ISAR-SAFE: No Difference in 6-Month vs 12-Month DAPT After DES

Written by Muriel Cunningham

Current treatment guidelines recommend that patients undergoing drug-eluting stent (DES) percutaneous coronary intervention (PCI) take dual antiplatelet therapy (DAPT) consisting of aspirin plus an adenosine diphosphate receptor inhibitor for at least 12 months after the procedure [Levine GN et al. *J Am Coll Cardiol*. 2011]. The Safety and Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting [ISAR-SAFE; Byrne RA et al. *Am Heart J*. 2009] trial was designed to determine whether 6 months of DAPT treatment was noninferior to 12 months. Patients undergoing DES PCI received open-label DAPT (aspirin plus clopidogrel) for 6 months and then were randomized 1:1 to aspirin plus blinded clopidogrel for 6 additional months (12-month group) or aspirin plus placebo (6-month group). Stefanie Schulz-Schüpke, MD, Deutsches Herzzentrum München, Munich, Germany, presented the results of the ISAR-SAFE trial.

This was an investigator-initiated, international, randomized, double-blind, placebo-controlled trial that recruited patients at 40 centers from October 2008 to April 2014. Eligible patients took clopidogrel for 6 months after DES placement. Patients were excluded if they had signs or symptoms of ischemia or lesions requiring revascularization, had active bleeding or a history of intracranial bleeding, had an STEMI or non-STEMI in the 6 months since DES placement, had a previous stent thrombosis (ST), had a DES in the left main coronary artery in the index PCI, were taking oral anticoagulants, or were planning surgery within 6 months that required the discontinuation of antiplatelet therapy.

The primary end point was a composite of death, myocardial infarction (MI), ST, stroke, or TIMI major bleeding at 9 months after randomization (15 months after the index PCI). Secondary end points were the individual components of the primary end point. The investigators planned to enroll 6000 patients, but the study was terminated early, when 4000 patients were randomized. This decision was made by the Data Safety Monitoring Board and the Steering Committee based on a lower-than-expected event rate (1.6% actual vs 10% estimated) and slow recruitment.

A total of 4005 patients were randomized, 1998 in the 6-month group and 2007 in the 12-month group. Demographic characteristics were similar between the 2 groups. The mean age was 67 years, the mean body mass index was 27 kg/m^2, 19% were women, 24% had diabetes, 15% were active smokers, and 25% had a prior MI. The 6-month group had an event rate of 1.5% in the primary composite end point compared with 1.6% in the 12-month group (observed difference, 0.1%; upper limit of 1-sided 95% CI, 0.5%; $P_{\text{Noninferiority}} < .001$). Other key results are presented in Table 1.

A subgroup analysis suggested that older patients may benefit from 6 months of DAPT, whereas younger patients may benefit from 12 months of DAPT (Table 2). No other factors had a significant interaction.

Table 1. ISAR-SAFE Clinical Outcomes

End Point	Incidence, %		HR (95% CI)	*P* Value
	6-Mo Group (n = 1997)	12-Mo Group (n = 2003)		
Death	0.4	0.6	0.66 (0.27 to 1.63)	.37
Myocardial infarction	0.7	0.7	0.93 (0.44 to 1.97)	.85
Stent thrombosis				
Definite or probable	0.3	0.2	1.25 (0.33 to 4.65)	.74
Definite	0.3	0.2	1.66 (0.40 to 6.96)	.49
Stroke	0.4	0.3	1.40 (0.44 to 4.41)	.57
TIMI bleeding				
Major or minor	0.3	0.7	0.46 (0.18 to 1.21)	.12
Major	0.2	0.3	0.80 (0.21 to 2.98)	.74
Minor	0.1	0.4	0.25 (0.05 to 1.17)	.08
BARC bleeding ≥class 2	1.0	2.0	0.50 (0.29 to 0.85)	.01

BARC, Bleeding Academic Research Consortium; ISAR-SAFE, Safety and Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting.

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Table 2. ISAR-SAFE Subgroup Analysis

Subgroup Analysis	6-Mo Group (n = 1997)	12-Mo Group (n = 2003)	HR (95% CI)	$P_{\text{Interaction}}$
Age ≥ 67.2 y	1.5	2.6	0.60 (0.31 to 1.13)	.03
Age < 67.2 y	1.4	0.7	2.02 (0.81 to 4.99)	.03

ISAR-SAFE, Safety and Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting.

