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EDITORIAL COMMENT

# The DAPT Trial and Peripheral Arterial Disease From a Vascular Medicine Perspective*

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The duration of dual antiplatelet therapy for prevention of thrombotic complications after coronary artery stenting has been a subject of debate for more than a decade. The main findings of the DAPT (Dual Antiplatelet Therapy) trial (1) were reduced rates of stent thrombosis and major cardiovascular and cerebrovascular adverse events, as well as an increased rate of moderate-to-severe bleeding in the dual antiplatelet arm as compared with antiplatelet monotherapy with aspirin.

Roughly 10% of all patients with a history of myocardial infarction (MI) also have peripheral arterial disease (PAD), and vice versa, about 20% of all PAD patients also have a history of MI (2). Similarly to the DAPT study, among 3,096 patients with PAD in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) trial, those randomized to aspirin and clopidogrel for 28 months experienced a 40% reduction in MI (2.3% vs. 3.7%) but an almost 2-fold increased risk of minor bleeding compared with aspirin alone (20.4% vs. 34.4%) (3). So, do the benefits of prolonged dual antiplatelet therapy in terms of ischemic events really outweigh the increased risk of bleeding?

SEE PAGE 942

In this issue of *JACC: Cardiovascular Interventions*, Secemsky et al. (4) address the subgroup of patients in the DAPT study with coronary heart disease (CHD) and PAD. Their main findings are:

1. PAD patients are more than 5 years older and have significantly more comorbidities and more severe coronary lesions.
2. Clinically, PAD patients benefit from extended dual antiplatelet therapy, with a 7% versus 4.7% reduced absolute risk of ischemic events.
3. However, similar to the main trial, a 30-month dual antiplatelet therapy is associated with an increased risk of moderate-to-severe bleeding of 6.3% versus 3.5%.

## THE DAPT STUDY FROM A VASCULAR MEDICINE PERSPECTIVE

Because the DAPT study was a coronary intervention trial, some comments should be made from the perspective of vascular medicine:

1. PAD status was determined by the investigating site at the time of the index coronary stenting procedure, on the basis of documented medical history only. Therefore, PAD might be underdiagnosed.
2. Typical PAD endpoints such as acute limb ischemia and limb revascularization or amputation were not addressed.
3. The statistical power calculation for the DAPT study considered the entire trial. Therefore, the subgroup analysis by Secemsky et al. (4) is underpowered. This, unfortunately, precludes robust and valid conclusions.
4. The vast majority of stents used in DAPT were first-generation drug-eluting stents (DES) or bare-metal stents. Because next-generation DES showed reduced rates of late stent thrombosis, the need for

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prolonged dual antiplatelet therapy is questionable. The impact of this observation on patients with PAD and CHD is unclear.

## DURATION OF DUAL ANTIPLATELET MEDICATION IN CORONARY DES PATIENTS WITH PAD

Undoubtedly, aspirin in combination with a $P2Y_{12}$ receptor inhibitor is of utmost importance for the prevention of coronary stent thrombosis in patients who had have received a DES intervention. The reduced rate of late stent thrombosis achieved by the introduction of newer-generation DES has resulted in guideline recommendations for dual antiplatelet therapy of 6 to 12 months (5). Furthermore, some studies indicate that a shorter dual antiplatelet therapy duration of 3 to 6 months after coronary DES might be as effective as a 12-month therapy. Because a shorter duration is surely associated with a decreased rate of major bleeding, this is good news for coronary patients without PAD. But is this approach also applicable and reasonable for patients with combined disease and a significantly larger atherosclerotic load? This is an open issue not answered by the presented DAPT subgroup analysis.

## ANTIPLATELET MEDICATION IN PAD: MONO OR DUAL?

In general, the major cardiovascular consensus guidelines recommend long-term antiplatelet therapy with aspirin *or* clopidogrel for patients with symptomatic lower-extremity PAD (6–8). Some landmark studies deserve mention:

