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META-ANALYSIS

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

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Aims Of patients with atrial fibrillation (AF), approximately 10% undergo percutaneous coronary intervention (PCI). We studied the safety and efficacy of dual vs. triple antithrombotic therapy (DAT vs. TAT) in this population.

Methods and results A systematic review and meta-analysis was conducted using PubMed, Embase, EBSCO, Cochrane database of systematic reviews, Web of Science, and relevant meeting abstracts for Phase 3, randomized trials that compared DAT vs. TAT in patients with AF following PCI. Four trials including 5317 patients were included, of whom 3039 (57%) received DAT. Compared with the TAT arm, Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding showed a reduction by 47% in the DAT arm [4.3% vs. 9.0%; hazard ratio (HR) 0.53, 95% credible interval (CrI) 0.36–0.85, $I^2 = 42.9\%$]. In addition, there was no difference in the trial-defined major adverse cardiac events (MACE) (10.4% vs. 10.0%, HR 0.85, 95% CrI 0.48–1.29, $I^2 = 58.4\%$), or in individual outcomes of all-cause mortality, cardiac death, myocardial infarction, stent thrombosis, or stroke between the two arms.

Conclusion Compared with TAT, DAT shows a reduction in TIMI major or minor bleeding by 47% with comparable outcomes of MACE. Our findings support the concept that DAT may be a better option than TAT in many patients with AF following PCI.

Keywords Atrial fibrillation • Antithrombotic therapy • Percutaneous coronary intervention • Dual therapy • Triple therapy

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Introduction

Atrial fibrillation (AF) is a major global health problem affecting 33.5 million individuals worldwide.[1] Oral anticoagulation (OAC) with either vitamin K antagonists (VKAs) or non-VKA oral anticoagulants (NOACs) is the mainstay for prevention of thrombo-embolic events in this population.[2] Approximately 5–10% of these patients also undergo percutaneous coronary intervention (PCI) for concomitant coronary artery disease (CAD).[3] This overlap poses significant challenges since prior data from randomized trials have shown superiority of dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor over aspirin and VKA for prevention of stent thrombosis and major adverse cardiac events (MACE) in patients post-PCI.[4,5] Consequently, most patients with AF following PCI are subjected to treatment with a combination of both these therapies (DAPT plus OAC), the so-called 'triple antithrombotic therapy (TAT)' approach.

While this approach is reasonable and endorsed by American College of Cardiology/American Heart Association/European Society of Cardiology guidelines[6,7] as well as expert consensus[8–10] for varying durations, the evidence supporting the same is sparse. A major limitation of TAT is bleeding.[11] One proposed approach is to curtail the TAT to a minimum duration with a goal to reduce bleeding events. However, this strategy has been challenged by data from the What is the Optimal AntiplatElet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing (WOEST) as well as Intracoronary Stenting and Antithrombotic Regimen: Testing of a Six-Week vs. a Six-Month Clopidogrel Treatment Regimen In Patients With Concomitant Aspirin and OraL Anticoagulant Therapy Following Drug-Eluting Stenting (ISAR-TRIPLE) trials which demonstrated that many of the bleeding events occur in the first few weeks after the initiation of TAT.[12,13]

In the last several years, a number of randomized trials[14,15] have attempted to evaluate the strategy of dual antithrombotic therapy (DAT) vs. TAT in this patient population with DAT defined as a combination of one antiplatelet agent and an anticoagulant.[16,17] In aggregate, studies have suggested reduction in bleeding by almost half in patients on DAT compared with TAT.[18–21] These results are complemented by similar incidence of thrombo-embolic and MACE between the two groups. A major criticism for all the randomized trials is that none of them is sufficiently powered to assess thrombo-embolic (efficacy) outcomes. To reduce the selection bias introduced by observational data and to enhance the power for assessment of efficacy outcomes, we conducted a systematic review and meta-analysis of Phase 3, randomized trials examining DAT vs. TAT in patients with AF, following PCI with inclusion of the most recently published Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI) trial, which is the largest of all the trials on this topic to date.

