Drug-Eluting or Bare-Metal Stents for ST Elevation Myocardial Infarction Can Observational Data Balance the Risk Benefit Equation?

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The randomized clinical trials leading to initial approval of drug-eluting stents (DES) by the United States Food and Drug Administration were conducted by design in a homogeneous group of lower risk patients with mostly noncomplex coronary lesions. These studies demonstrated a clear benefit in the reduction of restenosis without any evidence of a safety concern during 1 year follow-up. Shortly after approval of the sirolimus and paclitaxel-eluting stents, safety and effectiveness was reported from small nonrandomized studies in a variety of more complex patient and lesion subgroups and resulted in a large proportion of so-called off-label usage.

Increased concern over the safety of acute DES implantation during primary percutaneous coronary intervention for ST elevation myocardial infarction (MI) left this indication as one of the last to gain widespread usage in favor of bare-metal stents (BMS). A study from Rotterdam comparing 186 consecutive patients receiving a DES from April 2002 to January 2003 with 183 patients receiving a BMS during an immediately preceding time interval demonstrated no increase in subacute stent thrombosis (0% versus 1.6%, P=0.10) and a significantly lower risk for major adverse cardiac events at 300 days (9.4% versus 17.0%, P=0.02) due to a markedly lower risk for target lesion revascularization (TLR) (1.1% versus 8.2%, P<0.01). Based partly on these limited data, DES use increased substantially also in patients with ST elevation MI in the United States and contributed to the >80% penetration of DES among all percutaneous coronary intervention procedures by early 2006. Two small randomized trials of DES versus BMS conducted in Europe and published in September 2006, also showed no increase in stent thrombosis for DES within 1 year.

In the summer of 2006, there were new concerns regarding late safety of DES with reports of increased risk of death and MI beyond 1 year that was presumed to be due to late risk of stent thrombosis. In December 2006, a special Food and Drug Administration advisory panel concluded that DES were associated with a small increased risk in stent thrombosis beyond 1 year, but that the risk did not outweigh the benefits when used according to approved indications. They admonished, however, that off-label use of DES is associated with an increased risk of stent thrombosis, death, or MI compared with on-label use.

Since the advisory panel report, 2-year outcomes from large observational databases including patients with an array of off-label indications have been reported. These studies have been consistent in demonstrating significant advantages for reducing repeat revascularization without increased risk for death or MI. Indeed, both the New York and Massachusetts registries showed reduced risk for MI in DES patients, whereas the Massachusetts registry also demonstrated significantly lower all-cause mortality. These conclusions are limited due to the observational methods. Although the studies have all used propensity matching or Cox proportional hazards regression methods to adjust for measured confounders, other unknown factors leading to operator selection of BMS versus DES cannot be adequately controlled.

In this issue, Jensen et al expand on these observational studies in a report specific to the high-risk indication of ST elevation MI. The study includes 2-year outcomes in 3756 consecutive patients presenting with ST elevation MI and undergoing stenting in western Denmark between January 2002 and June 2005. Only after January 2003, both BMS and DES were available and were then used according to operator preference, such that the study population included only 783 (21%) DES.

The findings included higher unadjusted all cause and cardiac mortality among BMS patients, although there were no significant differences at any time point after adjustment for baseline differences. Repeat TLR was significantly lower for DES patients, with an adjusted 30% relative reduction. Stent thrombosis occurred in about 1% of DES and BMS patients within 30 days. There were more events among DES patients after 30 days, and although there were a small number of events, this difference was significantly different for events occurring beyond 12 months.

There are several questions before we can accept the validity of these data for making clinical decisions that depend on a reliable assessment of the balance between a benefit in reduced repeat revascularization and possible increased risk of late stent thrombosis. Can we make inferences on the effect of stent type in the absence of randomized treatment assignment? To what extent do the statistical
adjustments correct for the impact of operator stent selection? Although a randomized trial is the gold standard, prior efforts comparing DES and BMS have been too small to assess infrequent but severe safety events and as with most randomized trials are themselves limited by selective enrollment of subjects among whom differences in outcomes may not be apparent. Observational studies that include consecutively treated patients provide a so-called “real-world” assessment of outcomes. This real-world, however, necessarily incorporates the effect of physician- and patient-based choices, and as a result leads to serious potential bias when used for comparison between any of the variables involved in these choices, including DES versus BMS.

