group (0.94%) vs the heparin ± GPI group during the first 4 hours ($P < .0001$). From 4 to 24 hours, the ST event rate was 0.32% in the bivalirudin group vs 0.17% in the heparin ± GPI group ($P = .2675$).

The 30-day mortality rate for patients with acute ST was 2.8% in the bivalirudin group vs 16.7% in the heparin ± GPI group ($P = .14$). The 30-day mortality rate for patients with subacute ST was 12.0% in the bivalirudin group vs 44.1% in the heparin ± GPI group ($P = .01$). The 30-day mortality rate for all early ST was 6.7% with bivalirudin and 40% with heparin ± GPI ($P < .0002$).

Preprocedural TIMI flow of 0 or 1 predicted acute ST (OR 2.35; 95% CI 1.04 to 5.35; $P = .041$). Killip Class ≥ II during acute MI predicted subacute ST (OR 3.19; 95% CI 1.70 to 5.60; $P < .0003$).

The excess risk of ST associated with bivalirudin compared with heparin ± GPI occurred only in the acute phase on day 1 and more specifically during the first 4 hours after primary PCI. The mortality rate associated with subacute ST was higher than with acute ST. Thirty-day mortality after early ST was significantly lower in patients treated with bivalirudin than those treated with heparin ± GPI. These results were consistent for both acute and subacute ST.

Shorter Clopidogrel Therapy Not Superior Following Coronary DES Implantation

By Brian Hoyle

In the Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation trial [ISAR-TRIPLE; NCT00776633], 6 weeks of triple therapy including the oral antiplatelet compound clopidogrel is not superior to a 6-month regimen following implantation of a drug-eluting stent (DES). The results were reported by Nikolaus Sarafoff, MD, Technische Universität München, Munich, Germany.

Previous studies support the view that combined oral anticoagulant/antiplatelet therapy is advantageous in reducing adverse outcomes following cardiac surgeries [Connolly S et al. *Lancet.* 2006]. However, triple therapy comes with the drawback of increased risk of bleeding. The optimal length of therapy to maximize the benefits while minimizing bleeding risk following DES implantation is unknown.

The risk of stent thrombosis is greatest soon after percutaneous coronary intervention and declines thereafter. Also, bleeding risk depends on the length and intensity of oral anticoagulant therapy [Lip GYH et al. *Eur Heart J.* 2014]. Informed by this knowledge, the ISAR-TRIPLE prospective, randomized, open-label trial evaluated clinical outcomes of a 6-week and 6-month regimen of clopidogrel along with aspirin and oral anticoagulation following DES implantation in 614 patients [Fiedler KA et al. *Am Heart J.* 2014]. The hypothesis was that the shorter course of therapy is superior.

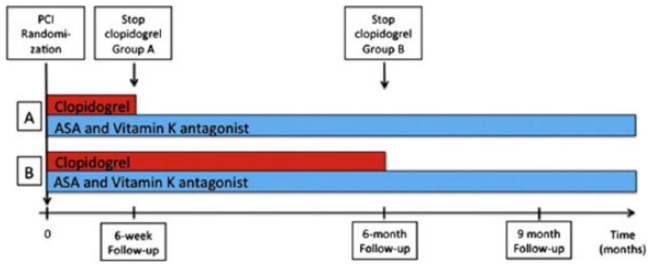
DES implantation and need for oral anticoagulation were the inclusion criteria. Exclusion criteria included prior stent thrombosis and DES implantation in the left main coronary artery. The primary end point was death, myocardial infarction (MI), confirmed stent thrombosis, stroke, or major bleeding at 9 months. Secondary end points included ischemic complications (cardiac death, MI, stent thrombosis, ischemic stroke) and major bleeding.

All patients received aspirin (75-200 mg QD) and vitamin K antagonist along with clopidogrel 75 mg QD for 6 weeks (n = 307) or 6 months (n = 307). Phenprocoumon or warfarin were used in patients with mechanical valves (5% and 9% of the 6-week and 6-month group, respectively) to achieve a target internal normalized ratio. Clinical follow-up was done after 9 months for most patients (n = 606 [98.7%]; Figure 1).

At baseline, the 2 groups were similar in age; sex; history of MI; prevalence of diabetes, acute coronary syndrome, and stable angina; and indication of oral anticoagulants. Compliance with all medications was excellent, with the exceptions of clopidogrel use by those in the 6-week group after 6 weeks (26% vs 87% in the 6-month group; $P < .001$) and at the 9-month follow-up (23% vs 35%; $P < .001$).

There were no significant differences between the 2 groups in either the primary end point (HR, 1.14; 95% CI, 0.68 to 1.91; $P = .63$) or the secondary end points of

Figure 1. ISAR-TRIPLE Design



ASA, aspirin; PCI, percutaneous coronary intervention.

A: 6-week group; B: 6-month group.