Methods

Search strategy and selection criteria

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for the systematic review and meta-analysis. All relevant Phase 3 randomized clinical trials comparing TAT (defined as DAPT plus an OAC) vs. DAT (defined as single antiplatelet agent plus an OAC) in patients with AF following PCI were eligible for inclusion. The primary exclusion criteria were observational non-randomized studies, registry data, ongoing trials without results, editorials, case series, and duplicate studies. A digital computerized search was conducted through PubMed, Embase, EBSCO, Cochrane database of systematic reviews, and Web of Science from its inception up to 25 July 2017 using the following search terms in various combinations: 'percutaneous coronary intervention', 'coronary stenting', 'coronary angioplasty', 'stents, angioplasty', 'PCI', 'triple antiplatelet therapy', 'dual antiplatelet therapy', 'triple antithrombotic therapy', 'triple therapy', 'dual therapy', 'double therapy', 'anticoagulants', 'antiplatelets', 'platelet aggregation inhibitors', 'vitamin K antagonists', 'warfarin', 'dabigatran', 'rivaroxaban', 'apixaban', 'edoxaban', 'aspirin', 'thienopyridine', 'clopidogrel', 'atrial fibrillation', and 'randomized clinical trial'. In addition, references of prior systematic reviews/meta-analysis, as well as abstracts from major cardiology meetings were screened for related studies. There were no restrictions on language, publication date, or publication status. Two investigators (H.G., A.Q.) independently reviewed the titles/abstracts and studies to determine their eligibility to meet the inclusion criteria. The same authors (H.G., A.Q.) independently extracted all the relevant outcomes of interest into a structured data set. The entire tabulated data set was reviewed, and disagreements were resolved via consensus and by a third author (D.L.B.).

Data analysis

We extracted information about the following outcomes from individual trials as well as their Supplementary material online[12–15,22]: Thrombolysis in Myocardial Infarction (TIMI) major and minor bleeding, intracranial bleeding, all-cause mortality, cardiac death, myocardial infarction (MI), stent thrombosis, and stroke. It is important to note that ISAR-TRIPLE had a slightly different trial design compared with other trials included in the analysis. In ISAR-TRIPLE trial, patients in both the arms were treated with the same triple therapy for the first 6 weeks, after which the DAT group received aspirin and warfarin whereas the TAT group received aspirin, clopidogrel, and warfarin. Henceforth, to have a valid comparison, our analysis incorporated the event data from landmark analysis of the ISAR-TRIPLE trial.

The primary safety outcome was a composite of TIMI major or minor bleeding. The secondary safety outcome was intracranial bleeding. The primary efficacy outcome was 'trial defined MACE' which followed the definition of MACE in the respective trials (Supplementary material online, *Table S3*). Secondary efficacy outcomes were the individual components of the primary efficacy outcome as well as cardiac death and stent thrombosis.

Effect size calculation

It was anticipated that the length of follow-up will differ between trials. Consequently, hazard ratios (HRs) with 95% confidence intervals for each endpoint were extracted for each of the trials when reported. For studies in which HR was not reported, the log (HR) and its variance were estimated using a previously validated method, as follows[23,24]:

Log-HR = 2 * [(# observed events Group 1) - (# observed events Group 2)]/[(# observed events Group 1) + (# observed events Group 2)]

Variance (log-HR) = 4/[(# observed events Group 1) + (# observed events Group 2)].

Statistical analysis

To accommodate the anticipated heterogeneity across studies, we used random effects meta-analysis to synthesize results. In particular, we used a Bayesian hierarchical model to estimate the random effects model. We assumed a Gaussian distribution for random effects. The freely available,

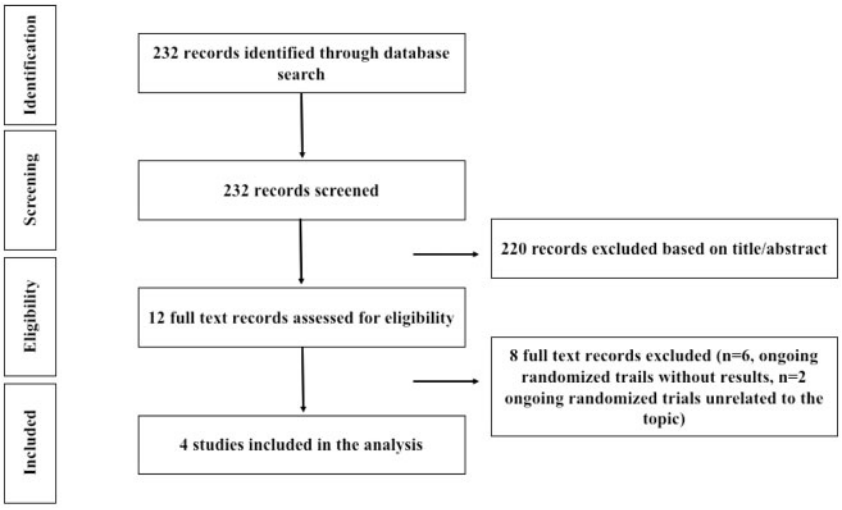


Figure 1 Study selection.

open-source programme OpenBUGS (Bayesian inference using Gibbs Sampling) was used to fit the model.[25] Non-informative priors (normal distribution with mean = 0, standard deviation = 1000) for the overall mean HR and inverse-gamma (0.001, 0.001) for the between study variance was used. Convergence of the Markov Chain Monte Carlo sampler was assessed using the Brooks–Gelman–Rubin method.[26] In particular, we employed four chains; convergence of the sampler was established if the ratio of within-chain and between-chain variability for the four chains starting at different initial values is close to 1.

