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EDITORIAL COMMENT

Second-Generation Drug-Eluting Stents

Moving the Field Forward*

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Drug-eluting stents (DES) have revolutionized interventional cardiology and have fueled vascular research. However, not all DES are created equal, and recently, second-generation DES became available (1–4). Some esteemed basic and clinical cardiovascular investigators openly argue that simply comparing stent "A" with stent "B" should not be considered as proper research. Although the value of this criticism should not be completely dismissed, the other side of the same coin is that clinical research should actually focus on improving patient care. In this regard, the potentially superior results of novel devices in the clinical arena should not be taken for granted, based on promising bench findings or surrogate endpoints, but rather carefully scrutinized and confirmed in rigorous clinical studies with robust methodology and long-term follow-up (1–4).

See pages 11 and 19

Interventional cardiology provides a tempting scenario for love at first sight with never-ending novel, highly attractive devices. Experience, however, consistently demonstrates that great expectations may soon vanish and also that improving patients' clinical prognosis tends to be much harder than initially anticipated. With a wide array of DES currently available, many scientific (and nonscientific) issues are considered in the catheterization laboratory during the decision-making-process involved in device selection. Quite recently we learned our lesson after embracing a rather liberal use of first-generation DES, pursuing their unprecedented late angiographic results (5). Therefore, we should avoid leaps of faith and stumbling over the same stone again. Critical skepticism on DES metamorphosis should temper the overriding enthusiasm generated by the newest devices.

Everolimus-eluting stents (EES) are second-generation DES that elute everolimus (rapamycin analog) from a thin biocompatible, durable fluoropolymer on very thin cobalt-chromium alloy struts. In this issue of the *Journal* (1,2), the long-term results of 2 pivotal randomized clinical trials comparing head-to-head EES with paclitaxel-eluting stents (PES) are presented. Both studies confirm the "clinical superiority" of EES over PES at 2 years. Notably, EES appear to be not only more effective (restenosis prevention), but also safer (thrombosis prevention) than their counterparts (1,2). In 1 study, additional benefits of EES were also demonstrated beyond the first year (2). Can we already consider second-generation DES qualitatively superior to first-generation DES? Is the attainable net benefit, clinically meaningful and cost effective? Is clinical follow-up important beyond the first year, or does it matter at all? Shall we just change our practice?

General Methodological Issues

Follow-up studies of patients treated with DES are plentiful. In many cases, however, major flaws in design are apparent. Retrospective follow-up strategies allow for uniquely long follow-up intervals but are vulnerable to missing data and inadequate quality of the retrieved information (6,7). Conversely, in prospective studies, data may be collected in optimized conditions to maximize their quality and completeness. Indeed, large, prospective, real-world registries provide valuable complementary data not obtainable from randomized studies. However, in registries, adjusting effect estimates for measured confounders—with data validation using propensity score calibration—may be reassuring, but results are never considered as definitive.

Randomized clinical trials remain the best tool to obtain unbiased estimates of treatment effect. Randomized trials minimize bias by controlling for potential confounders (known and unknown) that may affect outcome and distort the apparent treatment effect (8). Controlled clinical trials should be pragmatic enough to achieve a balance in the struggle between external and internal validity. Indeed, roaming through methodology and inclusion/exclusion criteria may disclose problems in generalizing results from selected patient cohorts to real-world clinical practice (8). Patients included in randomized trials tend to have favorable outcomes. Reasons for benefit include enrollment of lower-risk patients, use of highly standardized protocols with supportive care measures, and special efforts to prevent treatment hazards (8).

The most frequently used clinical indicator of stent efficacy is target lesion revascularization (9). Nevertheless, given the low rates of revascularization after DES, very large studies are required to demonstrate clinically relevant reductions in this event. Combined clinical endpoints are also frequently selected as a primary outcome measure. However, interpretation of composite outcome measures may be tarnished by uneven clinical relevance of individual events or

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divergent effects (10). Accordingly, the potential value of emerging devices is usually initially addressed by surrogate angiographic endpoints that guarantee efficacy (9). In a second phase, larger-scale studies, without systematic late angiography but with long-term clinical follow-up, are required to demonstrate noninferiority, or even better, superiority in safety endpoints.

