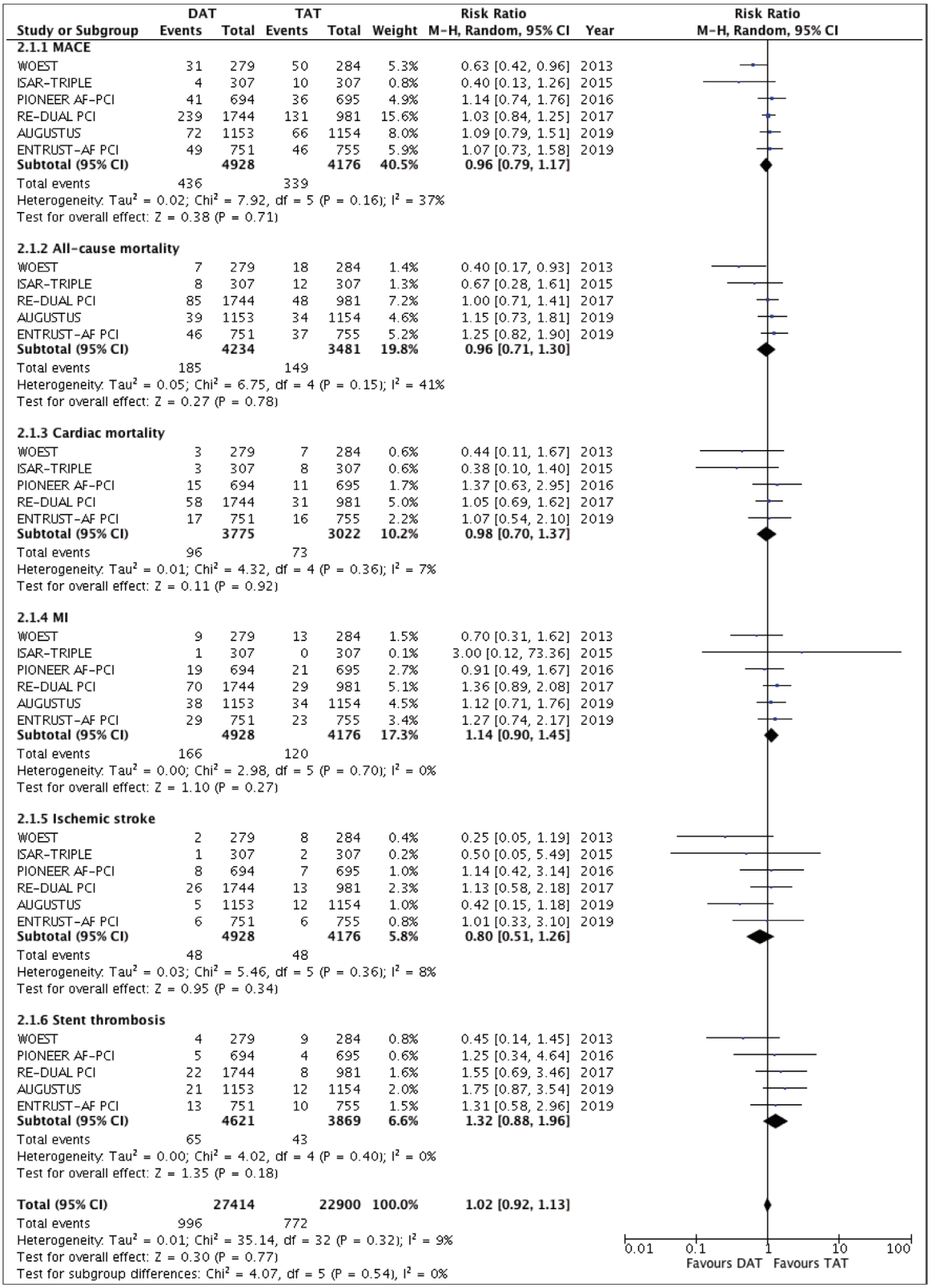

Figure 2: Summary forest plot of efficacy endpoint in DAT versus TAT groups

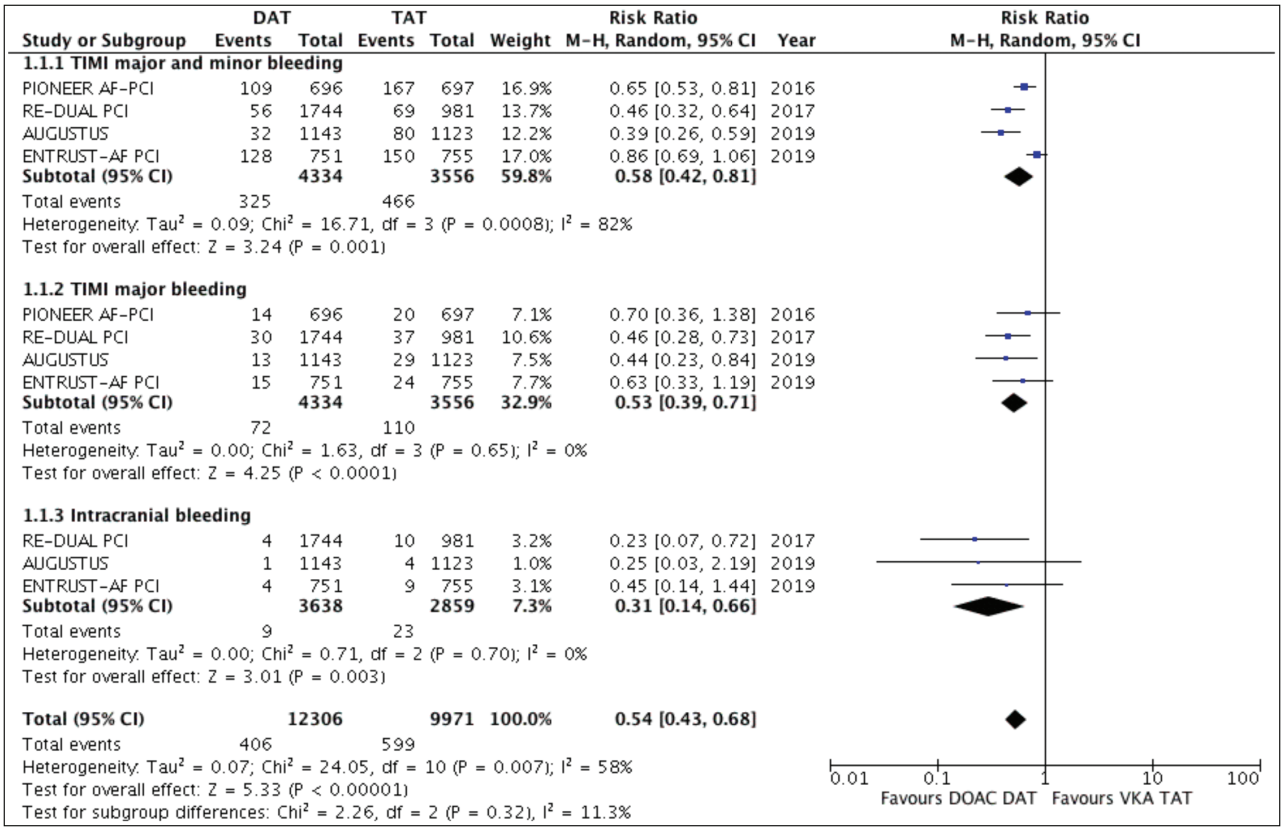

Figure 3: Summary forest plot of safety endpoint in DOAC-based DAT versus TAT groups—sensitivity analysis

On the contrary, no difference was observed between DAT and TAT in terms of composite of MACE (9.2% versus 7.8% RR 1.06 95% CI (0.91–1.22) $P = 0.45$], all-cause mortality [4.7%-4.1% RR 1.11 95% CI (0.88–1.39) $P = 0.39$], cardiac mortality [2.8% versus 2.4% RR 1.11 95% CI (0.80–1.54) $P = 0.54$], MI [3.6% versus 3% RR 1.18 95% CI (0.93–1.52) $P = 0.18$], or ischemic stroke [1% versus 1% RR 0.92 95% CI (0.59–1.44) $P = 0.72$]. Higher rate of stent thrombosis was found in DOAC-based DAT versus TAT but did not reach statistical significance [1.4 versus 0.9% 1.51 95% CI (0.99–2.31) $P = 0.05$] [Figure 4].