We are left then with evaluating the success of controlling for the bias in the choice of stent type. In terms of the effectiveness of statistical adjustment, the regression and propensity methods employed by Jensen et al are generally agreed to adequately correct for differences in measured confounders. In fact, there are several examples where the effect of treatment methods compared by randomized trials and well-designed observational studies are nearly identical. At issue, as stated earlier, is the impact of unmeasured factors that may be associated with both the selection of stent type and the outcome of interest—so-called unmeasured confounders. It is helpful to explore the 3 outcomes in the study in which a difference between DES and BMS was detected or excluded after statistical adjustment.

Jensen et al observed a significantly higher mortality for BMS compared with DES. This difference was not statistically different after adjustment using Cox proportional hazard regression, although a trend persisted \( P=0.09 \); and did remain significant in propensity adjusted analysis. The impact of unmeasured confounding is probably greatest for the mortality outcome. The leading unmeasured variables include severity of underlying comorbidities such as cancer and debilitated functional status, although there are likely numerous other factors that may be detected by an observant physician and are difficult to quantify in a digital record. Interpretation of mortality differences in observational studies should, therefore, be made with caution.

For the outcome of TLR, Jensen et al observed a small difference that was significant after adjustment for patient and lesion characteristics. In contrast to mortality, the risk factors for clinical restenosis are almost always available from a percutaneous coronary intervention database. It is unlikely that unmeasured confounders significantly affected the reported 30% relative risk reduction. Nevertheless, this restenosis benefit is considerably less than that observed in other studies of DES, including the randomized Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty (TYPHOON) trial of the sirolimus eluting stent versus BMS for ST elevation MI. As the authors note, some of this difference is related to the lower overall rate of TLR owing to the absence of routine follow-up angiography. It is also possible, however, that clinical restenosis after BMS for ST elevation MI is lower than for other lesion types or that the net benefit for DES over BMS is less as suggested by reported rates from 3-year follow-up of the Rotterdam registry and the randomized Paclitaxel-Eluting Stent Versus Conventional Stent in Myocardial Infarction With ST Segment Elevation (PASSION) trial.

Jensen et al also provide useful data regarding stent thrombosis. The early risk was high and not different between stent types. It is of note that use of glycoprotein IIb/IIIa inhibitors was protective, although this also has to be interpreted cautiously since selection bias could be a factor in this finding as well. The finding of an increased adjusted risk of stent thrombosis for DES after 1 year is of concern and unlikely to be related to unmeasured confounding. Delayed healing is the major risk factor for these very late thrombotic complications and recent pathological data indicate that healing may be impaired especially after DES in culprit lesions associated with ST elevation MI.

Does the study by Jensen et al assist the clinician in balancing the risk versus benefit equation for patients with ST elevation MI? The adjusted results for the major effectiveness end point of TLR and the major safety end point of stent thrombosis are actually qualitatively similar to that seen with on-label and other off-label indications. If we look more carefully observational data actually provide added insight. First, it must be noted that only 21% of the study population received DES, indicating that after the first year, when only BMS were available, BMS were selected over DES in >2 of 3 of cases. The unadjusted rates of TLR that reflect this selection, however, were only slightly and nonsignificantly in favor of DES (7.2% versus 8.7%, \( P=0.09 \)). Most would agree that these TLR rates in the selected BMS group are acceptable. Furthermore, such selective use, by reserving DES for patients and lesions at highest risk for restenosis, may also reduce the overall burden of very late stent thrombosis and remove the dilemma regarding the optimal duration of uninterrupted dual antiplatelet therapy in most of this high-risk group of patients who present in emergent situations often with limited medical history.

In conclusion, despite its observational design, the study by Jensen et al provides some solutions regarding the balance of safety and effectiveness for DES versus BMS in patients with ST elevation MI. The results demonstrate a significant reduction in TLR for DES without an increase in death or MI. There is a price, however, of prolonged dual antiplatelet therapy of uncertain duration and an increased risk of very late stent thrombosis. Moreover, the observational nature of the study allows recognition of the importance of the physician in the selection of a device for a specific patient, not only according to measured and quantifiable risk factors, but also likely with awareness of factors that may not be so easily assessed. Until DES or other treatment options are available that provide persistent reduction in TLR without the encumbrance of prolonged, uninterrupted dual-antiplatelet therapy and ongoing risk for stent thrombosis, applying the science and the art to a patient-specific practice of medicine will provide the best balance of the risk-benefit equation.

Disclosures

None.
References


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