Heterogeneity across studies was assessed using the Cochran Q test. Higgins I^2 statistics was used to determine the degree of in between study heterogeneity (I^2 < 25%—low, 25–50%—moderate, and >50%—high degree of heterogeneity). Sensitivity analyses were conducted to investigate the robustness of our results to assess whether any of the included studies had a large influence on the results.

The methodological quality of the randomized trials was assessed by Cochrane's Collaboration tool for assessing risk of bias. For each trial, bias was assessed qualitatively as low risk, intermediate risk, or high risk of bias by independent investigators. Publication bias was not assessed as there were small number of studies (<10) included in the analysis.

Results

A total of 232 studies were screened for eligibility, out of which four Phase 3, randomized trials including 5317 patients assessing the strategy of DAT vs. TAT in AF patients following PCI were included in the final analysis (*Figure 1*). Characteristics of the individual trials included in the analysis with its primary and secondary outcomes are depicted in the Supplementary material online, *Table S1*. One TAT arm of PIONEER AF-PCI[14] (aspirin, P2Y12 inhibitor, and low dose rivaroxaban 2.5 mg twice daily, 709 patients) was not included in the analysis as rivaroxaban 2.5 mg is not an approved dose for thrombo-embolic protection in patients with AF. Baseline characteristics of patients enrolled in the four trials included in this meta-analysis are shown in *Table 1*. Mean follow-up ranged from 9 to 14 months. Mean age of patients across the trials was 70.9 years in the DAT arm and 71.1 years in the TAT arm. About 47% patients in the DAT arm and 45% patients in the TAT arm underwent PCI for acute coronary syndrome (ACS), whereas the remaining 53% and 55% patients in the DAT and the TAT arm, respectively underwent PCI for non-ACS indications. Approximately, 75% of patients in the DAT arm and 82% of patients in the TAT arm had a CHA_2DS_2VASc score of >2. Furthermore, 66% of patients in the DAT arm and 71% of patients in the TAT arm had a HAS-BLED score of ≥3. Atrial fibrillation was present in 100% patients in the PIONEER AF-PCI and RE-DUAL PCI trials, whereas AF was present in 84% and 69% of patients enrolled in ISAR-TRIPLE and WOEST, respectively. All the trials were judged to be at low risk of bias via the Cochran's Collaboration tool for risk assessment (Supplementary material online, *Table S2*).

Compared with patients in the TAT arm, patients in the DAT arm demonstrated a 47% relative reduction in the risk of TIMI major or minor bleeding [4.3% vs. 9.0%; HR 0.53, 95% CrI 0.36–0.85, I^2 = 42.9%] (*Figure 2*). The risk of intracranial bleeding was 42% lower, although not achieving statistical significance (HR 0.58, 95% CrI 0.23–1.49, I^2 = 0%) (*Figure 3*). These outcomes did not differ when dabigatran 110 mg or 150 mg doses were analysed separately for the meta-analysis (Supplementary material online, *Figures S2A, B* and *S3A, B*).

'Trial-defined MACE' occurred in 10.4% patients in the DAT arm compared with 10.0% patients in the TAT arm (HR 0.85, 95% CrI 0.48–1.29, I^2 = 58.4%) (*Figure 4*). Inclusion of original results of the ISAR-TRIPLE trial did not alter our efficacy outcome results of trial-defined MACE (Supplementary material online, *Figure S1*). The individual end-points of all-cause mortality (HR 0.85, 95% CrI 0.46–1.37, I^2 = 39.3%), cardiac death (HR 0.89, 95% CrI 0.41–1.54, I^2 = 28.7%), MI (HR 1.07, 95% CrI 0.58–1.95, I^2 = 15.8%), stent thrombosis (HR 1.00, 95% CrI 0.32–2.82, I^2 = 32.1%), and stroke (HR 0.94, 95% CrI 0.45–1.84, I^2 = 0%) did not differ between the two groups (*Figures 5–7*). These outcomes did not differ when dabigatran 110 mg or 150 mg doses were analysed separately for the meta-analysis (Supplementary material online, *Figures S4–S9*). One-study-omitted sensitivity analysis showed that individual study data did not influence our results (Supplementary material online, *Figures S10* and *S11*).