Quality assessment and risk of bias

All trials reported random sequence generation, and concealment of allocation. Hence, the selection bias was deemed low in all the trials. Although all the trials had open-label study design, outcome assessment was performed by independent committees whose members were unaware of the patient's treatment assignment. Therefore, the studies design did not influence reported outcomes. Hence, the risk of detection and performance bias were considered low in all of them. Moreover, attrition and reporting bias were deemed low in all trials. Overall risk of bias was deemed low in all the trials [Table 1 Supplemental Material]. Body of evidence for the outcomes reached the level of high quality according to the Grades of Recommendation, Assessment, Development and Evaluation too [Table 2 Supplemental Material]. Publication bias was assessed by visual inspection of funnel plots [Figures 2 and 3 Supplemental Material].

DISCUSSION

In our meta-analysis we found that DAT was associated with reduction in bleeding events without significant difference in adverse cardiovascular events compared with TAT. First, omission of aspirin resulted in 42% relative risk reduction in TIMI major or minor bleeding, as well as 65% relative risk reduction in incidence of intracranial bleeding with DAT versus TAT. After excluding WOEST and ISAR TRIPLE trials, analysis of the 4 trials with DOAC-based DAT versus VKA based TAT (PIONEER AF, PCI- REDUAL PCI, AUGUSTUS and ENTRUST-AF PCI) re-demonstrated the significant reduction of TIMI major or minor bleeding and intracranial bleeding.[9,10,12-15] Majority of study population in DOAC-based DAT trials had HAS BLED score >=3 and were at high risk of bleeding. HAS BLED score was not implemented in WOEST and ISAR TRIPLE trials. Landmark analysis of ISAR TRIPLE trial did not show a significant reduction in bleeding events between 6 weeks to 6 months in VKA based DAT and TAT. However, short follow up period is one of the drawbacks of this study.[11] As of shown in a meta-analysis bleeding events could increase

