Drug eluting or bare metal stent for acute myocardial infarction: an issue of safety?

Aloke V. Finn¹, Gaku Nakazawa², Frank Kolodgie², and Renu Virmani²*

¹Emory University, Atlanta, Georgia; and ²CVPath Institute Inc., 19 Firstfield Road, Gaithersburg, MD 20878, USA

Despite the widespread use of coronary artery stenting for the treatment of ST-elevation acute myocardial infarction (STEMI), little information exists about the long-term outcomes of drug eluting stents (DES) in this setting. Although DES result in a marked reduction in the rate of restenosis, concern still exists about the long-term safety of this technology, especially with respect to late stent thrombosis (LST), a catastrophic event associated with significant morbidity and mortality. Observational studies have shown that this risk continues at a constant rate up to at least 4 years after stenting.¹ Our lab has demonstrated that delayed healing (i.e. lack of complete endothelialization) is the primary pathologic substrate underlying these events and that >50% of stent struts in humans are not covered by endothelium up to 24 months after DES placement.²

Given that myocardial infarction is one of the only clinical presentations in which percutaneous coronary intervention has been shown to decrease the risk of death compared with medical therapy alone, the long-term outcomes after DES for acute myocardial infarction (AMI) is of immense clinical importance.³,⁴ Recent data from our laboratory in patients dying after DES placement for the treatment of AMI vs. stable angina demonstrated vessel healing at culprit sites (CSs) of plaque rupture is substantially delayed compared with CSs of stable lesions, emphasizing the importance of plaque morphology in the arterial response to DES.⁵ While randomized trials and observational studies of patients receiving DES for AMI have yielded inconsistent results regarding the safety of this practice, our data offer a pathophysiologic underpinning for the possibility that the benefits of opening an infarct-related artery in this setting might be outweighed by long-term risks of death and myocardial infarction associated with DES-driven LST.

Previous studies of drug eluting stents for acute myocardial infarction

Several randomized trials have compared clinical outcomes for patients with STEMI treated with either bare metal stent (BMS) or DES.⁶–⁹ A meta-analysis of these trials (with a limited follow-up of 1–2 years) demonstrated a significant reduction in re-intervention with no differences in stent thrombosis, myocardial infarction, or death between patients treated with BMS vs. DES.¹⁰ However, it must also be noted that outcomes were generally good, with death occurring in just 4.6% of patients and re-infarction in 3.5%, raising the issue of how applicable these results are to a broad STEMI population.

Although several registries of DES for AMI have enrolled higher-risk patients, registry data are imperfect, subject to selection bias, and have demonstrated inconsistent outcomes regarding this subject. For example, Mauri et al.¹¹ reported data from the Massachusetts Registry in patients presenting with AMI receiving either BMS or DES. Treatment with DES resulted in significantly decreased repeat revascularization and 2 year mortality compared with BMS. However, at 2 days after the index procedure adjusted mortality for STEMI patients was already significantly lower for DES vs. BMS patients. This finding reinforces the notion that selection bias can heavily influence interpretation of data even after statistical adjustment.

Jensen et al.¹² reported 2 year outcomes in 3756 consecutive patients with STEMI treated with DES or BMS. Adjusted all-cause mortality was not different between the groups, though there was a significantly increased adjusted risk of stent thrombosis after 1 year for patients treated with DES vs. BMS (RR 6.74; 96% CI = 1.23–37.00, P = 0.03). This study illustrates the point that because healing is delayed for long periods of time (i.e. >1 year), the risk of late thrombosis is continuous over time. Therefore, the safety of using DES for AMI cannot be determined by relatively short-term clinical studies.

Steg et al.¹³ also published important data from a large multinational registry of 5093 patients receiving BMS or DES for STEMI demonstrating increased late mortality (i.e. from 6 months to 2 years) for DES vs. BMS patients. However, propensity- and risk-adjusted survival post discharge mortality was not different at 6 months or 1 year. It is tempting to speculate that the events accounting for these mortality differences were...
thrombotic in nature and linked to discontinuation of anti-platelet therapy since this has been shown in multiple clinical studies to be a risk factor for the development of LST. However, given that the follow-up was available only in half the patients enrolled and no data on causes of mortality were provided, it is impossible to draw any firm conclusions about whether there was or was not a causal relationship between withdrawal of anti-platelet therapy and mortality. There were also important differences in baseline characteristics between the groups enrolled in this registry. In general, BMS are placed into sicker patients and those who might not be compliant with dual anti-platelet therapy or other cardiac medications. Overall, Killip class was greater in patients with BMS even after statistical adjustment for Grace risk scores. However, risk factors such as diabetes, hypertension, and hyperlipidaemia that correlate with late disease progression (and therefore could account for differences in mortality) were higher in DES-treated patients.

