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Viewpoint

Advancing the Knowledge Base on the Efficacy–Safety Ratio With Drug-Eluting Stents

Contributions From the European Society of Cardiology Congress, Vienna, Austria, September 1–5, 2007

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One year after the World Congress in Barcelona in 2006 focused attention upon potential problems with drug-eluting stents (DES), the annual meeting of the European Society of Cardiology convened in Vienna, September 1 to 5, 2007. We summarize and attempt to place in perspective the newly released data on continued follow-up of patients treated with DES.

Summary of Key Presentations

The Bern group presented 2 additional abstracts on specific subsets (small-sized vessels and multivessel intervention) from the collaborative study group that involve 18,023 patients from 38 trials using bare-metal stents (BMS) and sirolimus- and paclitaxel-eluting stents (1). Although overall and cardiac mortality and rates of definite stent thrombosis associated with the use of BMS and DES are similar, the sirolimus-eluting stents appear clinically superior to paclitaxel-eluting stents. Comparing the need for target lesion revascularization at 4 years (hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.56 to 0.84) and the rate of myocardial infarction (HR 0.83, 95% CI 0.71 to 1.00), both seem to be reduced with the sirolimus-eluting stent ($p = 0.002$ and 0.045, respectively).

This collaborative network analysis predominantly stems from randomized clinical trial data. This type of meta-analysis compares stent A with stent B as well as stent C with stent B′ (direct within-trial comparison) and infers from these how A and C compare (indirect between-trials comparison). Such analysis assumes that BMS B and B′ are equally effective. This study adds to the knowledge base by suggesting that significant differences exist between specific brands of DES devices. However, the same statement may well hold true for BMS now that larger datasets have become available and differences between devices can become apparent. Critics have argued that the superior performance of BMS used as a comparator against paclitaxel-eluting stents (B′) compared with that used for sirolimus-eluting stents (B) might have contributed to some extent to the apparent superior performance of sirolimus- versus paclitaxel-eluting stents. In any case, it is no longer appropriate to assume class effects for any feature of DES, be it efficacy, safety, or effectiveness.

In Europe, nearly 20 different DES have received approval for market release (the CE mark), and many more BMS are available to the clinician. Given the widening spectrum of device characteristics with respect to strut thickness and material as well as use of various coatings or surface modification techniques, one can no longer pool data from individual members of either class of device and assume identical performance. Implications for future trial design are huge with respect to the most appropriate choice of comparator devices.

During the Hotline presentation on September 2, Stefan James (Uppsala, Sweden) presented an update on SCAAR (Swedish Coronary Angiography and Angioplasty Registry). Earlier publication of the 3-year follow-up of the 2003 to 2004 cohort (2) had led to the recommendation by the Swedish regulatory authorities to use DES only in the absence of other options, which was followed by a sharp decrease in DES use across the country. Extending the follow-up to 4 years and increasing the sample size from 24,215 to 39,432 procedures, there was no longer any significant difference in mortality, myocardial infarction, or combined events between BMS and DES. Up to 1 year, stent thrombosis rates seem to be higher with BMS, but thereafter cumulative rates of stent thrombosis accrue by 0.5% per year with DES use. At 3 years, the absolute restenosis rate remains below 10% in both groups, with an absolute difference of 3.5% in favor of DES.

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The strengths of this nationwide registry are the inclusion of consecutive unselected cases with complete follow-up and the large number of events, representative of real-world practice that includes "off-label" indications. Interpretation of the data is problematic, because outcomes are essentially driven by physician choices and patient characteristics. For example, the gradients in restenosis between BMS and DES may reflect the performance of physicians in selecting lesion or patient subsets at higher risk of restenosis for treatment with DES rather than the intrinsic antirestenosis properties of one type of device versus the other. Statistical adjustment for these baseline differences was adequately performed, but one cannot account for unknown or nonregistered confounders.

There was much speculation on the potential causes for the contradictory findings with respect to the earlier 2003 to 2004 report. Hypotheses included improved implantation technique, special attention to compliance with the prescribed dual antiplatelet regimen, and/or extended duration of therapy. It is essential to keep in mind that the proportion of patients with DES increased over time: 22% in 2003, 36% in 2004, and 53% in 2005. Accordingly, the proportion of DES patients with follow-up periods beyond 1 year (i.e., the risk period for [very] late stent thrombosis) was smaller in the 2007 analysis, compared with the previously published report (2). In any case, these results illustrate how difficult it is to monitor procedural outcomes on which to base regulatory decisions in the real world.

Single-center mortality data of 3 sequential cohorts of patients treated with BMS (n = 2,428), sirolimus-eluting stents (n = 856), and paclitaxel-eluting stents (n = 2,835) were presented by Joost Daemen (Rotterdam, the Netherlands). Groups were allocated according to the initial therapy. Patients and angiographic baseline characteristics indicate worsening of the risk profile over time. Survival was significantly better at 30 days in the cohort treated with sirolimus-eluting stents. By landmark analysis from 3 months to 4 years, there was no mortality difference between the 3 groups, including a subset of 938 patients with diabetes.