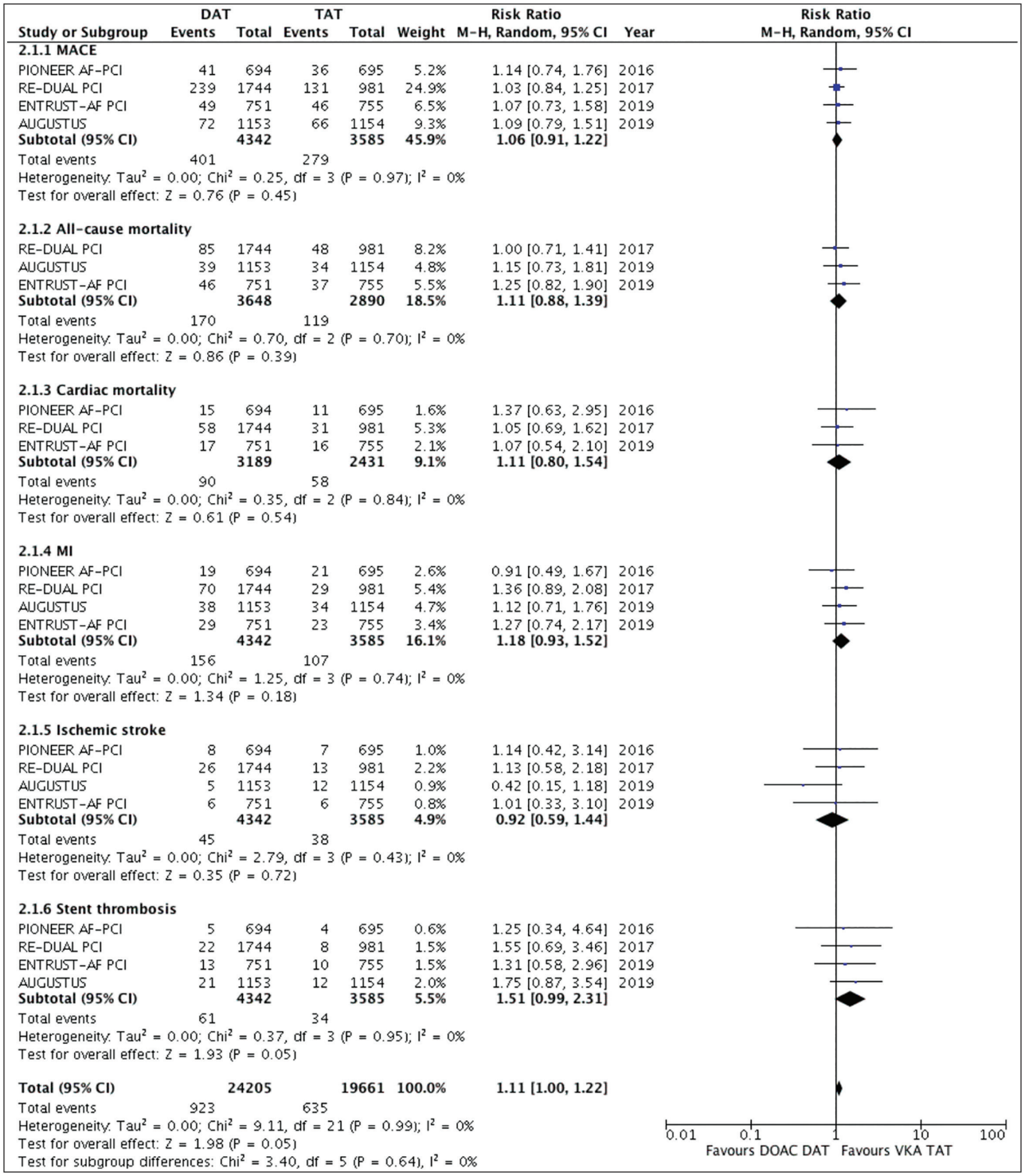

Figure 4: Summary forest plot of efficacy endpoint in DOAC-based DAT versus TAT groups—sensitivity analysis

by 6 folds by end of 12 month use of TAT.[8] Also, the trial was powered to detect any difference between shorter (6 weeks) and longer (6 months) of TAT treatment, and the results came in favor of shorter TAT duration that was not associated with increase in ischemic adverse cardiovascular events.

Second, although each individual trial showed no difference in composite or individual component MACE between the two groups, skepticism about the validity of the results arose as trials were not powered to detect differences in ischemic events. In our analysis of 11722 subjects, no significant difference in composite nor individual component of MACE

was observed between DAT and TAT groups. Nevertheless, Subgroup analysis including only DOAC-based DAT versus TAT showed tendency for higher stent thrombosis events in DAT versus TAT.

REDUAL PCI, PIONEER and AUGUSTUS population tended to have lower CHADS VASc scores, whereas ENTRUST AF-PCI and ISAR TRIPLE had higher average CHADS VASc score as shown in Table 2.[9,10,12-15] In PIONEER AF PCI trial, patients with prior history of stroke or TIA were excluded. Moreover, patients with GFR <30 were excluded from 3 trials (REDUAL PCI, PIONEER, and AUGUSTUS).[9,10,12-15] We did not include rivaroxaban 2.5 plus DAPT group in PIONEER trial as efficacy of rivaroxaban small dose 2.5 to prevent ischemic stroke was not tested before.[9,10,12-15] In REDUAl PCI, study only combined results of dabigatran 110 mg and 150 mg were included in the analysis.[9,10,12-15]

