Drug-Eluting Stents for STEMI

Can we improve long-term outcomes after primary PCI for AMI?

BY CHRISTIAN SPAULDING, MD, PhD, FACC, FESC

Primary percutaneous coronary intervention (PCI) is considered the optimal approach to manage myocardial infarction with ST-segment elevation (STEMI) when the procedure is performed expeditiously by an experienced team.[1] Drug-eluting stents (DES) have been shown to reduce the risks of both restenosis and target vessel revascularization (TVR) after elective PCI as compared with bare-metal stents (BMS) in a broad range of patients and lesions.[2] However, most randomized trials comparing DES to BMS have excluded patients with STEMI because of safety and efficacy concerns in this subgroup. Reports from registries have suggested that DES may be associated with increased rates of late stent thrombosis.[3] Thrombus is a major component of coronary artery occlusion in acute myocardial infarction (AMI). Therefore, angioplasty with DES in this setting could theoretically increase the rate of stent thrombosis; however, data on this issue are conflicting.[4] In addition, drug diffusion could be reduced in the presence of massive thrombus, leading to a potential loss of efficacy against neointimal proliferation.

To address these issues, several dedicated randomized controlled trials and registries have assessed the efficacy and safety of DES in the setting of primary PCI for AMI. Most of these studies were performed with sirolimus-eluting stents (SES) (Cypher, Cordis Corporation, Bridgewater, NJ) and, to a lesser extent, paclitaxel-eluting stents (PES) (Taxus, Boston Scientific Corporation, Natick, MA), which have yielded positive short- and long-term results in favor of SES and PES. Despite these positive findings, the use of DES in PCI for AMI remains controversial and is still considered off label in many countries. The currently available data will be reviewed and put in perspective with clinical practice.

RANDOMIZED STUDIES ASSESSING DES IN PRIMARY PCI FOR STEMI

STRATEGY was the first trial to assess DES in AMI.[5] Before obtaining the initial angiogram, patients with STEMI were randomly assigned to single high-dose bolus tirofiban infusion followed by SES implantation or abciximab and BMS implantation; 175 patients were included. Three patients in the tirofiban SES group and five in the abciximab BMS group did not undergo PCI. Overall, 74 patients (85%) in the tirofiban SES arm and 77 patients (88%) in the abciximab BMS arm received the protocol-mandated treatment combination. The primary endpoint, a composite of death, nonfatal MI, stroke, or binary restenosis at 8 months, was significantly lower in the tirofiban SES group (19% vs 50%; hazard ratio [HR], 0.33; 95% confidence interval [CI], 0.18–0.6; $P < .001$).

The TYPHOON trial was the first large randomized controlled trial evaluating SES in 712 STEMI patients.[6] The primary endpoint of the study, target vessel failure (TVF) at 1 year (a composite of TVR, recurrent infarction,

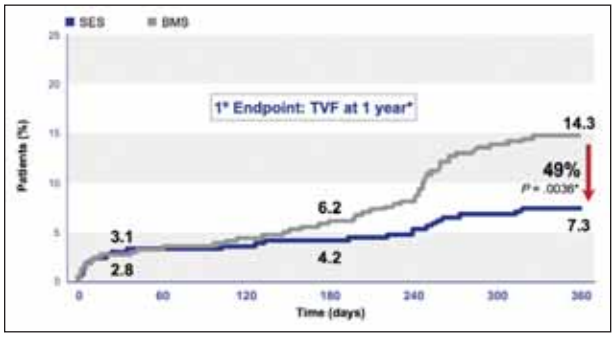

Figure 1. The TYPHOON trial. TVF at 1 year. *Defined as ischemia-driven TVR, recurrent MI, or target vessel-related cardiac death.

or target vessel-related cardiac death), occurred in 7.3% of patients in the SES group and in 14.3% of patients in the BMS group ($P = .004$) (Figure 1). This was driven by significant differences in TVR rates. There was no difference between SES and BMS groups in death (2.2% in both; $P = 1$), reinfarction (1.1 vs 1.4%; $P = 1$), or stent thrombosis rates (3.4% vs 3.6%; $P = 1$) (Figure 2). In the 210 patients in an angiographic substudy, SES were associated with significant reductions in in-stent late loss (0.14 ± 0.49 mm vs 0.83 ± 0.52 mm). TVF was also lower in patients who did not undergo a systematic angiographic control (6.8% vs 12.7%; $P = .034$), therefore indicating that the benefit of SES was not due to revascularization driven by the angiographic control.