- The CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events) trial showed a modest, but significant, advantage for clopidogrel over aspirin for the combined risk of ischemic stroke, MI, or symptomatic PAD (9). This benefit was mainly driven by the subgroup of patients with PAD, who benefitted most with a relative risk reduction of 24%.
- In the EUCLID trial (A Study Comparing Cardiovascular Effects of Ticagrelor and Clopidogrel in Patients With Peripheral Artery Disease) (10), in almost 14,000 patients with predominantly symptomatic PAD, no differences were detectable for a monotherapy with clopidogrel 75 mg *or* ticagrelor 2 × 90 mg after a median follow-up of 30 months for the composite risk of cardiovascular death, MI, or ischemic stroke (10.8% vs. 10.6%). Major bleeding occurred at similar rates in both groups (1.6% in both arms).
- The CASPAR (Clopidogrel and Acetyl Salicylic Acid in Bypass Surgery for Peripheral Arterial Disease) study is the only trial that compared dual antiplatelet therapy with 100-mg aspirin *and* 75-mg clopidogrel to aspirin monotherapy in patients with below-the-knee bypass grafts (11). After 6 to 24 months, dual antiplatelet therapy was not superior with respect to the composite endpoint of index graft occlusion or revascularization, above-ankle amputation, or death (hazard ratio [HR]: 0.98, 95% confidence interval [CI]: 0.78 to 1.23). However, in a pre-specified subgroup analysis, the primary endpoint was significantly reduced by clopidogrel in prosthetic graft (HR: 0.65, 95% CI: 0.45 to 0.95; $p = 0.025$), but not in venous graft patients (HR: 1.25, 95% CI: 0.94 to 1.67). There was no significant difference between the rates of severe bleeding in the clopidogrel and placebo (plus aspirin) groups (2.1% vs. 1.2%).

Unfortunately, no other relevant head-to-head trials comparing dual and mono antiplatelet therapy in PAD patients have been published to date. Two ongoing studies (ASPIRE [Antiplatelet Strategy for Peripheral Arterial Interventions for Revascularization of Lower Extremities; NCT02217501] and LONGDAPTPAD [Effects of Prolonged DAPT After Lower Extremity Percutaneous Transluminal Angioplasty (PTA) in Patients With LE-PAD; NCT02798913]) in PAD patients are investigating the effect of prolonged dual antiplatelet therapy with PAD-related endpoints, for example, major adverse limb events. Therefore, monotherapy—usually with aspirin *or* clopidogrel—is the standard; dual antiplatelet therapy is reserved for long prosthetic grafts, interval therapy after infrainguinal endovascular interventions (usually for 4 weeks), redo procedures, or patients with a coronary indication.

In conclusion, it is currently not possible to draw conclusions regarding the net benefit of prolonged dual antithrombotic therapy extending beyond 1 year in patients with PAD after drug-eluting coronary stenting. Fewer major cardiovascular events come at the price of higher bleeding rates, again with no clear evidence on the risk-benefit ratio. Whether a combination of antiplatelet agents with low-dose anticoagulation properties is better than antiplatelet monotherapy is currently being investigated in the COMPASS (Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease; NCT01776424) and VOYAGER PAD (Efficacy and Safety of Rivaroxaban in Reducing

the Risk of Major Thrombotic Vascular Events in Subjects With Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremities; NCT02504216) trials, although final results can only be expected in 2 or 3 years.

Nevertheless, the presented DAPT subgroup analysis (4) is an important contribution to the published reports, because data on this specific population with a high atherosclerotic burden are sparse. Future trials focusing on drug-based treatment of PAD with and without CHD are warranted. This paper represents a step in this direction.

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## REFERENCES

**1.** Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155–66.

**2.** Subherwal S, Patel MR, Kober L, et al. Peripheral artery disease is a coronary heart disease risk equivalent among both men and women: results from a nationwide study. Eur J Prev Cardiol 2015;22:317–25.

**3.** Cacoub PP, Bhatt DL, Steg PG, Topol EJ, Creager MA, CHARISMA Investigators. Patients with peripheral arterial disease in the CHARISMA trial. Eur Heart J 2009;30:192–201.

**4.** Secemsky EA, Yeh RW, Kereiakes DJ, et al., on behalf of the Dual Antiplatelet Therapy Study Investigators. Extended duration dual antiplatelet therapy after coronary stenting among patients with peripheral arterial disease: a subanalysis of the dual antiplatelet therapy study. J Am Coll Cardiol Intv 2017;10:942–54.

**5.** Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082–115.

**6.** Society for Vascular Surgery Lower Extremity Guidelines Writing Group, Conte MS, Pomposelli FB, Clair DG, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. J Vasc Surg 2015;61 Suppl:2S–41S.

**7.** Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;69:e71–126.

**8.** Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. JAMA 2009;301:1909–19.

**9.** Caprie Steering Committee. A randomised, blinded, trial of Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE). Lancet 1996;348:1329–39.

**10.** Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. N Engl J Med 2017;376:32–40.

**11.** Belch JJ, Dormandy J, CASPAR Writing Committee, et al. Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial. J Vasc Surg 2010;52:825–33, 833.e1–2.

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