JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 65, NO. 20, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.03.541

EDITORIAL COMMENT

Double Antiplatelet Therapy Duration

Standardize or Personalize?*

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The duration of dual antiplatelet therapy is the subject of debate. Prolonged dual antiplatelet therapy may prevent recurrence of thrombotic events, such as stroke or myocardial infarction (MI), caused by either iterative plaque rupture or complications related to previous revascularization, with increased risk of bleeding. Multiple factors have to be integrated: type of stent, clinical presentation, type of dual antiplatelet therapy, coronary lesion complexity, and patient compliance. The current European guidelines (1) recommend 6 months' dual antiplatelet therapy in stable patients with coronary artery disease undergoing elective percutaneous coronary intervention with second-generation drug-eluting stents, and 12 months in patients with acute coronary syndrome, unless there are contraindications, such as excessive risk of bleeding. Thereafter, patients should be switched to single antiplatelet therapy.

Seven randomized studies (2–8), comprising 15,378 patients, compared short versus long durations of dual antiplatelet therapy, consisting of aspirin and clopidogrel. Data suggested no difference in various combined clinical endpoints, and notably in ischemic risk; higher rates of bleeding were reported with long-duration dual antiplatelet therapy, although not in all studies.

The effect of longer treatment is not clear. Concern exists regarding the balance between reducing thrombotic events and increasing the risk of bleeding complications, associated with adverse outcome. Two recent double-blind randomized trials, Dual Antiplatelet Therapy (DAPT) (n = 9,961) and PEGASSUS-TIMI 54 (n = 21,162) (9,10), analyzed the effect of dual antiplatelet therapy in terms of secondary prevention in stable patients. The results suggest that long-duration dual antiplatelet therapy significantly reduced the rate of ischemic events as compared with placebo combined with aspirin, with an increase in moderate to severe bleeding. Mauri et al. (9) found excess mortality associated with clopidogrel or prasugrel, driven exclusively by an increase in noncardiovascular mortality. The populations of these 2 trials were different, with a higher burden of risk factors in PEGASUS trial.

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In this issue of the *Journal*, Yeh et al. (11) present a subanalysis of the DAPT study, according to patients' clinical presentation (MI vs. non-MI), in which 9,961 patients who had completed 12 months' dual antiplatelet therapy after implantation of a drug-eluting or bare-metal stent and free of major ischemic or bleeding events were randomly assigned to an additional 18 months' thienopyridine therapy (clopidogrel or prasugrel) or placebo; all patients continued to take aspirin. Continued dual antiplatelet therapy was associated with significant reduction in stent thrombosis and MI, but increased moderate to severe bleeding and noncardiovascular death. The authors examined whether the ischemic benefits and bleeding risks associated applied to both patient populations with and without acute MI. Of 11,648 patients randomized in the DAPT trial, 3,576 (30.7%) presented with acute MI; 1,680 of the MI patients (47%) presented with initial ST-segment elevation MI and the remainder with non-ST-segment elevation MI. Because this variable was not factored in the randomization, the characteristics of the 2 groups differed: non-MI patients were older; more often female; and showed higher rates of diabetes,

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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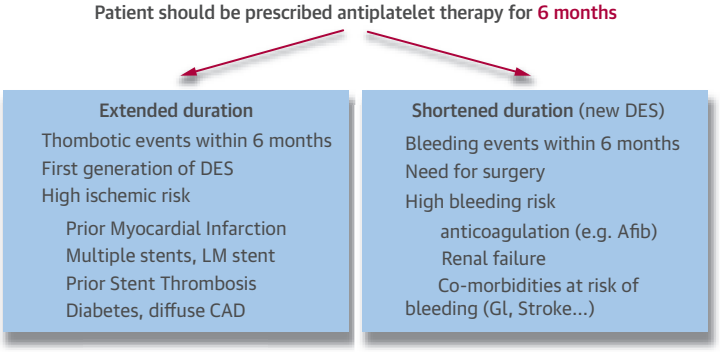
peripheral disease, and prior percutaneous coronary intervention. Patients with MI received a drug-eluting stent in 72.4% of cases, compared with 91.3% of patients without MI, and had a higher rate of prasugrel and less complex lesions. The authors found a significantly higher rate of definite or probable stent thrombosis (1.2% vs. 0.7%; p = 0.01) and recurrent MI (3.7% vs. 2.8%; p = 0.01), primarily related to stent thrombosis, in MI patients. Bleeding (Gusto moderate to severe and BARC 2 and 3) was less frequent in MI patients. There was no difference in the rates of death or stroke between the 2 groups. When Yeh et al. (11) analyzed the treatment effect, continuing therapy beyond 12 months was associated with significant reductions in stent thrombosis and MI rates in both groups, but with greater magnitude in MI patients and increased bleeding in both groups. In non-MI patients, however, the authors reported significantly increased mortality (2.1% vs. 1.5%; hazard ratio: 1.43; 95% confidence interval: 1.02 to 2.00; p = 0.04) and noncardiac death with continued thienopyridine therapy in non-MI patients (1.0% vs. 0.5%; hazard ratio: 2.26; 95% confidence interval: 1.3 to 3.94; p = 0.002). However, Yeh et al. (11) concluded that the effect of continued treatment was comparable in both groups.

According to the investigators, this increase in noncardiovascular mortality was not exclusively caused by an increase in bleeding-related death. A meta-analysis that they published in the *Lancet*, including 14 trials (n = 69,644) (12), reported that treatment duration had no significant effect on mortality across studies. However, the selected populations included might not be representative of current practice in patients with stable coronary artery disease. The trials included a mixture of patients presenting with elective and acute coronary syndromes, heterogeneity of stent type, a wide range of short (3, 6, and 12 months) and long (6, 12, 24, and 30 months) dual antiplatelet therapy regimes, and various P2Y12 inhibitors. In the recent meta-analysis by Palmerini et al. (13), including 10 recent trials (n = 31,666), all-cause mortality also was significantly lower for short-duration dual antiplatelet therapy, because of a 33% lower rate of noncardiovascular mortality despite a significantly lower rate of stent thrombosis in long-duration dual antiplatelet therapy. The PEGASUS trial, including only patients with previous MI, reported no difference in mortality rates. In the trial conducted by Yeh et al. (11), there was no difference in mortality in MI patients according to dual antiplatelet therapy duration. There is a possibility that only high-risk patients benefit from long-duration dual antiplatelet therapy. We are not convinced by the authors' argument that the significant increase in noncardiac mortality observed in the non-MI group could be incidental, and that the trial can be considered positive in the long-duration arm.

This requires further exploration before it can be recommended that dual antiplatelet therapy should be prolonged beyond 1 year. In the meantime, a personalized approach, in which the individual risk-benefit profile of each patient is carefully considered, should be recommended, rather than a 1-size-fits-all policy (**Figure 1**).

FIGURE 1 Optimal Duration of Dual Antiplatelet Therapy After the Index Percutaneous Coronary Intervention With Drug-Eluting Stent (DES) Implantation



CAD = coronary artery disease; GI = gastrointestinal; LM = left main.

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KEY WORDS acute coronary syndrome, bleeding risk, dual antiplatelet therapy, stent thrombosis