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Does dual vs. triple antithrombotic therapy after percutaneous coronary intervention in patients with atrial fibrillation lower the risk of bleeding at the cost of increased risk of ischemic events?☆

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A significant proportion of patients with atrial fibrillation (AF) undergo percutaneous coronary intervention (PCI) [1]. Use of triple antithrombotic therapy (TAT) in patients with AF undergoing PCI contributes to increased bleeding risk [2]. The optimum choice of antithrombotic therapy in patients with AF undergoing PCI is unclear, given the need for anticoagulation to prevent stroke, and antiplatelet therapy to prevent myocardial infarction (MI) and stent thrombosis [3].

Dual antithrombotic therapy (DAT) in these patients reduces bleeding events in randomized controls trials (RCTs) [4–8]. Some of these RCTs [7,8] raise a concern that this benefit may occur at the expense of an increased risk of ischemic events [1,9], however, none of these RCTs were powered for ischemic events. We, therefore, performed meta-analyses to evaluate the risk of ischemic and bleeding events with DAT vs. TAT using data from the RCTs [4–8]. We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Primary efficacy endpoint was composite ischemic events (composite of MI, stent thrombosis and ischemic stroke). Definitions of MI and ischemic stroke were comparable across all trials. Stent thrombosis was reported as definite in 3 RCTs [4,5,7], definite or probable in 1 RCT [8] and trial defined stent thrombosis events were used for PIONEER AF-PCI [6]. Primary safety endpoint was defined as major or minor bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) criteria. Secondary endpoints were TIMI major bleeding, intracranial bleeding, all-cause and cardiovascular (CV) mortality, and individual components of ischemic events. The outcomes were reported at 6 months [7,8], 9 months [5], or 12 months [4,6].

Random effects modeling was used to estimate the summary risk ratios (RRs). A two-sided $p < 0.05$ was considered statistically significant. Continuity correction was applied in case of zero events. We estimated the power of our pooled analysis to detect difference in ischemic events. We also estimated sample size of a future trial/meta-analysis with 80% power and a two-sided $\alpha = 0.05$ to detect the observed effect estimates for ischemic events in our pooled analysis.

Pooled number needed to harm (NNH) to cause one ischemic event and number needed to treat (NNT) to prevent one TIMI major or minor bleeding were calculated using meta-analysis of risk differences [10]. Additionally, the number needed to cause other secondary endpoint (s) were calculated. All analyses were performed using the STATA V15.0 (College Station, TX, USA) statistical software.

Five RCTs with 9931 patients met our eligibility criteria. There was an increased risk of ischemic events with DAT vs. TAT but this did not reach statistical significance (5.4% vs. 4.4%, RR: 1.12, $p = 0.423$) (Table 1 and Fig. 1). There was no difference in the risk of myocardial infarction or ischemic stroke ($p > 0.1$ for both) (Table 1). The risk of stent thrombosis was modestly increased with DAT as compared with TAT ($p = 0.088$) (Table 1). Given the lack of statistical significance for ischemic events, we performed a post-priori power calculation. The power of our meta-

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Table 1
Risk of outcomes with DAT vs. TAT.

Outcome	Events in DAT (%)	Events in TAT (%)	RR (95% CI)	*p*-Value
TIMI major or minor bleeding	4	7.7	0.53 (0.44–0.63)	<0.001
TIMI major bleeding	1.7	3	0.55 (0.43–0.72)	<0.001
Intracranial bleed	0.4	0.6	0.71 (0.29–1.76)	0.460
Ischemic events[a]	5.4	4.4	1.12 (0.85–1.47)	0.423
MI	3.3	2.9	1.17 (0.94–1.47)	0.164
Stent thrombosis	0.9	0.6	1.52 (0.94–2.45)	0.088
Stroke	1.1	1	1 (0.62–1.60)	0.993
MI/stent thrombosis	4.4	3.4	1.02 (0.68–1.54)	0.920
Mortality	3.7	3.8	0.91 (0.70–1.19)	0.493
Cardiovascular mortality	2.2	2.2	0.93 (0.57–1.50)	0.753

[a] Ischemic events defined as a composite of myocardial infarction, stent thrombosis and ischemic stroke. CI: confidence interval, DAT: dual antithrombotic therapy; MI: myocardial infarction, RR: Risk Ratio, TAT: triple antithrombotic therapy, TIMI: thrombolysis in myocardial infarction.

analysis to detect the observed effect estimate in ischemic events, MI and stent thrombosis was 34%, 28%, and 48%, respectively. We estimate that a future meta-analysis with 31,290, 39,106 and 20,016 patients for ischemic events, MI and stent thrombosis, respectively would be required to detect the observed effect estimates at 80% power and 5% significance.

The risk of TIMI major or minor bleeding was lower with DAT as compared with TAT (4% vs. 7.7%, RR: 0.52, $p < 0.001$) (Table 1). The major bleeding events were lower in DAT as compared with TAT whereas no difference was seen in the risk of intracranial bleeding, all-cause mortality or cardiovascular mortality. The estimated NNT to prevent one major or minor bleeding event was 27, and whereas the NNH to cause one ischemic event was 200 (Fig. 1).

Our meta-analysis confirms that among patients with AF undergoing PCI, DAT reduced the risk of bleeding as compared with TAT. We further observed a numerical excess in the risk of ischemic events in the DAT arm that did not reach statistical significance. The meta-analysis at the current sample size is inadequately powered to detect the observed difference. The NNH to cause one ischemic event with DAT was 7 times higher than the NNT to prevent one TIMI major or minor bleeding with TAT.

