Use of drug eluting stents in ST segment elevation myocardial infarction

Christian Spaulding, Julien Rosencher and Olivier Varenne

Heart 2010 96: 1073-1077
doi: 10.1136/hrt.2008.161422

Updated information and services can be found at:
http://heart.bmj.com/content/96/13/1073.full.html

References

This article cites 20 articles, 17 of which can be accessed free at:
http://heart.bmj.com/content/96/13/1073.full.html#ref-list-1

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic collections

Articles on similar topics can be found in the following collections

- Acute coronary syndromes (22 articles)
- Education in Heart (350 articles)

Notes

To order reprints of this article go to:
http://heart.bmj.com/cgi/reprintform

To subscribe to Heart go to:
http://heart.bmj.com/subscriptions
Primary percutaneous coronary intervention (PCI) is considered the optimal approach to the management of ST segment elevation myocardial infarction (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 revascularisation (TVR) after elective PCI, as compared with bare metal stents (BMS) in a broad range of patients and lesions.2 However, most randomised trials comparing DES to BMS have excluded patients with STEMI because of safety and efficacy concerns in this subgroup. Reports from randomised trials and 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). Angioplasty with DES in this setting could therefore theoretically increase the rate of stent thrombosis, but 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 randomised 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, Johnson and Johnson), and to a lesser extent with paclitaxel eluting stents (PES), Taxus (Boston Scientific) and have yielded positive short and long term results in favour of SES and PES. Yet, despite these positive findings, the use of DES during 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.

RANDOMISED STUDIES AND REGISTRIES ASSESSING SES OR PES IN PRIMARY PCI FOR STEMI
To date, 31 studies, 15 randomised trials, and 18 registries have directly compared SES or PES to BMS in the setting of AMI. STRATEGY was the first trial to assess DES in AMI.5 Patients with STEMI were randomly assigned before obtaining the initial angiogram to single high dose bolus tirofiban infusion followed by SES implantation or abciximab and BMS implantation. A total of 175 patients with STEMI were included. Three patients in the tirofiban–SES group and five in the abciximab–BMS group did not undergo PCI. Overall, 74 (85%) patients in the tirofiban–SES and 77 (88%) in the abciximab–BMS arm received the protocol mandated treatment combination. The primary end point—a composite of death, non-fatal myocardial infarction, stroke, or binary restenosis at 8 months—was significantly lower in the tirofiban plus SES group (19% vs 50%; hazard ratio (HR) 0.33, 95% confidence interval (CI) 0.18 to 0.60; p<0.001).

The TYPOON trial was the first large randomised controlled trial evaluating SES in 712 STEMI patients.6 The primary end point of the study, target vessel failure at 1 year (a composite of TVR, recurrent infarction, or target vessel related cardiac death), occurred in 7.3% of patients in the SES group, and in 14.3% in the BMS group (p=0.004) (figure 1). This difference was driven by significant differences in rates of TVR. There was no difference between SES and BMS groups in death (2.2% in both, p=1.0), re-infarction (1.1 vs 1.4%, p=1.0) or stent thrombosis rates (3.4 vs 3.6%, p=1.0) (figure 2). In the 210 patients of an angiographic substudy, SES were associated with significant reductions in in-stent late loss (0.14±0.49 vs 0.83±0.52 mm).

Target vessel failure was also reduced in patients who did not undergo a systematic angiographic control (6.8% vs 12.7%; p=0.034), therefore indicating that the benefit of SES was not due to revascularisation driven by the angiographic control.

The TYPOON trial was performed in selected patients. In contrast, the MULTISTRATEGY trial inclusion criteria were broad and close to daily practice. Seven hundred and forty-four patients were randomised to receive SES or BMS with abciximab or tirofiban.7 High risk patients, such as patients 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 favour of the SES: 7.8% vs 14.5% (adjusted HR 0.55, 95% CI 0.35 to 0.83; p=0.006) (figure 3).

The SESAMI trial included 320 patients with STEMI who were assigned to receive SES or BMS.8 The primary end point, binary restenosis at 1 year, was lower in the SES group than in the BMS group (9.3% vs 21.3%, respectively; p=0.032), as were the...
progression, and acute ischaemic events. Finally, follow-up was suboptimal, with data missing in over 30% of patients at 2 years.

A recent systematic review by Brar et al. included 7352 patients from 13 randomised trials and 26,521 patients from registry studies using SES or PES. In randomised trials, DES significantly reduced target vessel revascularisation (relative risk (RR) 0.44, 95% CI 0.35 to 0.55), without increasing death (RR 0.89, 95% CI 0.70 to 1.14), MI (RR 0.82, 95% CI 0.64 to 1.05), or stent thrombosis (RR 0.97, 95% CI 0.73 to 1.28). These observations endured over 2 years. Among 18 registries (n = 26,521), DES significantly reduced target vessel revascularisation (RR 0.54, 95% CI 0.40 to 0.74) without an increase in myocardial infarction (RR 0.87, 95% CI 0.62 to 1.23). Death was significantly lower in the DES group within 1 year of the index PCI, but there were no differences within 2 years (p = 0.45).

Thus, the use of DES appears safe and efficacious in randomised trials and registries of patients with STEMI. DES significantly reduce TVR compared with BMS, without an increase in death, myocardial infarction, or stent thrombosis within 2 years of the index procedure. This clearly favours the routine use of DES in AMI. However, several questions remain on the rate of stent thrombosis, long term safety, and the selection of compliant patients to prolonged dual antiplatelet treatment in an emergency setting.