The TYPHOON trial was performed in select patients. In contrast, the MULTISTRATEGY trial inclusion criteria were broad and close to daily practice. In MULTISTRATEGY, 744 patients were randomized to receive SES or BMS with abciximab or tirofiban.[7] High-risk patients, such as those with cardiac failure, were included. Furthermore, no angiographic control was performed, therefore eliminating a bias induced by inappropriate TVR during the control angiograms. At 8 months, a significant difference was noted in the occurrence of the major cardiac events in favor of the SES group: 7.8% versus 14.5% (adjusted HR, 0.53; CI, 0.33–0.83; $P = .006$) (Figure 3).

The SESAMI trial included 320 patients with STEMI who were assigned to receive SES or BMS.[8] The primary endpoint, binary restenosis at 1 year, was lower in the SES group than in the BMS group (9.3% vs 21.3%, respectively; $P = .032$), as were the rates of TVR (5% vs 13.1%; $P = .015$), major adverse cardiac events (6.8% vs 16.8%; $P < .005$), and TVF (8.7% vs 18.7%; $P = .007$). The incidence of angiographically documented stent thrombosis was 1.2% (n = 2) in the SES group and 0.6% (n = 1) in the BMS group.

The MISSION trial compared SES and BMS in 310 patients.[9] The primary endpoint was in-segment late lumen loss at follow-up. Angiography was performed at 9 months and demonstrated the efficacy of SES to reduce restenosis and late loss (0.12 mm vs 0.68 mm; $P < .01$).

The use of PES was first evaluated in the PASSION trial, which randomized patients to PES or BMS during primary angioplasty for STEMI.[10] The primary endpoint, major adverse cardiac events at 1 year, was not reached, although there was a trend toward fewer events in the PES group.

More recently, the HORIZONS-AMI trial randomized 3,006 patients to PES or BMS with the Express stent (Boston Scientific Corporation), with further randomization to bivalirudin or unfractionated heparin and abciximab.[11] The composite endpoint included ischemia-driven target lesion revascularization, all-cause mortality, reinfarction, and stent thrombosis (definite or probable according to the Academic Research Consortium criteria). At 1 year, ischemic target lesion revascularization was reduced with PES (7.5% vs 4.5%; $P = .02$), and ischemic events were similar between the two groups (Figure 4).

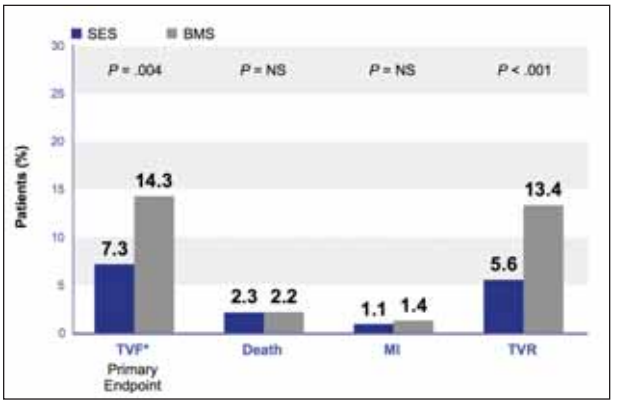

Figure 2. Primary and secondary endpoints of the TYPHOON trial. *Defined as ischemia-driven TVR, recurrent MI, or target vessel-related cardiac death.

Several registries have analyzed the outcome of patients receiving DES for AMI. The MASS-DAC registry[12] included 4,016 patients with STEMI and non-STEMI. The comparison of matched patients treated with DES (72% SES) or BMS shows a mortality reduction at 2 years in STEMI patients treated with DES (3.1%; 95% CI, 5.4%–0.8%; $P = .008$). In contrast, the GRACE registry reported an increased mortality rate in patients treated with DES between 6 months and 2 years after STEMI.[13] However, the overall mortality rate was significantly reduced among patients treated with DES during the 2 years (3.9% vs 5.3%; $P = .04$) and during hospital stay (2% vs 3.8%; $P = .018$). In addition, striking differences were noted in coronary risk factors between the two populations, therefore affecting long-term outcomes, atherosclerosis progression, and acute ischemic events. Finally, follow-up was suboptimal, with data missing for more than 30% of patients at 2 years.

