The risk of stent thrombosis of dual antithrombotic therapy for patients who require oral anticoagulant undergoing percutaneous coronary intervention: insights of a meta-analysis of randomized trials

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\textbf{ABSTRACT}

Recent meta-analyses investigating dual antithrombotic therapy (DAT) versus triple antithrombotic therapy (TAT) among patients who require oral anticoagulants especially with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) raised the concern of stent thrombosis (ST) and myocardial infarction (MI), however, these meta-analyses did not include all randomized trials who require oral anticoagulants. We aimed to investigate the efficacy of DAT versus TAT in these patients undergoing PCI. Our data showed the risk of ST was not significantly different in DAT vs. TAT (HR [95\%CI]: 1.50 [0.97–2.34], \textit{p} = .07; \textit{I}^2 = 0\%) and MI (HR [95\%CI]: 1.17 [0.95–1.45], \textit{p} = .14; \textit{I}^2 = 0\%).

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\textbf{Introduction}

Antithrombotic therapy with oral anticoagulants and antiplatelets are crucial for patients who require oral anticoagulant especially with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) to prevent stroke and stent thrombosis (ST) [1]. The recent meta-analyses of randomized controlled trials (RCTs) have shown favorable outcomes in bleeding of patients with AF with dual antithrombotic therapies (DAT) including P2Y\textsubscript{12} inhibitors and direct oral anticoagulants (DOAC), however they raised the concern of ST and myocardial infarction (MI) [2,3]. Since these meta-analyses did not include all RCTs investigating DAT vs. triple antithrombotic therapies (TAT), our object of this study was to investigate the efficacy of DAT versus TAT in patients who require oral anticoagulants undergoing PCI.

\textbf{Method}

All RCTs investigating the antithrombotic strategies of DAT versus TAT in patients with AF who underwent PCI, were searched using PUBMED and EMBASE through 2 March 2020. Search terms were \textit{percutaneous coronary intervention, atrial fibrillation, aspirin OR clopidogrel OR prasugrel OR ticagrelor OR P2Y\textsubscript{12} inhibitors OR antiplatelet, warfarin OR coumadin OR vitamin k antagonist OR apixaban OR dabigatran OR rivaroxaban OR edoxaban OR anticoagulant.}

Two independent and blinded authors (TK and HU) reviewed the search results to select the studies based on inclusion and exclusion criteria. When a consensus was not reached between the two authors, a third author (HT), who is an expert in the field of a meta-analysis [4], was consulted to reach a decision. We did not apply language restriction. Reference lists of included studies for the meta-analysis were reviewed to minimize missing relevant studies. The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [5].

Studies which met the following criteria were included: (1) the design was a RCT for patients who require oral anticoagulants undergoing PCI, comparing DAT vs. TAT (2) the study reported ST and MI as outcomes. The Review Manager (RevMan) Version 5.3 (Nordic Cochrane Centre, the Cochrane Collaboration, 2012, Copenhagen, Denmark) software was used to calculate the pooled risk ratios and hazard ratios (HRs) with 95\% confidence intervals (CI). Random-effects model was used in ST and MI regardless of the heterogeneity among studies because it allows more conservative assessment of the pooled effect size. Significant heterogeneity was considered to be present when the \textit{I}^2 index was over 50\%.
Results

Our search identified 5 RCTs including a total of 11,532 patients who require oral anticoagulant undergoing PCI [6–10]. The risk of ST was not significantly different in DAT vs. TAT (HR [95%CI]: 1.50 [0.97–2.34], \( p = .07; \ I^2 = 0\%\) (Figure 1(a)). In addition, the risk of MI was not significantly different in DAT vs. TAT (HR [95%CI]: 1.17 [0.95–1.45], \( p = .14; \ I^2 = 0\%\) (Figure 1(b)).

Discussion

Although dropping aspirin raises the concern of ST and MI after PCI for patients who require oral anticoagulants especially with atrial fibrillation, our meta-analysis also revealed non-significantly different in ST and MI.

The recent meta-analyses demonstrated increased risk of MI and ST in DAT, however, they did not include WOEST trial [2,3,8]. The main results of their study were driven from DAT versus TAT, not DOAC based DAT versus vitamin K antagonist (VKA) based TAT. Moreover, their study did not reveal significantly difference between DOAC based DAT vs VKA based TAT in ST and MI. As such, we consider a meta-analysis of DAT versus TAT should include WOEST trial although they included not only AF patients, but also patients who require oral anticoagulant for mechanical valve, pulmonary embolism, apical thrombus, reduced left ventricular ejection fraction, etc. Further large scale well-powered RCTs is needed to confirm the safety of DAT in ST and MI in this population.

Disclosure statement

Dr. Bangalore is an advisory board member for Abbott Vascular, Biotronik, Amgen, Pfizer, and Reata. Dr Cohen is a consultant for AstraZeneca, Medtronic, Merit Medical, Terumo Medical, Abiomed. Remaining authors have nothing to disclose.

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