Small randomized trials provide important mechanistic insights, but their clinical results may be difficult to interpret. In these trials, special randomization schemes (different from 1:1) may increase precision of estimates in the new device arm but may generate imbalances in baseline characteristics (8). Furthermore, devising clinical implications from small studies designed to assess surrogate angiographic endpoints may be misleading. Actually, some of these occurred in SPIRIT II, the first randomized study comparing EES with PES (11–13). This trial may be considered a clear example of unstable estimates from a trial not powered for clinical endpoints. Indeed, in this trial, the clinical superiority of EES detected at 1 year vanished at 2 years, but re-emerged at 3 years (yo-yo effect) (11–13). This was further complicated by the occurrence of a late angiographic and intravascular ultrasound catch-up phenomenon—in an even smaller patient subgroup—that obscured the interpretation of the 6-month angiographic primary endpoint favoring EES (12).

Currently, noninferiority trials are frequently selected to compare DES. In noninferiority trials, reference treatment's efficacy should be well established, and sample size requirements tend to be larger (14). However, given the low frequency of adverse events after DES, relatively large differences are allowed in the noninferiority design to enable realistic comparisons. This pays the price of degrading the confidence in demonstrating "equivalence" between devices. Often the noninferiority margin and assay consistency may be questionable, thus claims regarding efficacy of the new treatment require cautious interpretation (14). Although most of these trials are justified (economic reasons, placebo [bare-metal stent] considered unethical), others may be criticized for merely studying a new marketable product ("me too" device) (14). Actually, the DES selected as comparator is of upmost importance because randomized "play-the-winner" initiatives may be selected to increase the perception of superiority. In this regard, final publications of recent randomized studies comparing EES with sirolimus-eluting stents are eagerly awaited.

Finally, only very long-term clinical follow-up of large randomized studies allows identifying outcome differences not apparent in relatively short-term clinical trials (6–8). However, even in randomized studies, description of clinical course should document phenomena likely to induce outcome changes, as unbalanced concomitant medical treatment (6,8). Furthermore, quality of reporting harms in randomized studies remains a matter of concern because safety reporting is frequently neglected (15,16). This problem may be particularly relevant when very-long-term information is ascertained. Strict methodological guidelines have been issued to avoid these deficiencies (16). Assessing whether clinical results continuously diverge beyond 1 year may be particularly challenging.

Trial Similarities and Differences

The COMPARE and SPIRIT IV trials represent the largest and more recent efforts to compare EES with PES in clinical practice (1,2). Both were high-quality, large randomized clinical trials with a superiority design powered to detect differences in hard clinical endpoints and with a pre-specified, long-term clinical follow-up. The primary endpoint, set at 1 year, included a composite of safety and efficacy outcome measures. Routine follow-up angiography was not part of these protocols. By design, allocation concealment was preserved and ascertainment bias avoided, but, as occurs in most interventional studies, complete blinding was not possible. Although lack of masking might theoretically affect late revascularization indication, consistent results were found when total and "clinically driven" revascularization rates were compared. The population pools from which samples were drawn (patients not enrolled) remained poorly characterized. However, in both studies, the attrition rate over time of enrolled patients was minimal. Finally, SPIRIT IV started only 6 months earlier than COMPARE, so chronologic bias should not be an issue (1,2).

There are also important design differences between these trials. Basically, COMPARE was a single-center study that included complex, real-life patients, whereas SPIRIT IV was a larger multicenter trial that included relatively selected patients/lesions. Nevertheless, SPIRIT IV had less restrictive inclusion/exclusion criteria than those used in previous SPIRIT trials. Overall, COMPARE patients had worse clinical and angiographic baseline characteristics, although, surprisingly, the prevalence of diabetes was significantly higher in SPIRIT IV than in COMPARE (32% vs. 18%) (1,2). Of interest, SPIRIT III demonstrated diverging clinical results after 1 year, but this late diverging pattern was not detected in SPIRIT IV (1,17).