Table 1 Baseline characteristics of patients in intention-to-treat analysis of randomized trials included in the analysis

	WOEST[12]		ISAR-TRIPLE[13]		PIONEER AF-PCI[14]		RE-DUAL PCI[15]			Combined	
	DAT ($n = 279$)	TAT ($n = 284$)	DAT ($n = 307$)	TAT ($n = 307$)	DAT ($n = 709$)	TAT ($n = 706$)	DAT ($n = 981$) Dabigatran 110 mg	DAT ($n = 763$) Dabigatran 150 mg	TAT ($n = 981$)	DAT ($n = 3039$)	TAT ($n = 2278$)
Age (years)	70.3 (7.0)	69.5 (8.0)	73.9 (7.7)	73.3 (8.7)	70.4 (9.1)	69.9 (8.7)	71.5 (8.9)	68.6 (7.6)	71.7 (8.9)	70.9	71.1
Female (%)	23	18	25	21	26	27	26	22	24	25	23
BMI (kg/m^2)	27.5 (4.3)	27.9 (4.2)	27.5 (4.2)	27.9 (4.6)	28.6 (25.7–32.4)	29.0 (25.8–32.8)	NR	NR	NR	27.9	28.2
Diabetes (%)	24	25	28	24	29	31	37	34	39	32	32
Hypertension (%)	69	68	77	76	73	75	NR	NR	NR	73	74
Dyslipidaemia (%)	68	72	74	75	43	45	NR	NR	NR	56	58%
Current smoker (%)	22	15	9	10	5	7	NR	NR	NR	10	9
History of MI (%)	34	35	29	25	20	22	24	24	27	25	26
History of CABG (%)	20	26	24	17	NR	NR	10	10	11	13	15
History of PCI (%)	31	36	NR	NR	NR	NR	33	31	35	32	35
PPI use (%)	34	39	NR	NR	39	37	NR	NR	NR	37	37
Type of index event (%)											
ACS	25	30	33	31	51	52	52	51	48	47	45
Non-ACS	75	70	67	69	49	48	48	49	52	53	55
Type of stent (%)											
Drug-eluting stent	65	64	99	99	65	66	82	81	84	79	79
Bare-metal stent	32	30	1	0	33	32	15	16	13	19	19
Drug-eluting and bare-metal stents	1	4	0	0	2	2	2	1	1	1	1
PTCA/no stent	2	1	1	1	0	0	1	1	1	1	1
Indication for oral anti coagulation (%)											
Atrial fibrillation	69	69	83	85	100	100	100	100	100	96	95
Mechanical valve	10	11	6	9	0	0	0	0	0%	1	2
Other	20	20	12	6	0	0	0	0	0	3	3
CHA_2DS_2-VASc score (%)											
≤2	NR	NR	5	7	27	21	23	32	20	25	18
>2	NR	NR	95	93	73	79	77	68	80	75	82
HAS-BLED score (%)											
<3	NR	NR	NR	NR	28	29	33	41	29	34	29
≥3	NR	NR	NR	NR	72	71	67	56	71	66	71

Data are mean (SD), median (IQR), or percentage unless otherwise indicated.

BMI, body mass index; CABG, coronary artery bypass grafting; CHA_2DS_2-VASc, stroke risk factor scoring system in which one point is given for history of congestive heart failure, hypertension, age 65-74 years, diabetes, vascular disease, female gender and two points are given for history of age ≥75 years, and stroke or transient ischaemic attack; DAT, dual antithrombotic therapy; HAS-BLED, major bleeding risk factor scoring system in which one point is given to hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drug/alcohol use; MI, myocardial infarction; NR, not reported; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; PTCA, percutaneous transluminal coronary angioplasty; TAT, triple antithrombotic therapy.

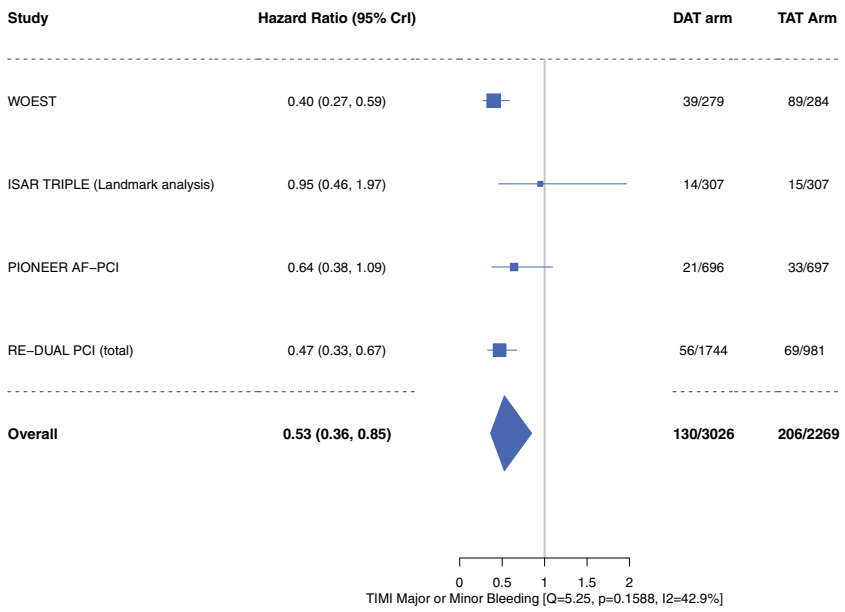


Figure 2 Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding. Data are *n*/*N* unless otherwise indicated. Hazard ratio <1 favours dual antithrombotic therapy and hazard ratio >1 favours triple antithrombotic therapy. CrI, credible interval; DAT, dual antithrombotic therapy; TAT, triple antithrombotic therapy.