DAPT for one year is the standard of care for all patients with ACS whether the patient has undergone stent placement or is being treated medically.[3,16-18] However, DAPT alone has failed to provide stroke prevention in AF population (annual risk of stroke with DAPT versus oral anticoagulant (OAC) was 5.60% versus 3.93%, with a relative risk of 1.44, 95% CI 1.18–1.76; $P = 0.0003$).[19] Adding VKA to DAPT in AF population with CAD resulted in 4.7%–6.6% major bleeding risk which commonly occur in the first month.[3,5,7,20] The risk of major bleeding continues to rise to up to 12% by the end of 12 months.[8] In our analysis, annual risk for bleeding in patient on TAT was 6.3%. The WOEST trial opened the gate for the possibility of dropping aspirin from TAT, with the result of a significant reduction of both bleeding and ischemic event. Lower MACCE events in DAT arm of WOEST trial can be explained with higher chance of DAPT interruption in TAT group as a result of more frequent bleeding events.[9,10,12-15] Indeed, all trials that compared DAT versus TAT showed a significant reduction in bleeding events with ISAR TRIPLE trial as an exception that showed no difference between 2 groups in landmark analysis. Our meta-analysis expanded to include the most recent evidence and our results came in line with the results of other meta-analysis.[21,22] Moreover, our analysis showed statistically significant lower intracranial bleed in favor of DAT group. A 50% increase in stent thrombosis in DOAC-based DAT versus TAT was an interesting finding in our analysis that included only DOAC-based DAT with $P = 0.05$. Further studies are needed to assess the significance of this finding.

According to the American Heart Association guidelines for AF that were published in 2014 and an update in 2019, it may be reasonable to use clopidogrel in combination with oral anticoagulants (without specifying a particular anticoagulant) without aspirin after coronary revascularization.[23,24] On the contrary, the ESC 2016 guidelines adopted a shorter period of TAT of 1 month followed by dual therapy (OAC plus a single antiplatelet).[25]

Data are scarce when it comes to other P2Y12 inhibitors impact as a part of DAT or TAT on bleeding and efficacy endpoints. In Re-Dual PCI trial, subgroup analysis showed a 15%–50% increase in bleeding event rate in patients who had taken ticagrelor as part of TT with VKA or DT with dabigatran versus. other P12Y2 inhibitors. Similar results were observed in AUGUSTUS trial where higher bleeding rate was found in patients who had received prasugrel and ticagrelor versus. clopidogrel.[3,13,15]

The results of the ongoing prospective MANJUSRI trial are eagerly awaited, as it would provide data on the better combination therapy (ticagrelor and warfarin versus. aspirin, clopidogrel, and warfarin) for patients with AF and CAD.[26]

CONCLUSION

In patient with AF after PCI, VKA or non-VKA-based DAT after omission of aspirin is as effective as TAT in preventing adverse cardiovascular events but with a significantly lower bleeding risk including major bleeding and intracranial hemorrhage. Tendency for higher stent thrombosis was found in DOAC-based DAT but did not reach statistical significance.

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Conflicts of interest
There are no conflicts of interest.

