Restenosis after coronary interventions was referred to as the “soft underbelly” of angioplasty by Richard Myler, MD, 30 years ago. However, restenosis was not demonstrated to be significantly related to a safety risk but was rather an “inconvenient truth,” which was reflected primarily by disruption of the patient’s schedule and increased costs. For the operator it provided an opportunity to perform rather easy angioplasty procedures with predictable results. Nonetheless, elimination of the “soft underbelly” was a dream for many, and after drug-eluting stents (DES) were shown to markedly reduce restenosis, Patrick Serruys, MD, PhD, declared that they were “a dream come true.” That dream seemed to be turning into a nightmare in 2006 when several reports pointed to the catastrophic complications of late stent thrombosis, which was more prevalent with DES than with bare metal stents (BMS).1 Despite the exaggerated benefit of DES seen in clinical trials, the reduction in restenosis in many lesion subsets was clear and a benefit not to be sacrificed lightly.2 The occurrence of late thrombosis, however, was also reported to be associated with an increased mortality rate for patients receiving DES. The Swedish Registry among others reported to be associated with an increased mortality rate for patients receiving DES. The Swedish Registry among others was sobering, and the use of DES plummeted from around 90% to close to 60% in the United States.3

Are Drug-Eluting Stents Dangerous?
As this bad news was being digested, pivotal trial data were examined and, although the small late thrombosis excess was confirmed, no signal for increased mortality was seen.4 Registries examining this issue agreed and began to show survival data that actually favored DES.5,6

Are Drug-Eluting Stents Safer?
In this issue of Circulation, Mauri et al7 examine the 2-year outcomes of patients treated with DES or BMS in the year when DES were introduced to the market and both stent types were used widely. In the period 2003 to 2004 in the State of Massachusetts, all patients who were residents of the state and received DES or BMS exclusively were followed. The mandatory data entry and the ability to link registries of vital statistics and death index to the Massachusetts registry of percutaneous coronary intervention cases enabled longitudinal follow-up. After matching to control for differences in patient and procedure characteristics, these investigators found a significantly better 2-year survival rate among the patients treated with DES compared to those treated with BMS (mortality 9.8% for DES and 12.0% for BMS, P=0.0002).

The methodology chosen for studying the difference was propensity matching. Of the 11 556 patients receiving DES and the 6237 receiving BMS, a 1:1 matching based on the estimated propensity score for each patient resulted in 5549 DES patients being compared with 5549 BMS patients. After this matching, the patient and procedural characteristics available for comparison were remarkably similar. The question of uncontrolled variables was raised by the authors. Given that all the patients and lesions were selected for DES or BMS, what drove that selection process? If it was random, then all the better because it would then mirror a comparison in a randomized trial. Many differences were present between the two groups, as reflected in the patient and procedural characteristics before the matching process began. Were there other variables that systematically drove the selection of stent type? Predictors of restenosis are closely related to 3 important variables: vessel size, lesion length, and presence or absence of diabetes mellitus. Unfortunately, 2 of these, vessel size and lesion length, were not available in the database. What else can influence selection? Patients who are unable to comply with long-term Plavix therapy may be selected for BMS preferentially. Features such as a patient’s socioeconomic status, reliability, and general health are hard to obtain, and although some surrogates are in the database, it is unclear why these considerations did not enter into stent selection.

Other Ways to Learn From Registries
The concurrent patient comparison used in this study has advantages and disadvantages. Although incremental improvements and unmeasured variables may be minimized, the potential for selection bias remains and therefore, in comparing DES and BMS in another large registry, we chose a nonconcurrent registry.5 The New York State Percutaneous Coronary Intervention Registry was used to study 11 436 patients stented in the 6 months preceding DES availability (October 1, 2002, to March 31, 2003) and 12 926 patients studied 6 months after DES were introduced (October 1, 2003, to March 31, 2004). This observation of the “BMS era”...
stenting and the “DES era” stenting reduces the problem of selection bias because the opportunity to choose DES in the BMS era did not exist, and DES adoption was very high 6 months to 1 year after its introduction as a replacement for BMS. Regardless of the methodology, the results in Massachusetts and New York are certainly comparable, with no signal for DES use to be associated with increased mortality but rather to have better intermediate outcomes.

Is There a Mechanism by Which DES Should Improve Hard Outcomes?

It is difficult to postulate why DES should produce improved results in the short term, before restenosis becomes an issue. After restenosis has a chance to develop (3 to 9 months) the renarrowed artery may play a roll or the complications of repeat procedures may effect survival. Is there evidence for these effects in the present study? Examination of the Kaplan–Meier curves in the event rates at 30, 180, 365, and 730 days is instructive. Until 30 days an absolute 1% reduction in death can be seen in the DES group. Can this be explained by characteristics of DES? It seems highly unlikely given the mechanism of action of DES, which is to reduce neointimal tissue growth and restenosis, which does not manifest until later. The difference at 30 days is probably due to some immeasurable confounders resulting from differences in selecting DES or BMS for patients. Despite the authors’ superb matching process, such clinical selection decisions are impossible to eliminate. Also, although not significant, the mortality difference at 2 days (0.23%, \( P=0.10 \)) is trending toward significance, and the rate for BMS (0.68%) is 1.5 times higher than the rate for DES (0.45%).

From 30 days to 1 year, another 1% absolute reduction in death can be seen in the DES group. Here restenosis could have played a role, but the other unmeasured variable of great importance is the prolonged use of dual antiplatelet therapy preferentially in the DES group. Examination of the Kaplan–Meier curves of reinterventions shows most repeat procedures occurring between 80 and 180 days. Little difference in mortality over this period was found, suggesting that mortality related to repeat procedures was an unlikely explanation for the difference. Because percutaneous revascularization commonly does not treat all lesions,8 the protective effect of this dual antiplatelet therapy cannot be discounted. The group of patients with established vascular disease in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial showed a significantly improved survival advantage for dual antiplatelet therapy even without the influence of stenting.9 Therefore, the difference between 30 days and 1 year may relate more to the dual antiplatelet therapy than to the stent selection. After 1 year, no survival difference can be found between BMS and DES. This is reassuring because late stent thrombosis may manifest itself in this time period, and, if it resulted in more deaths in the DES group, it would be seen. Such was not the case.

Finally, this carefully performed analysis by Dr Mauri and her colleagues adds to the comfort of selecting DES for appropriate patients and lesions but does not provide evidence that DES is correct for all situations. Improvements in stent technology should be applauded. However increased understanding of the impact of aggressive secondary prevention has improved outcomes not only for patients treated with DES and BMS but also for those patients treated with neither.

Disclosures

None.

References


Key Words: Editorsials ■ restenosis ■ stents ■ thrombosis ■ survival
Mounting Evidence for Safety and Improved Outcomes of Drug-Eluting Stenting: But Is It the Stent?
Spencer B. King III and Edward L. Hannan

Circulation. 2008;118:1783-1784; originally published online October 13, 2008;
doi: 10.1161/CIRCULATIONAHA.108.810754
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/118/18/1783

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/