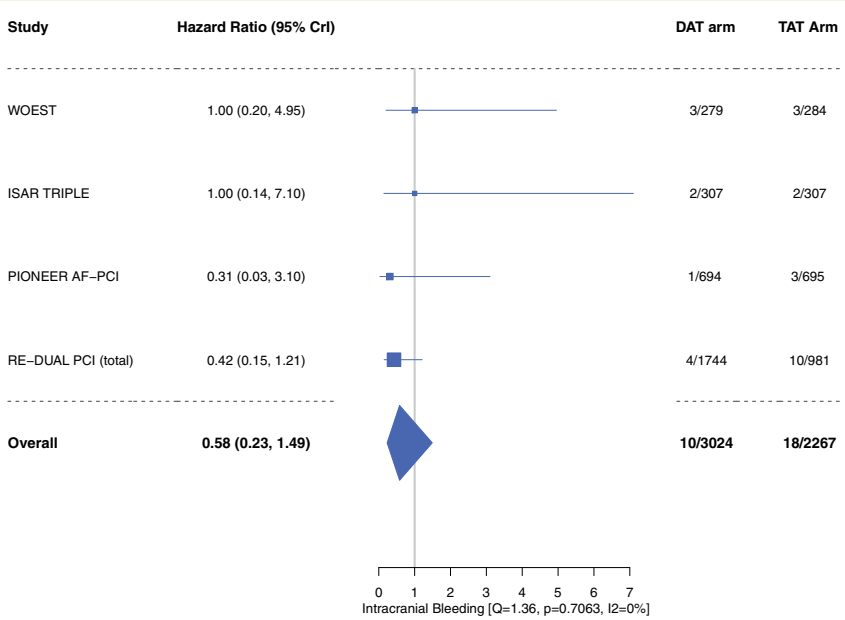


Figure 3 Intracranial bleeding. Data are *n*/*N* unless otherwise indicated. Hazard ratio <1 favours dual antithrombotic therapy and hazard ratio >1 favours triple antithrombotic therapy. Note: Primary haemorrhagic stroke reported in PIONEER AF-PCI trial was included as intracranial bleeding. Landmark analysis of ISAR-TRIPLE did not separately report intracranial bleeding rates and henceforth, the total reported event rates of intracranial bleeding reported in the trial are used. CrI, credible interval; DAT, dual antithrombotic therapy; TAT, triple antithrombotic therapy.

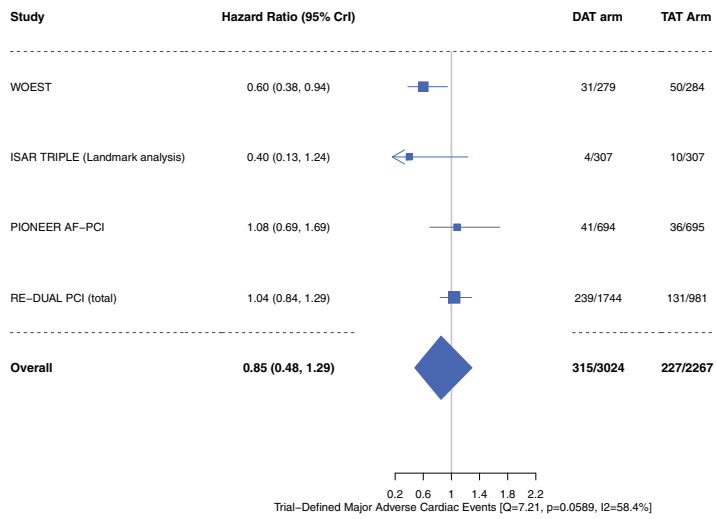


Figure 4 Trial-defined major adverse cardiac events. Data are *n*/*N* unless otherwise indicated. Hazard ratio <1 favours dual antithrombotic therapy and hazard ratio >1 favours triple antithrombotic therapy. CrI, credible interval; DAT, dual antithrombotic therapy; MI, myocardial infarction; TAT, triple antithrombotic therapy.

