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PERIPHERAL

Extended Duration Dual Antiplatelet Therapy After Coronary Stenting Among Patients With Peripheral Arterial Disease

A Subanalysis of the Dual Antiplatelet Therapy Study

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ABSTRACT

OBJECTIVES This study sought to determine whether patients with peripheral arterial disease (PAD) experience different reductions in ischemic event and increases in bleeding events with extended duration dual antiplatelet therapy versus those without PAD.

BACKGROUND Patients with PAD have increased ischemic and bleeding risks after coronary stenting.

METHODS The DAPT (Dual Antiplatelet Therapy) study randomized 11,648 patients free from ischemic and bleeding events 12 months after coronary stenting to continued thienopyridine plus aspirin therapy for an additional 18 months versus aspirin therapy alone. The effects of continued thienopyridine on myocardial infarction (MI) or stent thrombosis, major adverse cardiovascular and cerebrovascular events (death, MI, or stroke) and bleeding (GUSTO [Global Utilization of t-PA and Streptokinase for Occluded Coronary Arteries] moderate or severe) were assessed among those with versus without PAD.

RESULTS Among 11,648 randomized patients, 649 (5.57%) had PAD. Between 12 and 30 months, randomized patients with PAD had higher rates of MI/stent thrombosis (6.03% vs. 2.92%; $p < 0.001$), major adverse cardiovascular and cerebrovascular events (11.65% vs. 4.62%; $p < 0.001$), and bleeding (4.86% vs. 1.74%; $p < 0.001$). Continued thienopyridine versus placebo was associated with consistent treatment effects for MI/stent thrombosis (with PAD, HR: 0.63; 95% CI: 0.32 to 1.22; without PAD, HR: 0.53; 95% CI: 0.42, 0.66; interaction $p = 0.631$), major adverse cardiovascular and cerebrovascular events (with PAD, HR: 1.06; 95% CI: 0.67 to 1.67; without PAD, HR: 0.70; 95% CI: 0.59 to 0.84; interaction $p = 0.103$), and bleeding (with PAD, HR, 1.82; 95% CI: 0.87 to 3.83; without PAD, HR: 1.66; 95% CI: 1.23 to 2.24; interaction $p = 0.811$).

CONCLUSIONS Among patients undergoing coronary stenting, those with PAD have more ischemic and bleeding events versus those without PAD. Extended duration dual antiplatelet therapy is associated with consistent ischemic benefit and bleeding harm among patients with and without PAD. (J Am Coll Cardiol Intv 2017;10:942–54)

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Peripheral arterial disease (PAD), the systemic manifestation of atherosclerotic disease, affects more than 8.5 million Americans and 200 million people worldwide (1). Of those with PAD, approximately 2 of 3 have concomitant coronary artery disease, and up to 1 of 3 with coronary artery disease have PAD (2). Furthermore, patients with PAD have a 60% increased risk for myocardial infarction (MI) and a 2- to 6-fold increased risk of cardiovascular death (3). Those who require percutaneous coronary intervention (PCI) are at heightened risk of post-procedure events, with a 6-fold increased odds of stent thrombosis (4), 20% to 60% increased risk of bleeding (5,6), and a 2-fold greater risk of death (2).

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Antiplatelet therapy with either aspirin or a $P2Y_{12}$ inhibitor reduces the risk of MI, stroke, and vascular death among those with PAD (7,8). Yet, the ischemic benefits of prolonged dual antiplatelet therapy for patients with PAD may be counterbalanced by the increased risk of bleeding. For instance, among 3,096 patients with PAD from the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) trial (9), those randomized to aspirin and clopidogrel for 28 months versus aspirin alone experienced a 40% reduction in MI but a 2-fold increased hazard of bleeding. As such, current guidelines assign a Class IIb recommendation for use of combination aspirin and clopidogrel therapy to reduce the risk of ischemic events only among those with symptomatic PAD at high cardiovascular risk and low bleeding risk (10).

Similarly, among the general population of patients undergoing PCI, dual antiplatelet therapy for >12 months reduces the risk of MI and stent thrombosis, but increases the risk of moderate or severe bleeding (11). For patients with PAD, who are at greater risk of both ischemic and bleeding events, the optimal duration of dual antiplatelet therapy after PCI is uncertain. Findings from two recent analyses involving patients with PAD and either a prior history of MI (12) or PCI (13) conflict as to whether there is a greater benefit with longer term dual antiplatelet therapy in patients with PAD than in the rest of the PCI population.

The Dual Antiplatelet Therapy (DAPT) study, which enrolled 25,682 patients after coronary stenting and randomized 11,648 patients who were compliant with thienopyridine therapy and who remained free from ischemic and bleeding events after 12 months of dual antiplatelet therapy treatment, compared the effects of 30 months versus 12 months of dual antiplatelet therapy. Treatment with 30 months of dual antiplatelet therapy was associated with significant reductions in MI and stent thrombosis but increases in moderate or severe bleeding (14,15). Using these data, we sought to determine whether patients with PAD in the DAPT Study experienced different reductions in ischemic event and increases in bleeding events with extended duration dual antiplatelet therapy relative to those without PAD.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

MACCE = major adverse cardiovascular or cerebrovascular event(s)

MI = myocardial infarction

PAD = peripheral arterial disease

PCI = percutaneous coronary intervention

METHODS

STUDY POPULATION. The DAPT study (NCT00977938), described previously (14,15), was a randomized, double-blind, placebo-controlled trial comparing 30 months versus 12 months of thienopyridine therapy (clopidogrel or prasugrel) in addition to aspirin therapy in subjects undergoing coronary stenting with either drug-eluting or bare metal stents. Adults who were candidates for dual antiplatelet therapy were enrolled and treated with open-label aspirin plus thienopyridine therapy for 12 months after coronary stenting (enrollment period, 0 to 12 months). At 12

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