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Editorial

Triple or dual antithrombotic therapy post-percutaneous coronary intervention: which one is better?

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Dual antiplatelet therapy is the usual standard of care post-percutaneous coronary intervention (PCI)[1]. Nevertheless, in patients who are receiving concurrent systemic anticoagulation, there is a growing concern that the bleeding risk with the resulting triple antithrombotic therapy (TAT) may outweigh any potential benefits. This is further supported by the recognition that bleeding events post-PCI are associated with worse overall outcomes.[2] Several studies have reported that the use of TAT results in similar rates of major adverse cardiovascular events (MACE) and major bleeding when compared to dual antithrombotic therapy (DAT)[3–5]. However, many of these studies are observational and underpowered to detect such events. As a result, the optimal antithrombotic regimen post-PCI remains a subject of debate.

In the current issue of *Journal of Cardiovascular Electrophysiology*, Atti *et al.*[6] report findings from their systematic review and meta-analysis of studies comparing TAT and DAT in anticoagulated patients undergoing PCI. The authors performed a comprehensive literature search to identify all relevant studies ever published: 15 studies were eligible (5 randomised controlled trials (RCTs), 10 cohort studies) and included a total of 13,967 patients (7,349 TAT, 6,618 DAT). Meta-analysis using random-effects model demonstrated no difference in risk of trial defined MACE, all-cause mortality and stroke but significantly lower rates of myocardial infarction (MI) and stent thrombosis with TAT. However, TAT was associated with significantly higher rates of trial defined major bleeding and Thrombolysis in Myocardial Infarction (TIMI) major bleeding but no difference in risk of intracranial bleeding.

The findings from this meta-analysis are important and helps further our understanding of how to manage such challenging patients. Bleeding and thrombosis (ie. ischaemia) are often thought of as two distinct ends on the same spectrum. Using this principle, treatment that influences one should have the opposing effect on the other. However, the WOEST trial[7] challenged this belief by demonstrating that the omission of aspirin from a TAT regimen reduced the risk of both thrombotic outcomes and bleeding, perhaps suggesting that not all clots are equal. An alternative explanation is that bleeding events from TAT may result in cessation of antithrombotic agents that promote subsequent MACE. It is perhaps superficial to simply consider the number of antithrombotic agents used per se in a particular treatment regimen, since many of these drugs have different mechanism of actions. Another limitation of using terminologies such as DAT and TAT is that it encourages the reader to assume that every DAT and TAT regime is identical when this is in fact far from the truth.

Among patients with atrial fibrillation, the use of non-vitamin K antagonist oral anticoagulants (NOACs) has been associated with a reduced risk of major bleeding compared to warfarin, and have become the preferred option for thromboprophylaxis in patients with AF.[8,9] There are a paucity of data on the use of NOACs in TAT regimes. As acknowledged by the authors, the majority of studies included patients on warfarin rather than NOACs. However, the three largest studies (PIONEER AF PCI[10], REDUAL PCI[11] and AUGUSTUS[12]; with a combined number of patients that exceeded all the remaining studies) included patients on NOACs in their DAT arm. The agent of choice for oral anticoagulation (OAC) in the TAT arms for both PIONEER AF PCI[10] and REDUAL PCI[11] was warfarin. As a result, these studies were largely comparing the outcomes of DAT (with a NOAC) and TAT (with

warfarin). Therefore, the inclusion of these studies may have resulted in bias and inflated the risk of major bleeding with TAT.

Interestingly, neither the subgroup analysis of RCTs or cohort studies showed any difference in rates of MI or stent thrombosis, although lower rates were seen with TAT in the pooled analysis of all studies. Indeed, there was a numerical trend for more stent thrombosis and the composite ischaemic outcome in placebo-treated patients compared to aspirin, in the AUGUSTUS trial.

A few limitations to the study by Atti *et al.*[6] ought to be highlighted. First, it is important to consider the effects of selection bias of the individual trials, many of which are observational in nature, on the overall meta-analysis. The individual treatments were likely to have been influenced by clinicians after weighing up the risk of ischaemia versus bleeding. It may therefore be assumed that patients who given TAT were deemed to have high ischaemic risk and those given DAT were deemed to have high bleeding risk. Second, there are significant variations in the duration of TAT used in the individual studies. Third, the studies were published between 2007 and 2019. There are important advancements during this time from types of stents used to changes in medication regimens that may have influenced the outcomes. The significant changes over the past decade in favour of TAT and DAT are summarised in **Table 1**. Fourth, there is a lack of consistency between studies in the type of antiplatelets and anticoagulation agents used in DAT and TAT regimens.

In summary, the important study by Atti *et al.*[6] suggests that the use of TAT post-PCI may be associated with lower rates of MI and stent thrombosis but with increased risk of major bleeding. However, inter- and intra-group differences between those treated with DAT and TAT precludes drawing any strong conclusions from this meta-

analysis. For now, when choosing an OAC strategy in combination with one or more antiplatelets, a NOAC based strategy is likely to be safer compared to a warfarin based one.

What about the need for aspirin? For many patients, an OAC plus P2Y12 inhibitor based DAT strategy may be an option, although in patients at high risk of stent thrombosis or ischaemic outcomes, a short period of aspirin may still be warranted as part of a TAT regimen. Indeed, the use of the different treatment regimens should ultimately be guided by detailed risk profile assessment of each individual.

Disclosures:

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Table 1: Changes over the past decade:

Favouring TAT	**Favouring DAT**
Use of NOACs, which are associated with lower bleeding risk	Improved stents used in PCI
Better monitoring with warfarin	More potent antiplatelets
Increased use of PPIs	
Increased use of radial access for PCI	

TAT, triple antithrombotic therapy; DAT, dual antithrombotic therapy; PPI, proton pump inhibitors