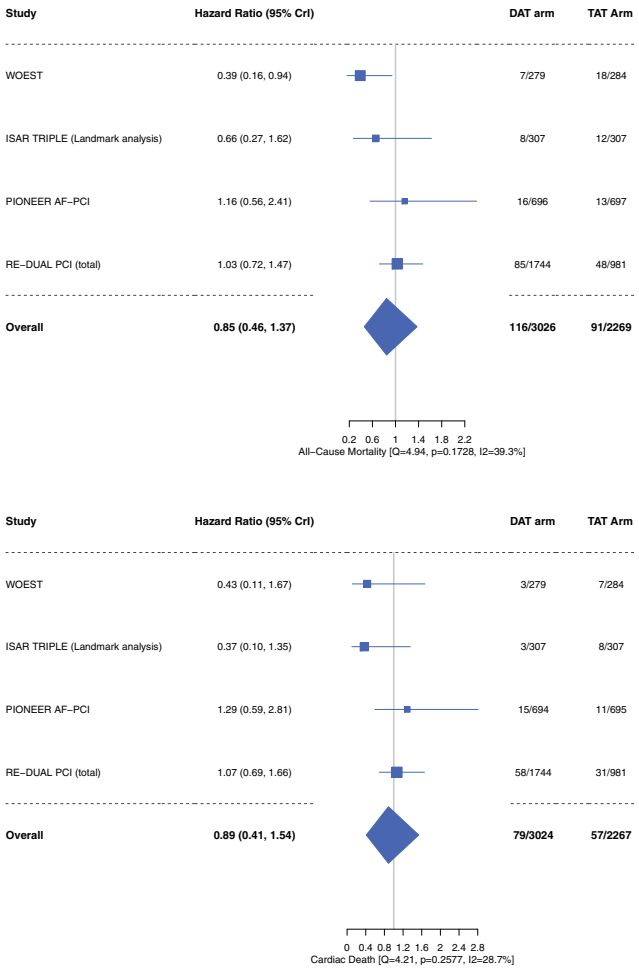


Figure 5 All-cause mortality and cardiac death. Data are *n*/*N* unless otherwise indicated. Hazard ratio <1 favours dual antithrombotic therapy and hazard ratio >1 favours triple antithrombotic therapy. CrI, credible interval; DAT, dual antithrombotic therapy; TAT, triple antithrombotic therapy.

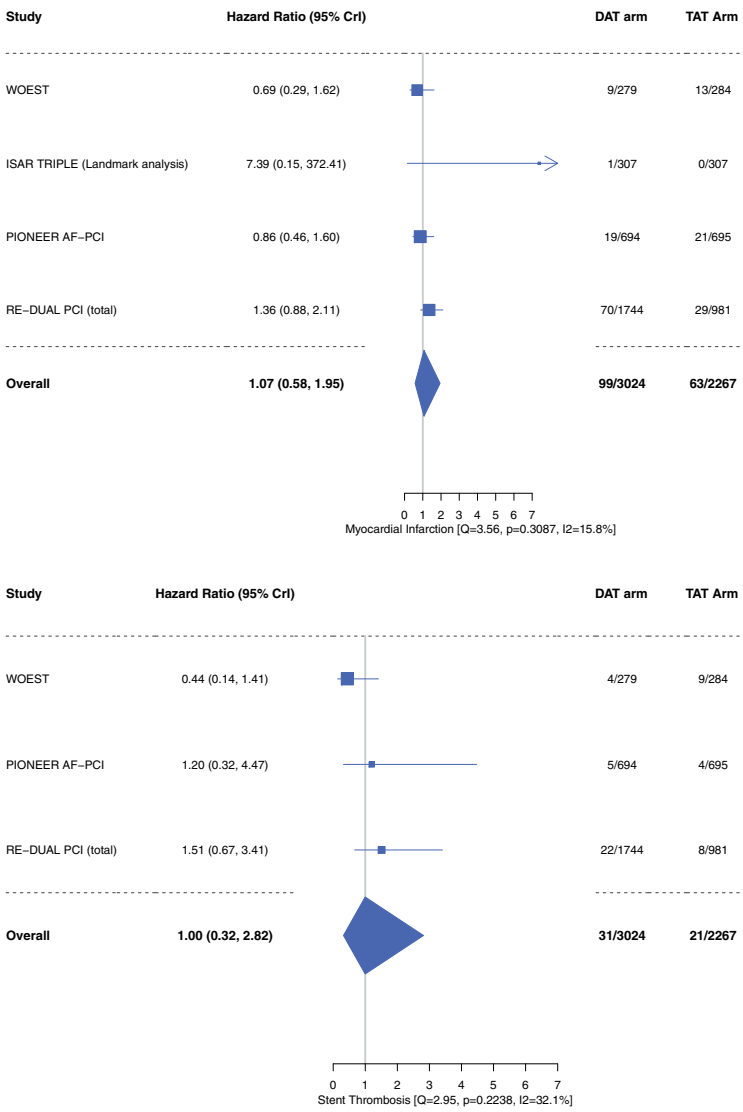


Figure 6 Myocardial infarction and stent thrombosis. Data are *n*/*N* unless otherwise indicated. Hazard ratio <1 favours dual antithrombotic therapy and hazard ratio >1 favours triple antithrombotic therapy. Note: There were no events of stent thrombosis in either group in the Landmark Analysis of the ISAR-TRIPLE trial and hence not included in this analysis. CrI, credible interval; DAT, dual antithrombotic therapy; TAT, triple antithrombotic therapy.