Reproduced from *American Heart Journal*, 167, Fiedler KA et al, Rationale and design of The Intracoronary Stenting and Antithrombotic Regimen—Testing of a six-week versus a six-month clopidogrel treatment Regimen In Patients with concomitant aspirin and oraL anticoagulant therapy following drug-Eluting stenting (ISAR-TRIPLE) study, 459-465, Copyright 2014, with permission from Elsevier.

ischemic complications (HR, 0.93; 95% CI, 0.43 to 2.05; $P = .87$) and major bleeding (HR, 1.35; 95% CI, 0.64 to 2.84; $P = .44$).

Parsing out the secondary end point data did reveal a significant difference in MI (6-week, n = 6 [2.0%]; 6-month, n = 0; $P = .029$). Bleeding Academic Research Consortium (BARC)-defined bleeding overall did not differ significantly between the groups (6-week, 37.6%; 6-month, 40.2%; HR, 0.94; 95% CI, 0.73 to 1.21; $P = .63$). But, comparison of BARC-defined bleeding prior to randomization with that occurring at 9 months was significant (6-week, 20.5%; 6-month, 27.9%; HR, 0.68; 95% CI, 0.47 to 0.98; $P = .04$).

Prof Sarafoff concluded that shortening clopidogrel therapy from 6 months to 6 weeks after DES implantation in patients who are also receiving aspirin and oral anticoagulation is not superior in terms of net clinical outcomes.

TAVR Suitable Procedure for High-Risk AS Patients: 5-Year Results From the PARTNER Trial

Written by Maria Vinall

Transcatheter aortic valve replacement (TAVR) is the recommended treatment for "inoperable" patients with severe aortic stenosis (AS). One-, 2-, and 3-year data from the Placement of Aortic Transcatheter Valves study [PARTNER; NCT00530894] showed significant reductions in all-cause mortality, cardiac mortality, and rehospitalization [Kapadia SR et al. *Circulation*. 2014; Makkar RR et al. *N Engl J Med*. 2012; Leon MB et al. *N Engl J Med*. 2010]. Samir R. Kapadia, MD, Cleveland Clinic Foundation, Cleveland, Ohio, USA, reported the 5-year outcomes for the PARTNER trial. Benefits as to all-cause and cardiovascular (CV) mortality, repeat hospitalization, and functional status were sustained in the TAVR-treated patients compared with those given standard therapy. Valve durability was demonstrated with no increase in transvalvular gradient or attrition of valve area.

The PARTNER trial included patients (n = 358) with severe symptomatic AS with aortic value area < 0.8 cm^2 (effective orifice area index < 0.5 cm^2/m^2), and mean gradient > 40 mm Hg or jet velocity > 4.0 m/second. Patients deemed "inoperable" (defined as risk of death or serious irreversible morbidity of AVR exceeding 50%) were assessed by a cardiologist and 2 surgeons. Participants were randomly assigned (1:1) to TAVR or standard therapy. After 3 years, 20 patients crossed over to TAVR from standard therapy.

The study's primary end point of all-cause mortality was evaluated when all patients reached 1-year follow-up. Key end points for the 5-year analysis included all-cause and cardiac mortality, rehospitalization, stroke, NYHA functional class, and echo-derived valve areas, transvalvular gradients, and paravalvular leak. Mortality outcomes were stratified by Society of Thoracic Surgeons (STS) risk score, paravalvular leak, and age.

At baseline, subjects were mean age 83 years with mean STS scores between 11.2 and 12.1. Most (> 90%) were NYHA III or IV and about 70% had coronary artery disease; 46% were men. Creatinine values > 2 mg/dL were present in 5.6% of TAVR patients and 9.6% receiving standard therapy. Frailty was 18.1% for TAVR and 28% for standard therapy. A porcelain aorta was present in 19% of TAVR subjects and 11.2% of patients receiving standard therapy ($P = .05$). The incidence of chronic obstructive pulmonary disease was significantly higher in the standard therapy group (52.5% vs 41.3% in the TAVR group; $P = .04$). Average chest wall radiation was 8.6%.

At 5 years, all-cause mortality in the intention to treat (ITT) population was 93.6% for standard therapy and 71.8% for TAVR (HR, 0.50; 95% CI, 0.39 to 0.65; $P < .0001$). Other key end point events are shown in Table 1.

The mortality benefit was similar in elderly (> 85 years) patients compared with those ≤ 85 years. A CV mortality

Table 1. Events at 5 Years in ITT Population

Event	TAVR	Standard Rx	Log-rank *P* Value
All-cause mortality, %	71.8	93.6	< .0001
STS < 5	55.9	100	.0012
STS 5-15	75.2	93.4	.0002
STS > 15	73.7	93.3	.0749
Median survival, mo	29.7	11.1	< .0001
Cardiovascular mortality, %	57.3	85.9	< .0001
STS < 5	41.1	100	< .0001
STS 5-15	61.6	82.4	< .0001
STS > 15	57.8	91.8	.0098
Repeat hospitalization, %	47.6	87.3	< .0001
NYHA Class III and IV, %	14.3	40.0	ns
Incidence of stroke, %	14.6	5.7	ns

STS, Society of Thoracic Surgeons risk score; TAVR, transcatheter aortic valve replacement.