A recent systematic review by Brar et al included 7,352 patients from 13 randomized trials and 26,521 patients from registry studies using SES or PES.[14] In the randomized trials, DES significantly reduced TVR (relative risk [RR], 0.44; 95% CI, 0.35–0.55) without increasing death (RR, 0.89; 95% CI, 0.7–1.14), MI (RR, 0.82; 95% CI, 0.64–1.05), or stent thrombosis (RR, 0.97; 95% CI, 0.73–1.28) (Figure 3). These observations were durable at 2 years. Among 18 registries (n = 26,521), DES signifi-

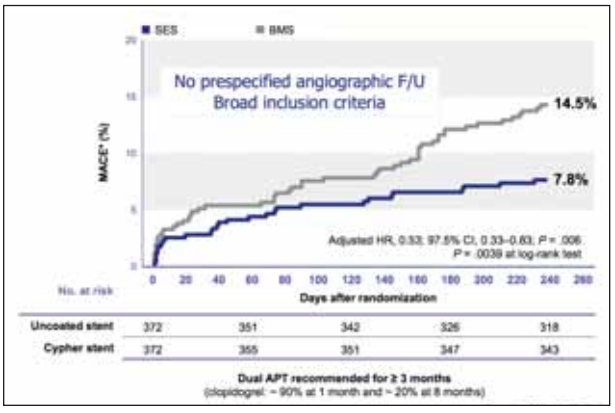

Figure 3. The MULTISTRATEGY trial. Primary endpoint: major cardiac events at 8 months. *Death, MI, or TVR.

cantly reduced TVR (RR, 0.54; 95% CI, 0.4–0.74) without an increase in MI (RR, 0.87; 95% CI, 0.62–1.23). Death was significantly lower in the DES group within 1 year of PCI, but there were no differences at 2 years (P = .45).

Thus, DES use appears to be safe and efficacious in randomized trials and registries of patients with STEMI. DES significantly reduced TVR compared with BMS, without an increase in death, MI, or stent thrombosis 2 years after the procedure. This clearly favors the routine use of DES in AMI. However, several questions remain regarding the rate of stent thrombosis, long-term safety, and the selection of compliant patients to prolonged dual-antiplatelet therapy in an emergency setting.

STENT THROMBOSIS RATES IN AMI AND LONG-TERM SAFETY OF DES IN AMI

Since the "ESC firestorm" in September 2006, thrombosis of DES has become an important topic for interventional cardiologists and clinicians despite several analyses showing that the increase of stent thrombosis with DES is modest with no rise in major events such as death or MI.[15] Thrombus, an important predictive factor for DES occlusion, is a major component of coronary artery occlusion in AMI. The first trials on DES in AMI reported high rates of stent thrombosis in both groups. In the TYPHOON study, protocol-defined stent thrombosis at 1 year was 3.4% and 3.6%, respectively, in the SES and BMS groups. Therefore, concerns were voiced after the publication of these results due to the risk of an increase of stent thrombosis after implantation of DES during AMI.[16] However, similar stent thrombosis rates were found in subsequent studies and registries with no difference at 1 or 2 years between DES and BMS. Recently, the TRITON-TIMI 38 study compared prasugrel to clopidogrel in patients with acute coronary syndromes.[17] The choice of DES or BMS was left to the discretion of the investigator. It is of interest to note that stent thrombosis rates increased according to the severity of clinical presentation, with the lowest rates in patients with unstable angina and the highest rates in those with STEMI. No difference was found in stent thrombus rates between DES and BMS in all subgroups of patients at 15 months. Stent thrombosis after PCI for AMI is therefore high but does not seem to increase with the use of DES. Pharmacological prevention of stent thrombosis in this setting is of paramount importance. In the subgroup of STEMI patients included in the TRITON-TIMI 38 study, the rate of stent thrombosis was halved in the prasugrel group (2.4% in the clopidogrel group vs 1.2% in the prasugrel group; HR, 0.49; CI, 0.28–0.84).[18]