Discussion

Our systematic review and meta-analysis demonstrates several findings that may impact clinical care. First, in patients with AF following PCI, DAT reduces the composite of TIMI major or minor bleeding by 47% compared with TAT. Second, DAT seems comparable to TAT in reducing the trial-defined MACE. Finally, there is no statistically significant difference in individual outcomes of all-cause mortality, cardiac death, MI, stent thrombosis, or stroke between the two arms.

Up to 30% of patients with AF are found to have concomitant CAD, of whom 5–10% undergo PCI.[3] It is evident that treating these patients with OAC for thrombo-embolic protection is essential; however, treatment of CAD post-PCI with antiplatelet agents is also equally important. Prior studies have demonstrated that TAT after PCI in these patients is associated with a two-fold increase in bleeding compared with DAT.[11,19,20,27] It is also known that bleeding events post-PCI are associated with worse outcomes.[28] In our analysis, we found that DAT was associated with a 47% reduction in the composite of TIMI major or minor bleeding compared with TAT. These findings have significant clinical implications, as bleeding is associated with interruption of antithrombotic therapy which in turn is associated with MACE.[29] Furthermore, intracranial bleeding, one of the most dreadful and feared complications of TAT, showed a strong numerical trend towards reduction with DAT, particularly driven by

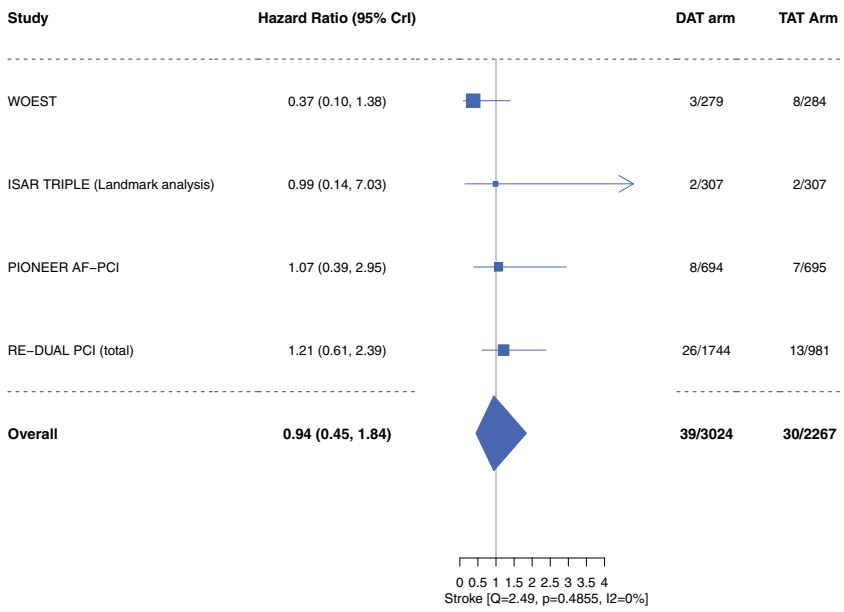
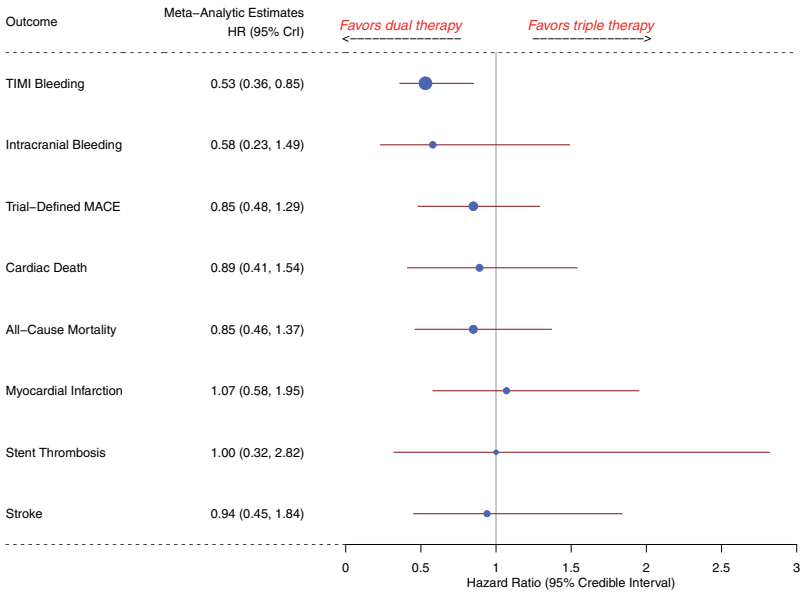


Figure 7 Stroke. Data are *n*/*N* unless otherwise indicated. Hazard ratio <1 favours dual antithrombotic therapy and hazard ratio >1 favours triple antithrombotic therapy. CrI, credible interval; DAT, dual antithrombotic therapy; TAT, triple antithrombotic therapy.