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

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 randomisation to bivalirudin or unfractionated heparin and abciximab. The composite end point included ischaemia driven target lesion revascularisation, all case mortality, reinfarction and stent thrombosis (definite or probable according to the ARC criteria). At 1 year, ischaemic target lesion revascularisation was reduced with PES (7.5% vs 4.5%; p = 0.02) and ischaemic events were similar between the two groups (figure 4).

Several registries have analysed the outcome of patients receiving DES for AMI. The MASS-DAC registry included 4016 patients with STEMI and non-STEMI (NSTEMI). The comparison of matched patients treated with DES (72% SES) or BMS shows a mortality reduction at 2 years (–3.1%, 95% CI –5.4 to –0.8%; p = 0.008) in STEMI patients treated with DES. In contrast, the GRACE registry reported an increased mortality in patients treated with DES, between 6 months and 2 years after STEMI. However, the overall mortality was significantly reduced among patients treated with DES over the 2 years (5.9% vs 5.5%; p = 0.04), and during hospital stay (2.0% vs 3.8%; p = 0.018). In addition, striking differences were noted in coronary risk factors between the two populations, therefore impacting long term outcomes, atherosclerosis progression, and acute ischaemic events. Finally, follow-up was suboptimal, with data missing in over 30% of patients at 2 years.

The MISSION trial compared SES and BMS in 310 patients. The primary end point 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 < 0.01).

The use of PES was first evaluated in the PASSION trial which randomised patients to PES or BMS during primary angioplasty for STEMI. The primary end point of major adverse cardiac events at 1 year was not reached, although there was a trend towards fewer events in the PES group.

More recently, the HORIZONS trial randomised 3006 patients to PES or Express BMS, with a further
major events such as death or myocardial infarction.\textsuperscript{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. Concerns were therefore voiced after the publication of these results over the risk of an increase of stent thrombosis after implantation of DES during AMI.\textsuperscript{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.\textsuperscript{17} The choice of DES or BMS was left to the discretion of the investigator. Of interest, stent thrombosis rates increased according to the severity of clinical presentation, with the lowest rates in patients with unstable angina and the highest in those with STEMI. No difference was found in stent thrombosis 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. Of interest, 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, 95\% CI 0.28 to 0.84).\textsuperscript{18}

Although most trials on DES in AMI were performed recently, long term data are emerging. In May 2009, results of the 5 year follow-up of STRATEGY and 4 year follow-up 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 end points such as death or myocardial infarction. Of interest, in the TYPHOON study, the majority of stent thrombosis occurred early in the first month, highlighting the importance of pharmacological prevention.

**Figure 3** The MULTISTRATEGY trial. Primary end point. BMS, bare metal stent; HR, hazard ratio; MACE, major adverse cardiac events defined as death or myocardial infarction or target vessel revascularisation; SES, sirolimus eluting stent. Adapted from Valgimigli et al.\textsuperscript{7}

**Patient Compliance with Dual Antiplatelet Therapy After Primary PCI for AMI**

Non-compliance with dual antiplatelet therapy during the first 6 months after implantation has
Use of drug eluting stents in STEMI: key points

- Based on data from 7352 patients in 13 randomised trials and 26,521 patients from registry studies, the implantation of an SES and to a lesser extent a PES during primary PCI for AMI reduces the rate of repeat revascularisation with no increase in death, myocardial infarction or stent thrombosis.
- Similar stent thrombosis rates were found in randomised trials and registries with no difference at 1 or 2 years between DES and BMS. The 5 year follow-up of the STRATEGY trial and 4 year follow-up of the TYPHOON trial yielded similar results with a sustained effect of SES on the reduction of target vessel revascularisation without difference in safety endpoints such as death or myocardial infarction.
- Proper preparation of the culprit vessel is of paramount importance to assess the size and length of the stent. Implantation should therefore be performed after adequately visualising the lesion and nitrate injection.

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 compared to patients on clopidogrel. In the setting of an AMI, it is often difficult to assess a patient’s potential for compliance to medication and to enquire on a contraindication to prolonged dual antiplatelet therapy such as planned surgery. This could be a limitation to the implantation of a DES during primary PCI for AMI. However, in most European countries, patients with AMI are triaged by pre-hospital or hospital emergency physicians who assess the patient’s past history and understanding of medication compliance. Furthermore, several randomised studies and a recently published registry study clearly show that dual antiplatelet therapy with clopidogrel for at least a year reduces major events in all AMI patients, including those who receive a BMS. Therefore, long term compliance with 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 IN AMI IN CLINICAL PRACTICE

Based on data from 7352 patients in 13 randomised 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 revascularisation with no increase in death, myocardial infarction 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. Implantation should therefore be performed after visualising the lesion and 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 treatment compliance should start in the catheterisation laboratory, be continued during the hospital stay, and pursued during follow-up.

CONCLUSION

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

Competing interests: In compliance with EBAC/EACCME guidelines, all authors participating in Education in Heart have disclosed potential conflicts of interest that might cause a bias in the article. Christian Spaulding and Olivier Varenne have received speaker fee’s from Cordis, Abbott Vascular, Boston Scientific and are part of the Scientific Advisory Board of Cordis. Julien Rosencher has no competing interests.

Provenance and peer review: Not commissioned; not externally peer reviewed.

REFERENCES


First randomised trial comparing SES to BMS in primary PCI for STEMI.