Although most trials on DES in AMI were performed recently, long-term data are emerging. At the PCR meeting in May 2009, the 5-year follow-up of STRATEGY and 4-year follow-up results of TYPHOON were presented. Both studies yielded similar results, with a sustained effect of SES on the reduction of TVR and no difference in safety endpoints such as death or MI. Furthermore, in the TYPHOON study, the majority of stent thrombosis occurred early in the first month, highlighting the importance of pharmacological prevention. At the 2010 American College of Cardiology i2 meeting, the long-term outcomes of the PASSION trial demonstrated no differences in stent thrombosis between groups. A smaller trial, DEDICATION, showed sustained differences in MACE and TVR rates in favor of DES. However, a significantly superior rate of cardiac death was noted in the DES group, albeit with no increase in stent thrombosis.

PATIENT COMPLIANCE TO DUAL-ANTIPLATELET THERAPY AFTER PRIMARY PCI FOR AMI

Noncompliance to dual-antiplatelet therapy during the first 6 months after implantation has been demonstrated as a predictive factor for DES thrombosis. In the PREMIER registry, patients treated with primary PCI for AMI who discontinued clopidogrel after 30 days had a higher mortality rate compared to patients on clopido-

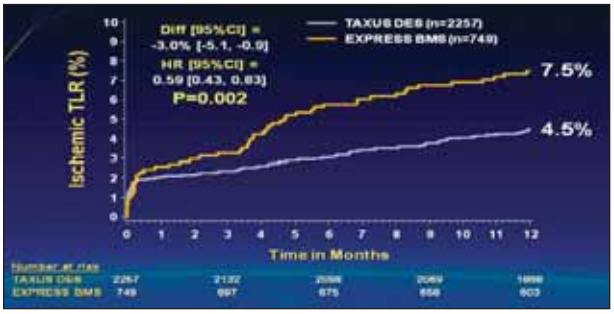

Figure 4. The HORIZONS trial. Ischemic target lesion revascularization rates at 1 year.

grel.[19] In the setting of AMI, it is often difficult to assess a patient's potential for compliance to medication and to inquire on a contraindication to prolonged dual-antiplatelet therapy, such as planned surgery. This could be a limitation to DES implantation during primary PCI for AMI. However, in most European countries, patients with AMI are triaged by prehospital or hospital emergency physicians who assess the patient's history and understanding of medication compliance. Furthermore, several randomized studies and a recently published registry study[20] clearly show that when dual-antiplatelet therapy with clopidogrel is taken for at least a year, major events in all AMI patients are reduced, including patients who receive a BMS. Therefore, long-term compliance to dual-antiplatelet therapy after AMI should be achieved by careful education in all AMI patients with or without BMS or DES implantation.

USE OF DES FOR AMI IN CLINICAL PRACTICE

Based on data from 7,352 patients in 13 randomized trials and 26,521 patients from registry studies, the implantation of an SES and, to a lesser extent, PES during primary PCI for AMI reduces the rate of repeat revascularization with no increase in death, MI, or stent thrombosis. Cost-effectiveness studies in stable patients have shown that the implantation of a DES is mostly beneficial in patients with a high risk of restenosis, such as small vessels or long lesions. In primary PCI for AMI, it seems reasonable to implant a DES in patients with high-risk features for restenosis, such as long lesions, small vessels, or diabetes. Proper preparation of the culprit vessel is of paramount importance to assess the size and length of the stent. Therefore, implantation should be performed after visualizing the lesion and administering a nitrate injection. DES implantation should be avoided in patients with permanent or temporary contraindications to dual-antiplatelet therapy. Patient education on risk factor management and therapy compliance should start in the catheterization laboratory, be continued during the hospital stay, and be pursued during follow-up.

CONCLUSION

During the past 30 years, dramatic decreases in AMI mortality rates have been achieved by increasing the number of reperfused patients, reducing prehospital and hospital delays, and obtaining adequate coronary artery flow by primary angioplasty. DES reduce the rate of repeat revascularization and therefore are an interesting asset to primary PCI in selected patients. ■

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