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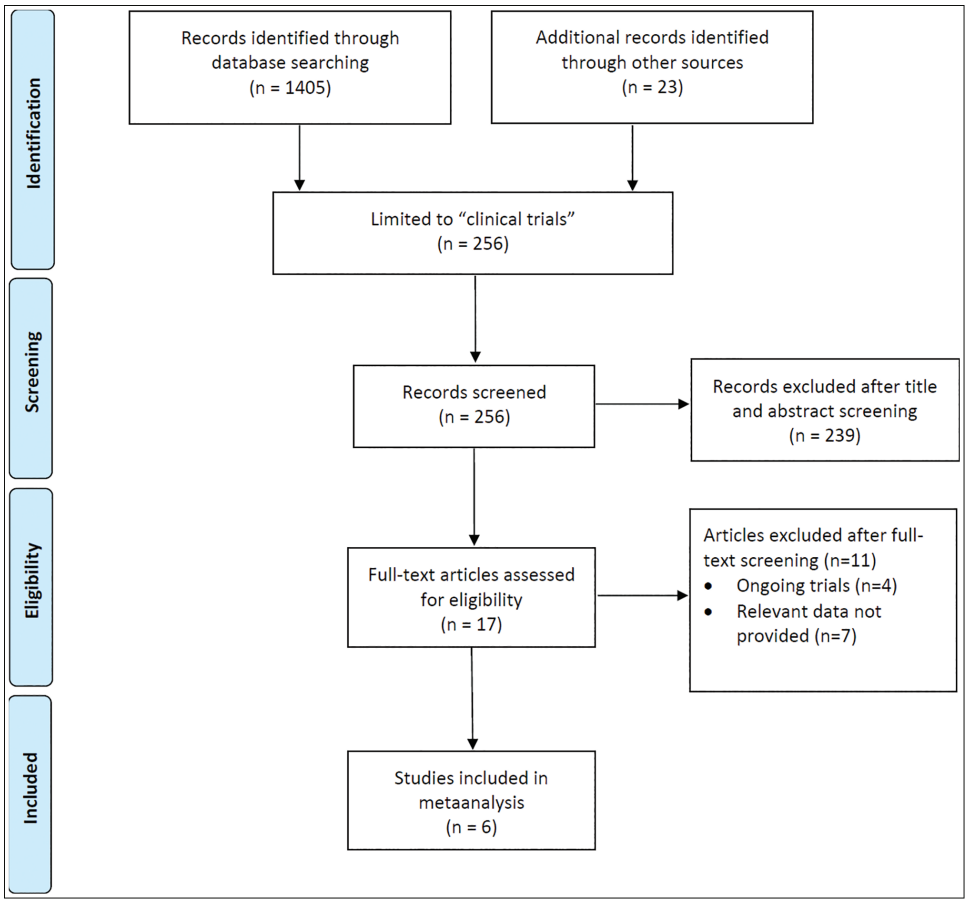
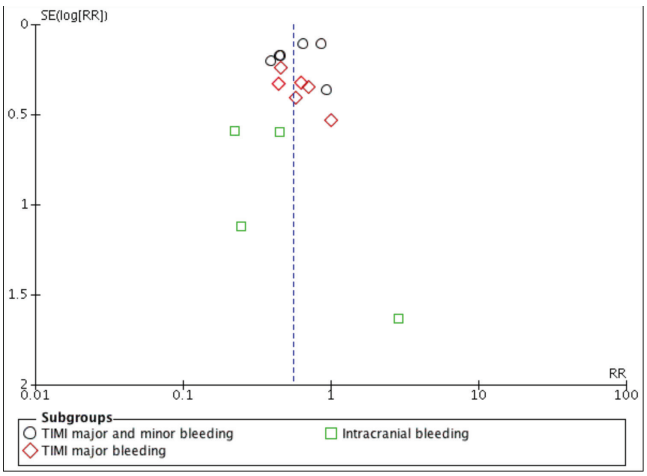
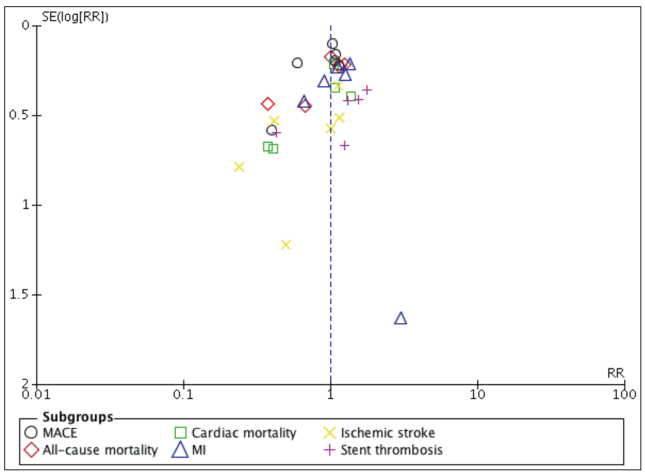
SUPPLEMENTAL MATERIAL



Online figure 1: PRISMA flow diagram for search strategy



Online figure 2: Funnel plot for safety endpoint



Online figure 3: Funnel plot for efficacy endpoint

APPENDIX 1: SEARCH STRATEGY

Detailed search strategy used for PubMed which yielded 638 results; the same search strategy was extrapolated to Embase and Cochrane Central databases. The final details of the search were included in PRISMA flow diagram

