were randomly assigned to FFR-guided PCI plus the best available MT or the best available MT alone. Patients who had no evidence of ischemia (FFR >0.80) were treated with MT alone and were followed in a registry. The primary endpoint was a composite of death, myocardial infarction (MI), or UR. The trial was designed as a superiority study in 1632 patients and powered to test whether FFR-guided PCI resulted in a 30% relative risk reduction of the primary endpoint over an intended average follow-up of 2 years.

An important first finding was that 27% (n=322) of the patients evaluated for the study had no hemodynamically significant stenosis, and were thus followed in the trial registry. The remaining 73% (n=888) had an FFR ≤0.80 in at least 1 large epicardial artery and were randomly assigned to FFR-guided PCI plus MT (n=447) or MT alone (n=441). The trial was stopped prematurely in January 2012 after 1220 patients were randomized with an average follow-up of 7 months, when the independent Data Safety Monitoring Board judged highly significant differences in the primary endpoint rates between patients randomized to MT alone compared with those who recieved FFR-guided PCI plus MT (4.3% vs 12.7%; HR with PCI, 0.32; 95% CI, 0.19 to 0.53; p<0.001). A large difference in the rate of UR (1.6% vs 11.1%; HR, 0.13; 95% CI, 0.06 to 0.30; p<0.001) was the major factor responsible for the difference in the composite endpoint between the groups. Rates of mortality or MI were infrequent and did not differ significantly between the 2 randomized groups. In the registry, MT alone led to an excellent outcome for patients without FFR-determined ischemia, regardless of the angiographic appearance of the stenoses; the primary endpoint occurred in only 5/166 (3.0%) patients with FFR >0.80.

Science Advisors' Note

Although the reduction in the composite primary endpoint with PCI is provocative, it is worth noting that this observation was predominantly dependent on a difference in the "softer" endpoint of UR, and that the premature termination of this randomized study resulted in the enrollment of only 75% of the patients planned with less than a third of the intended average follow-up. Two additional limitations warrant mention. First, an early signal towards a potential harm as a result of definite or probable stent thrombosis in patients randomized to FFR-guided PCI plus MT (all of whom received a second-generation drug-eluting stent) compared with MT alone (1.1% vs. 0.2% by 12 months; HR with PCI, 4.98; 95% CI, 0.59 to 42.25) could have been better defined with further follow-up and greater event accrual. Second, the non-blinded nature of this study (the patients managed with MT alone did not undergo sham PCI) could have led to a selection bias in referral for "urgent" revascularization, with a lower threshold to refer patients to PCI if they had been randomized to optimal MT without PCI. As Dr. William Boden, one of the lead investigators of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation [COURAGE] trial, concluded in his editorial to FAME-2, neither FAME-2 with 7 months of mean follow-up or the COURAGE trial with 55 months of mean follow-up showed a reduction with PCI in "hard" clinical endpoints, such as death or MI [Boden WE. *N Engl J Med* 2012]. Further insight regarding the comparison of PCI with best available MT in patients with stable CAD and moderate-to-severe ischemia may come from the results of the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial [ISCHEMIA; NCT01471522].

Results from the IABP-SHOCK II Trial

Written by Maria Vinall

The Intra-Aortic Balloon Pump (IABP) in Cardiogenic Shock II [IABP-SHOCK II; NCT00491036] trial, presented by Holger Thiele, MD, University of Leipzig Heart Center, Leipzig, Germany, failed to demonstrate a significant reduction in 30-day mortality with use of an IABP compared with best available medical therapy (BAT) alone in patients with acute myocardial infarction (AMI) complicated by cardiogenic shock.

IABPs have been used for almost 5 decades in the treatment of cardiogenic shock [Thiele H et al. *Eur Heart J* 2010]. Although considered a Class I recommendation in patients with AMI complicated by cardiogenic shock in both US and European guidelines [Van de Werf EM et al. *Eur Heart J* 2008; Wijns F et al. *Eur Heart J* 2010; Antman W et al. *Circulation* 2004], there is no evidence for a mortality benefit. IABP-SHOCK II was an investigator-initiated, randomized, prospective, open-label, multicenter trial, designed to compare IABP with BAT in patients presenting with an AMI complicated by cardiogenic shock and for whom early revascularization (using either percutaneous coronary intervention [PCI] or coronary artery bypass graft) was planned. Subjects were assigned to IABP (n=301) or BAT (n=299). The primary efficacy end point was 30-day all-cause mortality. Secondary endpoints included hemodynamic parameters, serum-lactate, Simplified Acute Physiology Score–II (SAPS-II), serial creatinine level and creatinine clearance, and inflammatory reaction (as measured by C-reactive protein). Safety assessments included major bleeding, peripheral ischemic complications, sepsis, and stroke [Thiele H et al. *Am Heart J* 2012; Thiele H et al. *N Engl J Med* 2012].

The median age of subjects was 70 years and 77% were men. Almost 50% had undergone resucitation (for 30 or fewer minutes) before randomization and about 80% had

multivessel disease. Approximately 95% of subjects in both groups underwent primary PCI. There was a trend toward more frequent use of ventricular assist devices in the BAT group (7.4% of patients vs 3.7% in the IABP group; p=0.053); however, the duration of mechanical ventilation, the number of days in the intensive care unit, the number of subjects receiving renal replacement therapy, and the time to hemodynamic stabilization did not differ.