Despite these weaknesses, the data of Steg et al. are strengthened by our own pathological findings and should at least make clinicians aware of the possibility that there may be very serious long-term risks to the strategy of using DES for the treatment of AMI.

Most recently, 1 year results from HORIZONS AMI trial which randomized 3006 patients with STEMI to unfractionated heparin plus tirofiban or bivalirudin and then to either paclitaxel eluting or BMS implantation (3:1 fashion) and followed them for 1 year were reported.14 All patients received aspirin and clopidogrel for 1 year. The incidence of all cause mortality, stent thrombosis, and MI were not different between BMS and DES groups, though target lesion revascularization was significantly lower in the DES group. Although these data are encouraging, because DES delay healing for long periods of time, long-term follow-up is needed to confirm these results. Moreover, while this trial may provide more answers regarding the safety and benefits of DES in STEMI patients, it is not powered to address the relative risk of stent thrombosis or mortality with DES compared with BMS.

**Pathophysiology of late stent thrombosis in acute myocardial infarction**

Because plaque rupture is the most frequent cause of AMI (accounting for >75% of acute coronary thrombi), strut penetration of necrotic core is frequently found at these CSs. In our autopsy examination of patients with stents implanted >30 days, the CSs of patients presenting with AMI had less neointimal growth and greater inflammation, fibrin deposition, and uncovered struts compared with non-CSs within the same stent.5 These CSs in AMI patients also showed a greater delayed arterial healing with evidence of persistent fibrin deposition and incomplete strut stent coverage compared with the CSs of patients presenting with stable angina with underlying fibroatheromas and thick fibrous caps (Figure 1). In our cases, the prevalence of LST in patients with AMI vs. those with stable angina was also significantly higher. Late stent thrombosis is not just limited to DES but also has been reported after the use of BMS. We previously reported 13 cases of LST following BMS implantation.15 The underlying mechanisms of LST were bifurcation stenting (n = 5), radiation therapy (n = 3), plaque disruption in an adjoining non-stented artery (n = 2), restenosis (n = 1), and lipid core prolapse after stenting (n = 2). Among 132 patients with BMS, LST incidence at autopsy was 9.8%, a much lower rate of thrombosis compared with our DES cases (i.e. 50%). Similarly, the median time to thrombosis in BMS was 70 days (inter quartile range (IQR) 33–127 days), which was a much shorter period than that reported in the previously published study of DES (173 days, IQR 66–433), consistent with the prolonged duration of healing with DES compared with BMS. These data also fit nicely with that of Steg et al. in that differences in mortality would not be expected to differ between DES and BMS until after healing is complete in BMS (i.e. 6 months).

They also emphasize the underlying role that plaque morphology may play in the arterial response to DES. Although it is not known how plaque morphology affects healing, there are several likely possibilities. Because sirolimus and paclitaxel are highly lipophilic,16 it is likely that these agents have high affinity for lipid-rich plaques (i.e. necrotic core) and dwell there for longer periods of time because of greater strut penetration compared with struts exposed to more fibrotic types of plaque. In addition, the lipid-rich necrotic cores are more avascular and less cellular compared with the more cellular stable lesions. Therefore, these areas are less likely to be covered by adjacent migrating and proliferating cells.
Thrombus burden may also play a role by increasing drug uptake by the thrombus as shown by Hwang et al. with paclitaxel-eluting stents. Clinical correlation of this last findings can be found in the data of Sianos et al. who investigated the impact of thrombus burden on clinical outcomes in patients treated with DES for ST-segment elevation myocardial infarction. They found that patients with large thrombus burden (LTB) had significantly higher mortality, MACE, and stent thrombosis when compared with those with small thrombus burden.

Conclusion
Collectively, these data emphasize the complex impact of DES in the setting of AMI on vascular healing responses and the potential for untoward effects which may increase risk of LST. Although clinical data regarding the safety of using DES for the routine treatment of AMI have yielded inconsistent results in regards to mortality and risk of stent thrombosis, most of these studies have serious shortcomings and fall far short of settling this issue. Human pathologic analysis clearly indicate that healing is delayed by DES in the setting of plaque rupture vs. stable angina and that an increased risk of late thrombotic events should be expected in this setting. We believe there is a need for more rigorous larger randomized controlled trials before new technologies are used for unapproved indications such as AMI. Until these data become available, routine implantation of DES for AMI cannot be recommended.

References