INTERVENTIONAL CARDIOLOGY

Effectiveness of stents in high-risk and 'real world' patients

Gennaro Sardella and Massimo Mancone

There are concerns about long-term outcomes associated with drug-eluting stent implantation in high-risk and 'real world' patients, and few data from these settings have been published. Two new papers add to our knowledge on drug-eluting stent use in acute myocardial infarction and for off-label indications.

Drug-eluting stents (DESs) have been demonstrated to be safe and highly effective in reducing the incidence of repeat revascularization among patients with stable coronary artery disease and simple coronary lesions.[1,2] However, concerns have been raised about the safety and efficacy of DES use during primary percutaneous coronary intervention (PCI) and for off-label indications because of the lack of data on outcomes after stent implantation in these settings. Two studies, published in the *New England Journal of Medicine*, have now shown that DES implantation is associated with excellent outcomes in individuals undergoing primary PCI for acute ST-segment elevation myocardial infarction (STEMI), and in a 'real-world' population of patients.[3,4] In addition, two meta-analyses have shown that the use of DESs is safe and effective when compared with bare-metal stents (BMSs) across randomized trials of patients with acute myocardial infarction, and in registries of individuals with diverse characteristics and treatment indications.[5,6]

The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial[3] was a multicenter, prospective, open-label, randomized trial comparing paclitaxel-eluting stents (PESs) with BMSs in patients presenting with STEMI. One of the key objectives of this study was to provide data about the safety of DES implantation during primary PCI. For this reason, the study was powered to demonstrate the superiority of PESs in terms of 12-month rates of ischemia-driven target-lesion revascularization (primary end point), and the noninferiority of PESs for a composite safety outcome (death, reinfarction, stroke, or stent thrombosis; secondary end point). Angiographic evidence of restenosis at 13 months was also assessed as a secondary end point. To limit the rate of revascularization caused by the 'oculostenotic reflex', angiographic follow-up was performed only after that the primary clinical end point had been evaluated.

One of the strengths of this trial was that there were few exclusion criteria. Of 3,602 patients with STEMI, 3,006 (83.5%) were randomly assigned to a stent type; 2,257 received a PES (Taxus Express®, Boston Scientific Scimed, Inc., Maple Grove, MN) and 749 received a BMS (Express®, Boston Scientific Scimed, Inc.).[7,8] Patients with unprotected left main or bifurcation lesions requiring planned dual-stent treatment, and those who were not compliant with at least 6 months of dual antiplatelet therapy, were not included in the randomization.

Patients who received PESs had significantly lower 12-month rates of ischemia-driven target-lesion revascularization compared with those who received BMSs (4.5% versus 7.5%, hazard ratio [HR] 0.59, 95% CI 0.43–0.83, $P = 0.002$), and lower rates of target vessel revascularization (5.8% versus 8.7%, HR 0.65, 95% CI 0.48–0.89, $P = 0.006$), with noninferior rates of the composite safety end point (8.1% versus 8.0%, HR 1.02, 95% CI 0.76–1.36; absolute difference 0.1 percentage point, 95% CI −2.1 to 2.4, $P = 0.01$ noninferiority; $P = 0.92$ superiority). Patients treated with PESs and those treated with BMSs had similar 12-month rates of death (3.5% for both) and stent thrombosis (3.2% and 3.4%, respectively). The 13-month rate of angiographic binary restenosis was significantly lower in patients with PESs ($n = 910$) than in those with BMSs ($n = 293$; 10.0% versus 22.9%; HR 0.44, 95% CI 0.33–0.57, $P < 0.001$). Late luminal loss was also significantly lower with PESs than with BMSs (0.41 ± 0.64 mm versus 0.82 ± 0.70 mm, $P < 0.001$). Importantly, compliance to aspirin therapy was high in both groups. Although thienopyridine discontinuation was slightly higher at 6 and 12 months among patients who received BMSs, the efficacy and safety end points were not significantly altered after multivariable adjustment.

These data indicate that PES implantation during primary PCI in patients with STEMI reduces angiographic restenosis and recurrent ischemia requiring repeat revascularization, when compared with BMS implantation, without undermining safety. As the investigators point out, long-term follow-up is required to characterize the late safety and efficacy profile of PESs in this setting, particularly with regard to the use of dual antiplatelet agents over time. The researchers are, therefore, planning to follow-up the patients enrolled in the HORIZONS-AMI trial on a yearly basis for a total of 5 years.

To date, no randomized trials have been prospectively designed and powered to evaluate the rare outcome events that occur during very long-term follow-up, such as those seen in 'real-world' registries. Lagerqvist *et al.* have previously reported on outcomes among all patients who received coronary stents in Sweden during the period 2003–2004, as recorded in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR).[9] In their latest paper,[4] which represents a continuum of the previous study, the SCAAR Study Group sought to obtain a reliable estimate of the long-term efficacy and outcomes associated with DES use. This report includes all patients in Sweden who received a stent during the period 2003–2006 and for whom follow-up data were available for at least 1 year (maximum 5 years; mean 2.7 years).

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The primary end point was the composite of death or myocardial infarction after the implantation of a DES. Secondary end points were death, myocardial infarction, and restenosis. In the primary analysis, patients who received only one DES ($n = 10,294$) during the index PCI were compared with patients who received only one BMS ($n = 18,659$). In a secondary analysis,

all patients who received at least one DES were assigned to the DES group ($n = 19,681$). All other patients who received one or more BMS were assigned to the BMS group ($n = 28,286$). To minimize the nonrandomization approach, a complex and appropriate statistical methodology was used. In particular, propensity-score adjustment, to correct for measured baseline differences, and a landmark analysis, to provide separate descriptions of the early and late relative risks (RR) of events, were performed.