Despite differences in trial design, considerable perspective can be gained by lumping together the results of both trials with previous data in a new meta-analysis (Fig. 1) (1–4,12,17,18). Consistent and robust results emerge in favor of EES. Reasons for the reduced rate of myocardial infarction after EES remain poorly understood, and their precise appraisal would require patient-level data analyses. Periprocedural myocardial infarctions may be reduced by the thinner struts of EES, leading to superior side-branch patency. Alternatively, improved endothelization, as previously demonstrated "in vivo" (19), may reduce the thrombosis rate. In the combined analysis the risk of stent thrombosis was strikingly reduced by EES. According to the temporal patterns seen in the current reports, both mechanisms appear to explain the reduced rate of myocardial infarction. This meta-analysis further emphasizes the superior efficacy of EES over PES to reduce revascularization rates (Fig. 1).

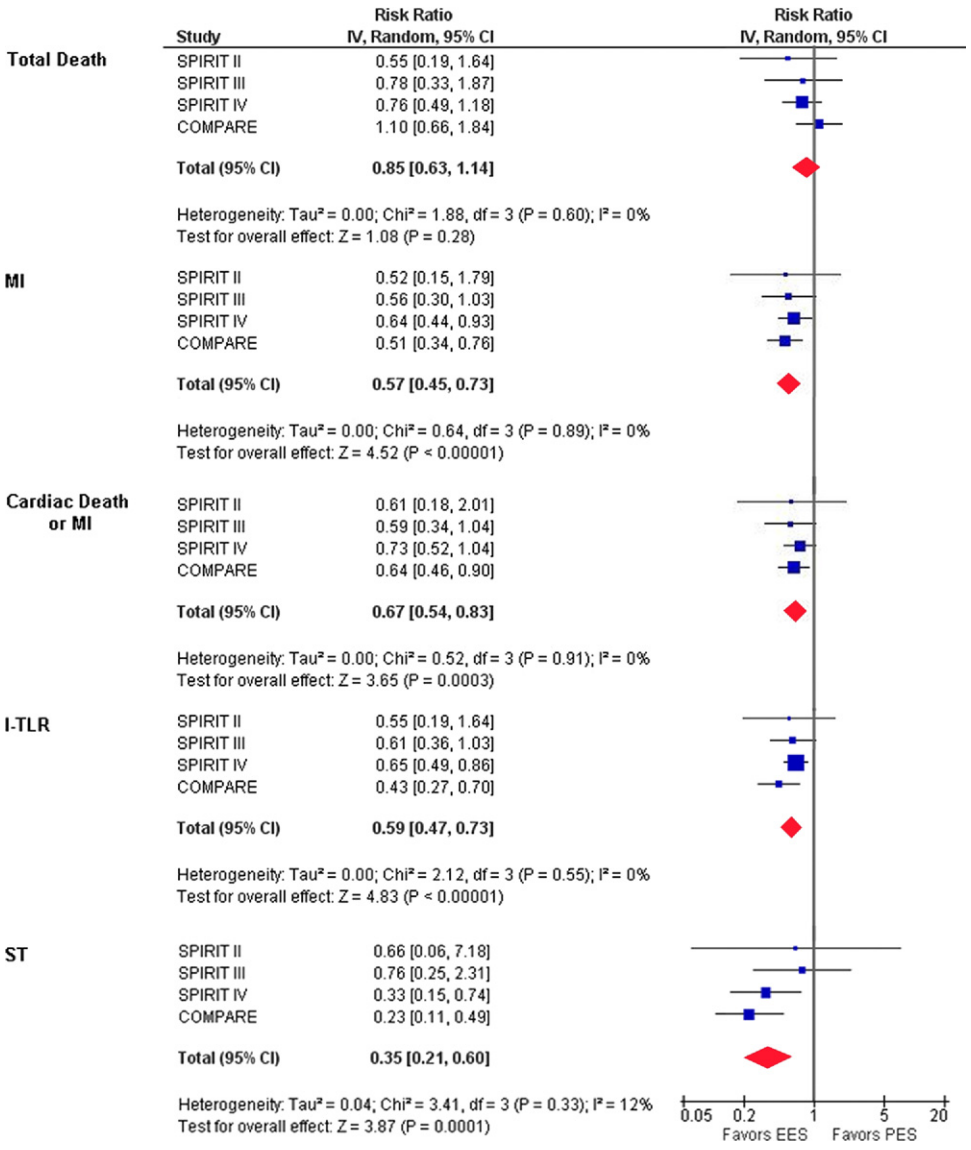

Figure 1 **Random-Effects Meta-Analysis of the 2-Year Results of the 4 Randomized Clinical Trials Comparing EES With PES**