(("Atrial Fibrillation"[Mesh] OR AFIB[tiab] OR atrial fibrillation[tiab]) AND ("Percutaneous Coronary Intervention"[Mesh] OR Percutaneous coronary intervention[tiab] OR PCI[tiab] OR ((Coronary disease[MeSH] OR coronary[tiab]) AND (Stents[MeSH] OR stent*[tiab] OR Angioplasty[MeSH] OR angioplasty[tiab])))) AND ((antithrombotic[tiab] OR double therapy[tiab] OR dual therapy[tiab] OR dual-therapy[tiab] OR double antithrombotic therapy[tiab] OR DAT[tiab] OR dual antiplatelet therapy[tiab] OR triple therapy[tiab] OR triple-therapy[tiab] OR triple antithrombotic therapy[tiab] OR TAT[tiab] OR "Platelet Aggregation Inhibitors"[Mesh]))

Table 1: Risk of bias assessment

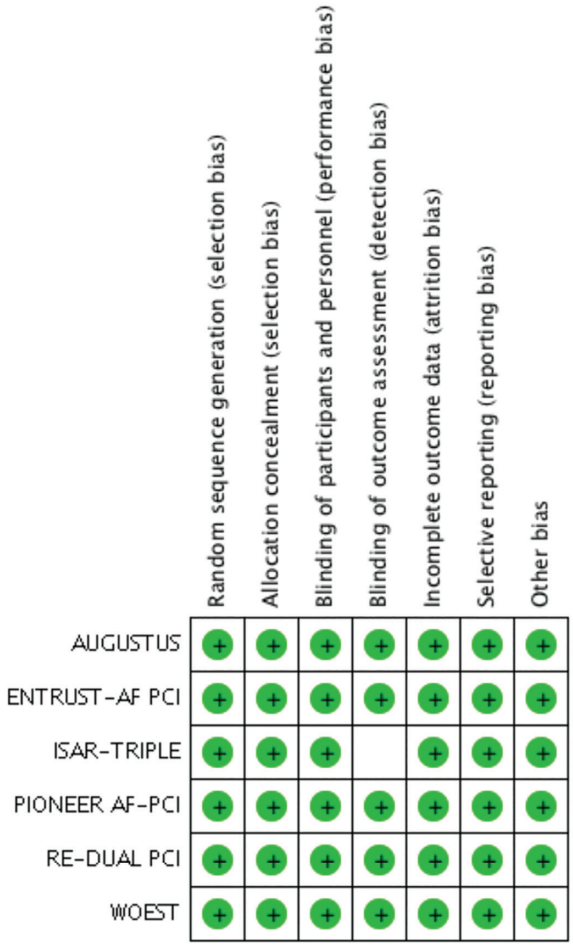


Table 2: GRADE tool for assessment of quality of the body of evidence

No of participant	Risk of bias	inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence
TIMI major and minor bleeding 9067	Not serious	Not serious	Not serious	Not serious	none	⁎⁎⁎⁎ High
TIMI major bleeding 9067	Not serious	Not serious	Not serious	Not serious	none	⁎⁎⁎⁎ High
Intracranial bleeding 7078	Not serious	Not serious	Not serious	Not serious	none	⁎⁎⁎⁎ High
MACE 9122	Not serious	Not serious	Not serious	Not serious	none	⁎⁎⁎⁎ High
All cause mortality 7733	Not serious	Not serious	Not serious	Not serious	none	⁎⁎⁎⁎ High
Cardiac mortality 6815	Not serious	Not serious	Not serious	Not serious	none	⁎⁎⁎⁎ High
MI 9122	Not serious	Not serious	Not serious	Not serious	none	⁎⁎⁎⁎ High
Ischemic stroke 9122	Not serious	Not serious	Not serious	Not serious	none	⁎⁎⁎⁎ High
Stent thrombosis 8508	Not serious	Not serious	Not serious	Not serious	none	⁎⁎⁎⁎ High