Take home figure Summary of bleeding and ischaemic risks for dual versus triple antithrombotic therapy.

patients enrolled in trials evaluating NOACs. This finding is crucial for management of patients at high risk of bleeding in which TAT may carry an even higher risk.

While all the four trials[12–15] have demonstrated a reduction in bleeding with DAT compared with TAT, a criticism of all these trials is that they were underpowered to assess efficacy outcomes. In our pooled analysis, we found that DAT may not only reduce bleeding events but is comparable to TAT for the reduction of MACE (*Take home figure*). These results support the data from prior observational studies.[18,21] The precise reasons for similar efficacy of DAT vs. TAT cannot be elucidated from our analysis; however, several mechanisms are possible. Newer generation drug-eluting stents with extremely low (<1%) incidence of stent thrombosis may have played a role.[30] In addition, clopidogrel on a biological basis has more platelet inhibition

compared with aspirin with less gastrointestinal bleeding which could in combination with OAC avoid the need for aspirin.[31,32] This hypothesis has been supported by two randomized trials which demonstrated that OAC is equivalent (or even better) than aspirin for protection against thrombotic events.[5,33] Finally, increased bleeding related to TAT has been shown to interrupt DAPT which in turn could increase MACE in the TAT arm.[29,34,35]

Our results may have several clinical implications. In an era where the balance of ischaemic vs. bleeding benefit after PCI is gaining importance, it is prudent that we understand the best approach to antithrombotic therapy in patients with AF following PCI. In this context, several factors that may affect therapeutic decision-making as listed by the recent 2017 ESC focused update on DAPT in CAD (i.e. risk stratification via assessment of ischaemic and bleeding risks using predictor tools such as the CHA_2DS_2-VASc and HAS-BLED scoring systems) should be emphasized.[36] Our study demonstrates that DAT is better than TAT for bleeding outcomes and comparable to TAT for efficacy outcomes. Taking this a step further, the major question that yet remains unanswered is the most appropriate combination for DAT (aspirin, clopidogrel, prasugrel, or ticagrelor with VKAs or any specific NOAC) which provides us with the right balance for minimizing thrombo-embolic vs. bleeding risks in an individual patient. With several such combinations possible, future trials are needed to answer these critical questions.

This meta-analysis has limitations. First, we used trial level data for assessment of outcomes, and hence we could not evaluate if baseline characteristics across various trials were different. Furthermore, several patient level characteristics (e.g. older age, diabetes, renal failure, or prior history of bleeding) as well as procedure related factors (e.g. coronary anatomy complexity, stent length, left main stenting) which could affect the intensity/duration of antithrombotic therapy use were not analysed in our study. Second, we pooled results of all the patients included in WOEST and ISAR-TRIPLE trials, although 69% of patients in the WOEST trial and 84% patients in ISAR-TRIPLE trial had AF. However, subgroup analysis of these trials did not demonstrate any statistical differences in their primary outcomes based on indication of OAC (AF, mechanical valves, or others), and hence we feel that inclusion of all patients enrolled in these trials would be unlikely to affect the final summary estimates of the meta-analysis. Third, in the studies included in our analysis, apart from ISAR-TRIPLE which had aspirin as the antiplatelet agent, the other three trials used a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) combined with either warfarin (WOEST) or NOACs (PIONEER AF, RE-DUAL PCI). However, our one-study-omitted sensitivity analysis does affirm that removal of the ISAR-TRIPLE trial from the analysis does not affect our primary analysis estimate for either safety or efficacy outcomes, indicating robustness of our results. Fourth, due to limited number of studies reporting the data, we could not analyse interaction between several key subgroups such as type of index event (ACS vs. non-ACS), type of stent (drug-eluting vs. bare-metal), CHA_2DS_2/HAS-BLED risk score etc. and MACE. Finally, substantial heterogeneity exists in between trials in terms of trial design as well as type and duration of antiplatelet/antithrombotic therapy used, which could affect interpretation of our results.

In summary, our systematic review and meta-analysis supports that DAT may be a better option than TAT in many patients with AF following PCI.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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