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estenosis 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 dis-
ruption 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 re-
ported 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 longitudi-
nal 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 6,237 receiving BMS, a 1:1 matching based on the
estimated propensity score for each patient resulted in 5,549
DES patients being compared with 5,549 BMS patients. After
this matching, the patient and procedural characteristics
available for comparison were remarkably similar. The ques-
tion 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 impor-
tant 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 im-
provements and unmeasured variables may be minimized, the
potential for selection bias remains and therefore, in compar-
ing 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”

Mounting Evidence for Safety and Improved Outcomes of
Drug-Eluting Stenting
But Is It the Stent?
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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 occur 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, 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. 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: Editorials ■ restenosis ■ stents ■ thrombosis ■ survival
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