There was no overall difference between the two groups in terms of the combined end point (RR for DES 0.96, 95% CI 0.89–1.03), death (RR 0.94, 95% CI 0.85–1.05), or myocardial infarction (RR 0.97, 95% CI 0.88–1.06), and there was no significant difference in outcome among subgroups stratified according to the indication for stent implantation. Patients who received DESs in 2003 had a significantly higher rate of late events than did patients who received BMSs in the same year, but no difference in outcomes was observed among patients treated in later years. These data confirm the supposition that treatment with DESs has improved yearly in terms of appropriate use of clopidogrel, higher balloon-inflation pressures, and correct selection of patients. The average rate of restenosis during the first year was 3.0 events per 100 patient-years with DESs versus 4.7 with BMSs (adjusted RR 0.43, 95% CI 0.36–0.52); therefore, 39 patients would need to be treated with DESs to prevent one case of restenosis. Among high-risk patients (stent diameter <3 mm and length ≥20 mm, patients with diabetes), the adjusted risk of restenosis was 74% lower with DESs than with BMSs, and 10 lesions would need to be treated to prevent one case of restenosis, confirming that the use of DESs is justified in patients at high-risk of restenosis.

The results of this large registry study and those of the HORIZONS-AMI trial confirm that DESs are effective, both in the setting of acute myocardial infarction and in high-risk patients, providing a clinically important decrease in the rate of restenosis without jeopardizing safety of patients. These data provide important information about the safety of first-generation DESs, erasing some of the concerns about their use in the 'off-label' setting. Two major limitations to these studies should, however, be taken into consideration when interpreting the results—the short length of follow-up in the HORIZONS-AMI trial and the nonrandomized design in the SCAAR registry. These positive results should now be confirmed by future research involving new-generation DESs.

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Competing interests
The authors declare no competing interests.

1. Stone, G. W. *et al.* Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N. Engl. J. Med.* **356**, 998–1008 (2007).
2. Mauri, L. *et al.* Stent thrombosis in randomized clinical trials of drug-eluting stents. *N. Engl. J. Med.* **356**, 1020–1029 (2007).
3. Stone, G. W. *et al.* Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. *N. Engl. J. Med.* **360**, 1946–1959 (2009).
4. James, S. K. *et al.* Long-term safety and efficacy of drug-eluting versus bare-metal stents in Sweden. *N. Engl. J. Med.* **360**, 1933–1945 (2009).
5. Brar, S. S. *et al.* Use of drug-eluting stents in acute myocardial Infarction: a systematic review and meta-analysis. *J. Am. Coll. Cardiol.* **53**, 1677–1689 (2009).
6. Roukoz, H. *et al.* Comprehensive meta-analysis on drug-eluting stents versus bare-metal stents during extended follow-up. *Am. J. Med.* **122**, 581.e1–10 (2009).
7. Mehran, R. *et al.* The Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial: study design and rationale. *Am. Heart J.* **156**, 44–56 (2008).
8. Stone, G. W. *et al.* Bivalirudin during primary PCI in acute myocardial infarction. *N. Engl. J. Med.* **358**, 2218–2230 (2008).
9. Lagerqvist, B. *et al.* Long term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N. Engl. J. Med.* **356**, 1009–1019 (2007).

ACUTE CORONARY SYNDROMES

BNP measurement predicts AMI risk in the elderly

Eugene Braunwald

With the aging of the population, the frequency of acute myocardial infarction is rising most rapidly among the elderly, a subgroup at high risk of a fatal outcome. Lorgis *et al.* observe that N-terminal pro-brain natriuretic peptide, combined with a simple clinical risk score, provides an accurate estimate of prognosis.

Outcomes for patients with acute myocardial infarction (AMI) who reach a hospital are influenced by two opposing forces. On one hand, the improvement of care, particularly early myocardial reperfusion and complete revascularization followed by secondary prevention, has steadily lowered mortality. On the other hand, the progressive aging of the population has resulted in an increase in the proportion of patients in whom the mortality rate remains stubbornly high.[1] Lorgis *et al.*[2] have, therefore, appropriately directed attention to elderly patients with AMI in a study assessing whether aging influences the prognostic value of N-terminal pro-brain natriuretic peptide (NT-pro-BNP).

As a first step, it is important to develop risk stratification tools for this most rapidly growing subgroup of patients. The natriuretic peptides, brain natriuretic peptide (BNP) and NT-pro-BNP, are well established biomarkers of mortality in patients with heart failure.[3] For example, a single measurement of NT-pro-BNP in patients with acute dyspnea presenting to an emergency department has been shown to facilitate care, resulting in shorter hospital stays and lower costs of hospitalization.[4] Natriuretic peptide levels after initial therapy of patients with acute heart failure might be of even greater prognostic value.[5] In 2001, de Lemos *et al.* reported from the OPUS-TIMI 16 trial that elevated levels of circulating BNP are also valuable as a predictor of mortality in patients across the spectrum of acute coronary syndromes.[6] Richards *et al.* confirmed this observation in patients with AMI.[7] This elevation of BNP in acute coronary syndromes might be related to ischemia-mediated wall stress or myocardial hypoxia.