At 30 days, 119 patients in the IABP group (39.7%) and 123 patients in the control group (41.3%) had died (RR with IABP, 0.96; 95% CI, 0.79 to 1.17; p=0.69). An analysis of prespecified post hoc subgroups showed no benefit for IABP based on sex, age, diabetes, or hypertension status, blood pressure (<80 vs ≥80 mm Hg), ST-segment elevation myocardial infarction (STEMI) versus non–STEMI, or previous history of MI. The groups did not differ significantly with respect to the rates of major bleeding (3.3% vs 4.4%, respectively; p=0.51), peripheral ischemic complications (4.3% vs 3.4%; p=0.53), sepsis (15.7% vs 20.5%; p=0.15), or stroke (0.7% and 1.7%; p=0.28) [Thiele H et al. *N Engl J Med* 2012].

Concerning the secondary endpoints and process-of-care measures, there was an early trend toward improved SAP-II scores in the IABP group but this did not persist beyond Day 4. There was no benefit with respect to renal function or serum lactate in the IABP group and no difference in C-reactive protein levels.

Prof. Thiele concluded that while IABP support in cardiogenic shock is safe, it does not improve 30-day mortality in patients with cardiogenic shock complicating AMI who underwent early revascularization in the IABP-SHOCK II trial.

STEMI Mortality Decreases in France While Some Key Risk Factors Increase

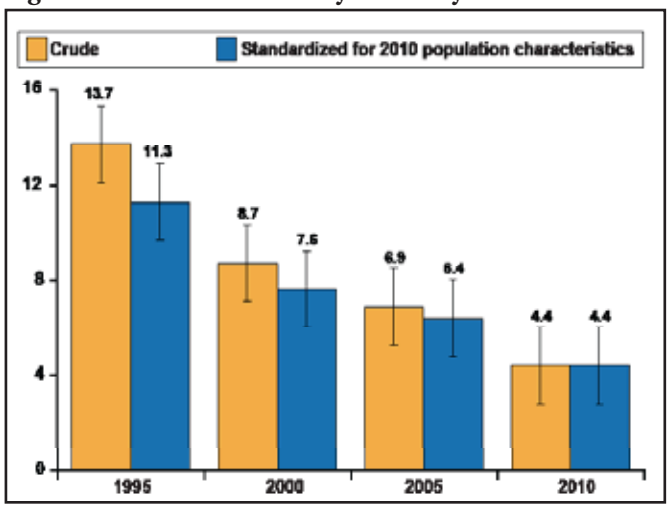
Written by Lori Alexander

The overall rate of cardiovascular (CV) mortality among patients with ST-segment elevation myocardial infarction (STEMI) in France has decreased 68% over the past 15 years, but the profile of patients hospitalized for STEMI has changed, with a higher prevalence of younger patients with no comorbidities or history of CV disease. The change has occurred especially among women, with the proportion of women <60 years with STEMI doubling from 1995 to 2010. Increases in smoking and obesity in that population seem to be the cause, said Nicolas Danchin, MD, Hospital European Georges Pompidou, Paris, France, who reported the findings.

Prof. Danchin and his colleagues reviewed data from 4 nationwide French registries (USIK 1995, USIC [Unite´ de Soins Intensifs Coronaires] 2000, FAST-MI [French Registry of Acute Coronary Syndrome With or Without ST Elevation; NCT00673036] 2005, and FAST-MI 2010 [NCT01237418]), with 1-month surveys conducted every 5 years from 1995 to 2010. Lower mortality rates associated with STEMI have been attributed to improved interventions, but the investigators hypothesized that temporal changes in patient characteristics may have also played a role in the mortality decline.

The study, which was published to coincide with its presentation at the European Society of Cardiology Congress [Puymirat E et al. *JAMA* 2012], included data from 6707 patients with STEMI who were admitted to an intensive care or cardiac care unit. The primary endpoint of the study was 30-day all-cause mortality. The crude 30-day mortality decreased from 13.7% to 4.4%, and the standardized mortality decreased from 11.3% to 4.4% (Figure 1). In a multivariate analysis, mortality decreased consistently from 1995 to 2010 after controlling for clinical characteristics such as age, sex, body-mass index, risk factors, CV history, and use and type of reperfusion therapy. The odds ratio for mortality was 0.39 (95% CI, 0.29 to 0.53; p<0.001) in 2010 compared with 1995.

Figure 1. Evolution of 30-Day Mortality.



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The average age of patients with STEMI in France significantly decreased (from 66.2 years in 1995 to 63.3 years in 2010; p<0.001). The greatest change occurred among women, with the proportion of women <60 years with STEMI increasing from 11.8% in 1995 to 25.5% in 2010 (p<0.001).

Many other patient characteristics changed significantly over the 15 years; most notably the percentage of current smokers (32.0% to 40.9%; p<0.001) and the rate of obesity (14.3% to 20.1%; p<0.001). These increases were greater

Continued on page 20