The 4 trials currently available are SPIRIT II, III, IV, and COMPARE (1–4,11,12,17,18). Horizontal axis has a logarithmic scale. CI = confidence interval; EES = everolimus-eluting stent(s); I-TLR = ischemia-driven target lesion revascularization; MI = myocardial infarction; PES = paclitaxel-eluting stent(s); ST = definitive or probable stent thrombosis according to the Academic Research Consortium (ARC) definition.

In both trials, dual antiplatelet therapy was mandated for only 12 months (1,2). However, an unexpected, yet relevant, management difference emerged during follow-up: namely, a drastic difference in the maintenance of the dual antiplatelet regimen (70% and 13% in COMPARE vs. 92% and 69% in SPIRIT IV, at 1 and 2 years, respectively) (1,2). This might favor SPIRIT IV clinical outcomes. Interestingly, at 2 years, COMPARE patients treated with EES received less frequently the combined antiplatelet regimen than those assigned to PES (11.4% vs. 15.4%, p = 0.02). If anything, this would favor PES outcomes unless the dual antiplatelet therapy would had been re-initiated following the occurrence of an event. On the other hand, equal (1:1) allocation during randomization—as performed in COMPARE—has the greatest power to detect differences in clinical outcome. Whether this may explain the differences beyond the first year that were detected in COMPARE despite its smaller size remains speculative. The more complex patient population included in COMPARE, coupled to the shorter dual antiplatelet regimen, might explain why minor—yet significant—differences in the clinical efficacy and safety outcome measures were detected after the first year. A complex clinical/anatomic scenario may be required to unravel subtle late clinical differences among DES. Furthermore, PES used in COMPARE were the newer generation of

those used in SPIRIT IV (Taxus Liberté vs. Taxus Express) so that it is unlikely that this factor would explain the diverging late clinical outcomes. Further studies will be required to confirm the continuous divergence of event rates after 1 year between EES and PES.

Overall, SPIRIT IV might still be considered an efficacy trial (study under relatively ideal conditions), whereas the smaller COMPARE trial might be paradoxically labeled as a pragmatic or effectiveness trial (study under routine "real-world" circumstances). Although this classification might be too simplistic, the combined analysis of both trials (Fig. 1) would take the best of each world since efficacy trials maximize internal validity (true estimation of the association between the intervention and outcome), whereas effectiveness trials emphasize external validity (generalizability of results). Actually, sample characteristics may be more powerfully correlated with the long-term clinical course than the compared treatment interventions (6,8).

Finally, stratification (performed in both trials for diabetes) not only avoids potential imbalances caused by chance in carefully selected important variables, but also increases the validity of subsequent subgroup analyses (8). Indeed, stratification partially protects against type 1 and 2 errors. This is of interest, because diabetes presented a significant interaction with outcome results in both studies, further corroborating previous observations from earlier EES versus PES comparisons. If EES do not confer a distinct benefit over PES in diabetic patients, the higher prevalence of diabetics in SPIRIT IV could prevent the recognition of diverging outcomes beyond 1 year. Eventually, the way out of this conundrum would require a specific study in diabetic patients.

Final Remarks

Interventional cardiology is a rapidly evolving field, where new devices take the position of former generations still under evaluation. Indeed, the newer generations of EES (Xience Prime, Promus Element) and PES (Taxus Element), with advanced platform designs, have already replaced in the catheterization laboratory shelves the stents being compared herein. Again scientific prudence and genuine safety concerns should temper overriding enthusiasm. Clinical benefit from technical advancements should not be impeded, but short-cuts may lead to serious errors. The field and, above all, our patients, deserve that high methodological standards are kept in future studies to ensure a critical, comprehensive, and exhaustive appraisal of DES long-term results. We should be grateful to Stone et al. (1) and Smits et al. (2) for performing a systematic late clinical follow-up analysis of their patients. Their findings demonstrate that second-generation DES help the field to move beyond momentum.

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