A previously published meta-analysis [2] of 4 RCTs reported a similar 47% reduction in the risk of major or minor bleeding with DAT vs. TAT, without a significant difference in the risk of MI or stent thrombosis. The subsequently published AUGUSTUS trial [8] suggested that the risk of stent thrombosis with DAT was modestly increased (0.9% and 0.5% with DAT and TAT, respectively) which was not statistically significant [8]. Interestingly, the two trials which reported a higher risk of MI and stent thrombosis with DAT (RE-DUAL PCI and AUGUSTUS) also had a higher prevalence of diabetes and ACS as compared with the other three. Previous studies have identified these risk factors as important predictors of ischemic events after PCI [11].

The risk of MI and stent thrombosis after PCI also varies according to the target vessel re-vascularized, the type of occlusion (acute vs. chronic), type of stent, coronary anatomy, and re-intervention status; a single antithrombotic therapy approach is hence unlikely to be the solution for all patients. Certain patients with a higher risk of ischemic events and lower bleeding risks may still benefit from at least a short period of TAT. Further, with the increasing use of non-vitamin K antagonist oral anticoagulants and broader application of bleeding-reduction strategies, it is expected that the relative risk of bleeding with TAT may decrease in clinical practice. Future studies (RT-AF; NCT02334254; SAFE-A, UMIN000015923; ENTRUST-AF PCI, NCT02866175) and meta-analyses will be required to reliably estimate the increased risk of ischemic events with DAT vs. TAT.

Heterogeneity in the indication for anticoagulation, PCI, revascularization strategy, variable follow-up, and lack of patient level data limits the understanding of the ideal antithrombotic strategy and the ideal candidate for TAT in patients with AF undergoing PCI. It is important to recognize that these trials and our meta-analysis were not adequately powered to estimate the risk of ischemic events.

DAT decreases the risk of major or minor bleeding with a possible increase in the risk ischemic events among patients with AF undergoing

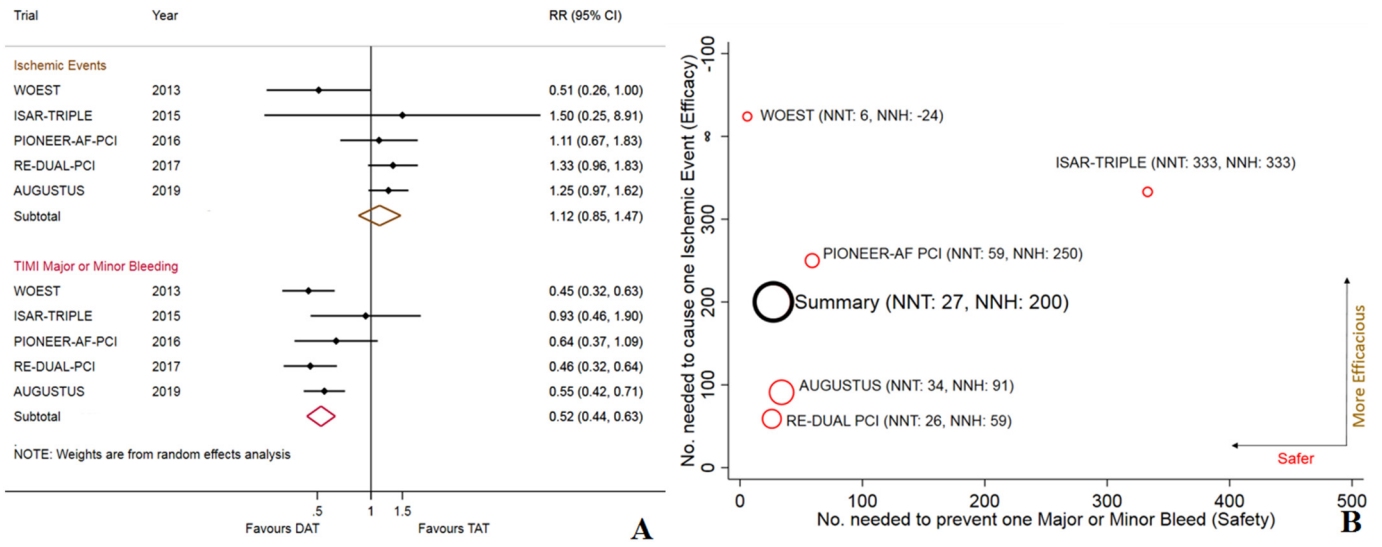

Fig. 1. Forest Plot comparing DAT versus TAT for primary efficacy endpoint (ischemic events) and primary safety endpoint (TIMI major or minor bleeding) (**Panel A**). The estimates in the right columns are RRs with 95% CI. In the case of zero events, continuity correction was applied. The number needed to treat (NNT) to prevent one major or minor bleed and number needed to harm (NNH) to cause one ischemic event for individual trials and summary estimates. The size of the bubbles is proportional to the number of patients. More efficacious implies higher NNH to cause one ischemic event; safer implies lower NNT to prevent one bleeding event (**Panel B**).

PCI. Choice of DAT vs. TAT should continue to be individualized based on the patient's clinical risk, coronary anatomy, and PCI factors.

Declaration of Competing Interest

Dr. Vaduganathan is supported by the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst (NIH/NCATS Award UL 1TR002541), serves on advisory boards for Amgen, AstraZeneca, Bayer AG, and Baxter Healthcare, and participates on clinical endpoint committees for studies sponsored by Novartis and the NIH. Dr. Mering serves on the advisory board of Boston Scientific. Dr. Ahmed receives honoraria for teaching activities from Abbott and Medtronic and is an investigator for the SUMMIT trial (ClinicalTrials.gov Identifier: NCT03433274). The other authors declare no competing interests.

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