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Although no differences in key clinical outcomes were seen between the 2 arms, Dr Schulz-Schüpke noted that these findings should be interpreted carefully due to the early termination of the study and the lower-than-anticipated event rates.

DAPT Study: Benefits Seen With Prolonged DAPT After DES Treatment

Written by Muriel Cunningham

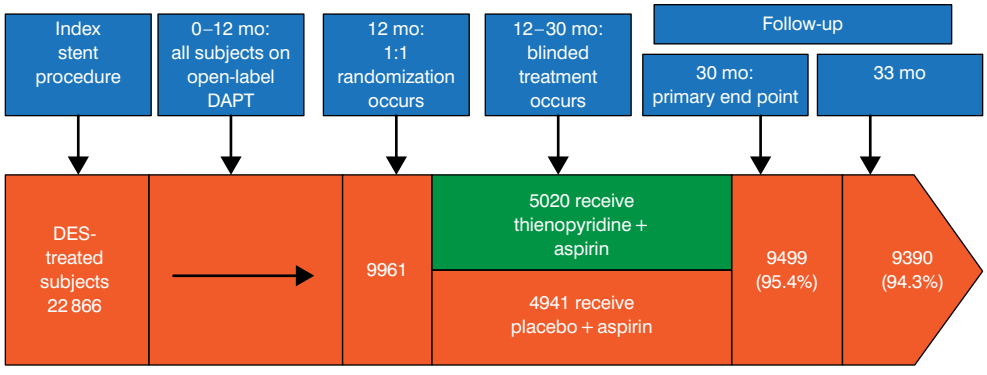
The Dual Antiplatelet Therapy [DAPT; Mauri L et al. *N Engl J Med.* 2014] trial recruited patients from 5 studies conducted at 452 sites in 11 countries. Research institutions and stent manufacturers collaborated to conduct this trial at the request of the US Food and Drug Administration (FDA). The objective was to assess the efficacy and safety of dual antiplatelet therapy (DAPT) between 12 and 30 months in patients treated with coronary stents. Laura Mauri, MD, MSc, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented the primary results of the DAPT trial in the cohort treated with drug-eluting stents (DESs).

To study a broad patient population, there were few exclusion criteria. Patients treated with any FDA–approved DES or bare metal stent could enroll provided they were not taking oral anticoagulant therapy and had a life expectancy >3 years. After 12 months of open-label DAPT (aspirin plus thienopyridine), patients who had no myocardial infarction (MI), stroke, repeat revascularization, or moderate or severe bleeding and who were considered compliant with thienopyridine therapy were randomized to blinded treatment (aspirin plus thienopyridine or aspirin plus placebo). Randomization was stratified by site, DES versus bare metal stent, clopidogrel vs prasugrel, and presence of ≥ 1 stent thrombosis (ST) risk factors. The co–primary end points were definite or probable ST (Academic Research Consortium definition) and major adverse cardiac or cerebrovascular events (MACCEs; death, MI, or stroke). The primary safety end point was moderate or severe bleeding (GUSTO classification). Study design and patient disposition are presented in Figure 1.

Of the 9961 patients randomized, 25% were women; the mean age was 61 years; 30% had diabetes mellitus; and 26% had evidence of MI at the index procedure. The stent lengths were relatively long (mean, 27 mm), and the left anterior descending artery was treated in 40% of patients. Half the patients had at least 1 ST risk factor—most commonly, presentation with MI (26%), lesion length ≥ 30 mm (10%), and bifurcation lesion (7%). Forty-seven percent of the patients were treated with everolimus-eluting stents, and 35% took prasugrel. The study results are presented in Table 1.

In the primary end point analysis, relative risk reductions of 71% for ST and 29% for MACCEs were seen in patients who continued thienopyridine treatment ($P < .001$). While all-cause mortality favored the placebo group, the number of cancer-related deaths in the continued therapy group (n = 31) was significantly higher than in the placebo group (n = 14; $P = .02$). When a sensitivity analysis was conducted after removal of the 9 patients whose deaths were related to cancers

Figure 1. Dual Antiplatelet Therapy Trial Design and Patient Disposition



DAPT, dual antiplatelet therapy; DES, drug-eluting stent.

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