EDITORIAL

Is meta-analysis the optimal method to decide the duration of antiplatelet therapy in diabetic patients treated with drug-eluting stenting?

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At least 6 to 12 months of dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor is recommended by the guidelines in patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation to reduce the risk of recurrent atherothrombotic events.[1,2] Potent $P2Y_{12}$ inhibitors are preferred in high-risk coronary artery disease (CAD) patients, whereas the duration of DAPT is still being deliberated.[1,2] In addition, ambiguity exists regarding which single antiplatelet agent (aspirin vs $P2Y_{12}$ receptor inhibitor) is optimal after the discontinuation of DAPT. Numerous network meta-analyses have been used to establish the optimal length of DAPT following DES implantation by comparing clinical efficacy and safety of various durations of DAPT (≤3 months vs ≤6 months vs 12 months vs >12 months). It was reported that short-term DAPT lasting up to 6 months followed by monotherapy with a $P2Y_{12}$ receptor inhibitor was associated with reduced bleeding without an elevated risk for myocardial infarction (MI) or stent thrombosis compared with DAPT lasting 12 months or longer following DES implantation.[3] Another network meta-analysis demonstrated that DAPT shorter than 6 months followed by a $P2Y_{12}$ inhibitor was associated with reduced major bleeding and over 12 months of DAPT was associated with reduced MI at the expense of increased incidence of major bleeding.[4] A Bayesian network meta-analysis of various de-escalation strategies revealed that de-escalation of DAPT after 1 to 3 months to monotherapy with a $P2Y_{12}$ inhibitor, but not aspirin, might be a safer and equally effective strategy compared with 12-month DAPT.[5]

The scenario is more complicated in individuals with CAD and diabetes who are treated with DES implantation. Guidelines do not differentiate patients with or without diabetes while recommending the DAPT duration.[1,2] In this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), An et al[6] report the results of a Bayesian network meta-analysis to address this issue. Instead of a pairwise comparison applied in traditional meta-analysis, a Bayesian network meta-analysis is used for 3-way or more comparisons to find a solution for an optimal DAPT duration and the best choice of single antiplatelet agent.[6] They included 18 eligible trials with 20 536 patients with diabetes treated with short-term (≤3 months), medium-term (6 months), standard-term (12 months), or extended-term (>12 months) DAPT following DES implantation. The main findings of this analysis with respect to the primary outcome (as defined in each trial) were that short-term DAPT was the "best" strategy and was associated with a lower odds ratio (OR) for reducing the primary endpoint versus extended-term DAPT. Standard-term DAPT was also associated with a lower OR versus extended-term DAPT. Short-term DAPT followed by monotherapy with a $P2Y_{12}$ inhibitor was better than short-term DAPT followed by aspirin monotherapy. Secondary outcomes (an individual components of the primary outcome) were statistically similar between the treatment regimens. Finally, medium-term DAPT was associated with the highest risk for mortality, MI, and definite or probable stent thrombosis.[6]

The authors should be commended for their efforts to address a very clinically relevant question with data that are available. Although this analysis suggested that short- or standard-term DAPT is an optimal strategy in CAD patients with diabetes treated with DES implantation, there are numerous issues that need to be discussed before considering these results for routine therapy. For example, it is well known that patients with diabetes are inherently prothrombotic—they exhibit heightened platelet function, inflammation, hypercoagulability, and impaired fibrinolysis.[7-10]

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The incidence of post-PCI ischemic events is comparatively higher in patients with diabetes compared with those without diabetes despite treatment with ticagrelor or prasugrel, and the rate of post-PCI events is continuously elevated during long-term DAPT.[11,12] In this scenario, short--term DAPT may not be a plausible strategy and the choice of antiplatelet agent (aspirin, ticagrelor, or prasugrel) remains uncertain.

In a prespecified analysis of the DAPT (Dual Antiplatelet Therapy) Study,[13] patients with diabetes (n = 3391) had higher rates of major adverse cardiovascular and cerebrovascular events compared with individuals without diabetes, both within the first year of follow-up and beyond. Although the rates of MI were lower in patients with diabetes who continued the therapy with thienopyridine (nearly two-thirds of patients were treated with clopidogrel) beyond 1 year compared with 1-year therapy, the treatment benefit was attenuated in diabetic patients in comparison with those without diabetes. Bleeding Academic Research Consortium type 2, 3, or 5 bleeding risk was higher with continued thienopyridine therapy. Patients with diabetes may benefit from long--term DAPT with more potent $P2Y_{12}$ inhibitors. In a prespecified analysis of the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54) trial[14] involving patients with a history of MI 1 to 3 years prior and diabetes (approximately 80% of patients had prior PCI), individuals treated with ticagrelor (90 or 60 mg twice daily) plus aspirin versus aspirin had a 16% reduction in major adverse cardiovascular events of cardiovascular death, MI, and stroke (P = 0.035), and a 2.6-fold higher risk for TIMI major bleeding (P = 0.0004). Finally, in a prospective PCI registry study of high-risk "TWILIGHT-like" patients with diabetes who were event-free at 1 year after PCI, extended DAPT of more than 1 year versus up to 1 year was associated with a significant reduction in death, MI, or stroke, without a significant difference in clinically relevant bleeding.[15] In a prespecified subanalysis of THEMIS-PCI (The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study-Percutaneous Coronary Intervention) trial[16,17] (n = 11154), ticagrelor plus aspirin was associated with lower net clinical outcome (9.3% vs 11.0%; hazard ratio, 0.85; 95% CI, 0.75–0.95; P = 0.0005), but not in stable patients with CAD and diabetes. Thus, these contemporary trials indicate that patients with diabetes treated with DES implantation benefit from extended--term DAPT or ticagrelor alone.

In the presence of attenuated pharmacodynamic effect that is more prevalent among patients with diabetes and is associated with elevated risk for ischemic events, clopidogrel is definitely not a treatment of choice for a $P2Y_{12}$ receptor inhibitor. In the presence of heightened platelet function in patients with diabetes, 81 mg daily low-dose aspirin is also not a choice of single antiplatelet agent.[8,18] Thus, 3 to 6 months of DAPT with aspirin and ticagrelor followed by ticagrelor alone may be an optimal strategy in patients with diabetes treated with DES implantation. The latter strategy may be associated with optimal anti--ischemic efficacy and acceptable bleeding risk. A dedicated large-scale study comparing less than 3 months versus 1 year of DAPT with ticagrelor followed by long-term ticagrelor may help to better address this unending enigma of the duration of antiplatelet therapy in patients with diabetes treated with DES implantation.

ARTICLE INFORMATION

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