The same authors presented a 4-year update on the observed rates of definite stent thrombosis from the combined Rotterdam-Bern experience in all-comer patients (96.4% complete follow-up in 8,146 patients). Angiographically proven stent thrombosis continued to accrue linearly by 0.6% per year up to a cumulative rate of 3.3% (incidence density of 1/100 patient-years).

Stent thrombosis rates up to 3 years were also reported for the ARTS (Arterial Revascularization Therapies)-II registry, in which patients with multivessel disease were treated with multiple sirolimus-eluting stents. Based on Academic Research Consortium definitions (3), the rates were 3.3% for definite (proven by angiography or pathology), 5.3% for definite and probable (myocardial infarction in the stent area), and 6.4% for definite, probable, and possible (any unexplained death) stent thrombosis. Major adverse coronary event-free survival decreased progressively to 79% at 3 years. However, out of 127 adverse events, only 31% could be attributed to stent thrombosis. Similar data were presented by Juan Mieres (Buenos Aires, Argentina) on behalf of the ERACI (Argentinian Randomized Study of Angioplasty vs. Surgery) III Investigators, showing a progressive loss of benefit from DES use over 3 years in patients with multivessel disease, particularly in the presence of diabetes.

Lastly, during the Hotline session on September 4, P. Gabriel Steg (Paris, France) reported, on behalf of the international GRACE (Global Registry of Acute Coronary Events) registry, an increased mortality with DES versus BMS for acute coronary syndromes. In 2,298 patients with ST-segment elevation myocardial infarction, in-hospital outcome was better with DES, in keeping with the lower risk profile of patients selected for DES implantation. However, mortality from 6 months after admission to 2 years was 8.6% with use of DES, significantly ($p < 0.001$) greater than 1.6% with BMS. Markers of long-term risk, such as prior revascularization procedures, comorbidity, or extent of coronary disease, were more frequently present in patients receiving DES, and the duration of dual antiplatelet therapy was prolonged. After adjusting for the GRACE risk score and other variables, the odds ratio for increased mortality with DES remained unfavorable: approximately 6 ($p = 0.002$). Of note, no such increased risk was seen in the 4,149 patients undergoing stent implantation for non–ST-segment elevation myocardial infarction: mortality at 2 years was 3.9% for BMS and 2.9% for DES ($p = 0.50$).

Interpretation of these registry data is challenging, given the possibility that selection biases for one or another therapy could have an even stronger impact on outcome than the selected device itself. Some have received these observations with skepticism, because no such excess in mortality was seen in other registries, including the subset of patients with ST-segment elevation myocardial infarction in the SCAAR. Mechanical revascularization with stents or bypass surgery represents a life-saving indication in patients with both ST- and non–ST-segment elevation myocardial infarction. In that case, one should not extrapolate short-term results of small randomized trials to practice until longer-term follow-up data on safety are available, so as not to jeopardize the proven survival benefit that was derived from the long-term analysis of FRISC (Fragmin and Fast Revascularization During Instability in Coronary Artery Disease)-II, RITA (Randomized Intervention Treatment of Angina)-III, and other randomized trials.

Summary Statements

Despite sometimes contradictory findings, a number of converging observations are emerging:

- The efficacy–safety ratio with the use of DES appears to depend on the balance between the early benefit, the unquestionable antirestenosis effect, and the late hazard,

driven by the rare but severe complication of stent thrombosis.
- Rates of stent thrombosis beyond 1 year depend on definitions, but the problem persists and remains a source of concern, with an incidence density of at least 1/100 patient-years that is stable for up to 4 years.
- The net clinical performance profile of various stents, DES or BMS, cannot be assumed to be identical, which has important implications for approval of new drug–device combinations.

Given the low rate of adverse events and the need to collect long-term data, interpretation of the datasets entails many complexities and interferences by confounding variables. It should not come as a surprise if reported signals, positive or negative, seem to lack robustness.

Three major complicating issues can be identified:

- Clinical symptoms such as death or myocardial infarction are common to the disease itself and the potential complication of its therapy using stents.
- The obligatory use of prolonged systemic antiplatelet therapy can interfere with outcome in opposing ways by reducing the risk of stent thrombosis but at the same time causing bleeding complications and/or morbid interactions with intercurrent events.
- With durations of follow-up that are extended for several years, a number of patients will likely receive several devices of different types, and these cross-over cases complicate further data interpretation. Of particular relevance is the use of DES (or, in the past, vascular brachytherapy) for treatment of restenosis in patients initially treated with BMS.

As new drug–device combinations become available, it is essential that reliable data continue to be accumulated to advance our understanding of the benefit-risk balance of percutaneous revascularization using either BMS or DES, especially over the longer term. Such an effort will require continued collaboration between stakeholders across boundaries and frontiers.

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