Drug-eluting stents (DES) represent a breakthrough technology owing to their potent reduction of restenosis, which is a nuisance in the quality of life of affected patients, a rare cause of myocardial infarction (MI), and the principal shortcoming of stents compared with coronary artery bypass surgery. First-generation DES with controlled release of sirolimus or paclitaxel from durable polymers reduce the need of target lesion revascularization by 50 to 70% compared with bare metal stents, requiring treatment of only 8 patients (number needed to treat 6 to 10) to prevent 1 revascularization event. The benefit, albeit attenuated, persists in studies without protocol-mandated angiographic follow-up, is particularly pronounced in diabetic patients, and endures during long-term follow-up extending to 5 years. The safety of first-generation DES has been scrutinized in unprecedented depth and comprehensiveness after insinuation of impaired clinical outcome. Even though mortality and MI were found to be similar or even lower with the use of first-generation DES in randomized trials, meta-analyses, and large-scale registries, very late stent thrombosis (ie, sudden thrombotic occlusion of the device >1 year after implantation) emerged as a distinct entity complicating their use.

Later-generation DES have been developed with the objective to improve clinical outcomes by providing better deliverability and optimized long-term biocompatibility of polymer coatings and by introducing new antiproliferative drugs. One of these new DES is the everolimus-eluting stent (Abbott Vascular, Santa Clara, Calif), recently approved by the US Food and Drug Administration for percutaneous coronary interventions. The underlying stent platform is the Multilink Vision stent made of L-605 cobalt chromium alloy with an open cell nonlinear link design and the lowest strut thickness (81 μm) currently available with DES. Everolimus is a sirolimus derivative in which the hydroxyl at position C40 of sirolimus has been alkylated with a 2-hydroxyethyl solvents and galenic excipients. Although binding of everolimus to the FKBP 12 domain is 3-fold and immunosuppressive activity in vitro is 2- to 5-fold lower than with sirolimus, oral everolimus proved at least as potent as sirolimus in models of autoimmune disease and heart transplantation. Everolimus is blended into a 6-μm- to 8-μm-thick durable polymer at a concentration of ~100 μg/cm² stent surface area. The polymer consists of 2 layers, including a thin primer adhesion layer of poly n-butyl methacrylate (PBMA) and a drug reservoir layer of poly vinylidene fluoride coated hexafluoropropylene (PVDF-HFP), which releases ~80% of the drug within 30 days after implantation.

The everolimus-eluting stent has been directly compared with paclitaxel-eluting stents in the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions (SPIRIT) II (N=300) and SPIRIT III (N=1002) noninferiority trials. The everolimus-eluting stent was found not only noninferior but superior to paclitaxel-eluting stents in terms of late lumen loss, with trends toward reduced restenosis in both trials. Although SPIRIT III had a primary angiographic end point, the sample size of the trial allowed a meaningful assessment of clinical end points including target vessel failure and major adverse cardiac events. As recently reported, the everolimus-eluting stent was found noninferior in terms of target vessel failure at 9 months (7.2% versus 9.0%, difference −1.9%, 95% confidence interval (CI) −5.6% to 1.8%, P noninferiority <0.001) and superior with regard to major adverse cardiac events at 1 year (6.0% versus 10.3%, risk ratio=0.58, 95% CI 0.37 to 0.90, P superiority=0.02) compared with paclitaxel-eluting stents.

In the current issue of Circulation, Stone and colleagues explore the 2-year follow-up results of SPIRIT III with focus on changes in clinical events during the observation period between 1 and 2 years. The results are important and timely because they address the critical time window beyond 1 year when adverse effects such as very late stent thrombosis with first-generation DES may become apparent. The investigators report a significant 32% reduction in target-vessel failure (10.7% versus 15.4%, hazard ratio=0.68, 95% CI 0.48 to 0.98, P=0.04) and a 45% reduction in major adverse cardiac events (7.3% versus 12.8%, hazard ratio=0.55, 95% CI 0.36 to 0.83, P=0.004) in favor of the everolimus-eluting stent at 2 years of follow-up owing to trends toward lower rates of MI (3.3% versus 5.9%, P=0.08), very late stent thrombosis (0.2% versus 1.0%, P=0.10), and ischemia-driven target lesion revascularization (4.6% versus paclitaxel-eluting stents: 7.5%, P=0.07). As suggested by the Academic Research Consortium, a device-specific composite end point (cardiac death, MI, or target-lesion revascularization) should serve in the initial evaluation of newer-generation DES. Here, we will focus separately on the efficacy and safety components of the composite: target-lesion revascularization for efficacy and cardiac death and MI for safety.
Efficacy of Everolimus-Eluting Stents

To critically appraise results reported by Stone et al, we will investigate the consistency and strength of the findings in light of a meta-analysis of available data comparing everolimus-eluting stents and paclitaxel-eluting stents. In the pooled analysis (Figure), efficacy as measured by the device-specific metric of ischemia-driven target lesion revascularization is reduced by 39% in favor of everolimus-eluting stent (relative risk 0.61, 95% CI 0.38 to 0.99, \( P < 0.04 \)) up to 2 years. The relative risk reduction is of a similar magnitude in SPIRIT II and SPIRIT III. The superior efficacy of everolimus-eluting stents over paclitaxel-eluting stents is biologically plausible because in-stent late loss, a validated surrogate marker of target lesion revascularization\(^{10}\) was consistently lower with everolimus-eluting stents (0.16±0.41 mm) than with paclitaxel-eluting stents (0.30±0.53 mm, \( P = 0.002 \)).\(^7\) Along this line, previous experience with sirolimus-eluting stents achieving late loss comparable to that of everolimus-eluting stents produced similar results by reducing target lesion revascularization by 26% to 30% in pooled analyses.\(^1,11\)

The benefit of everolimus-eluting stents over paclitaxel-eluting stents in terms of target lesion revascularization emerged during the first year, whereas rates of target lesion revascularization were much the same in the period between 1 and 2 years. This is noteworthy because angiographic follow-up at 2 years in SPIRIT II showed significantly increased late loss with everolimus-eluting stents but not with paclitaxel-eluting stents suggesting a potential catch-up phenomenon with the former.\(^12\) This concern can be put at rest because angiographic data were obtained only in a small subgroup of patients and failed to translate into increased rates of restenosis or target lesion revascularization in either trial. In light of the consistent clinical and angiographic outcome, the therapeutic benefit of everolimus-eluting stents over paclitaxel-eluting stents can be considered well established although longer term-follow-up is still required for everolimus-eluting stent to endure the test of time.

Safety of Everolimus-Eluting Stents

The safety data of SPIRIT III are intriguing because the investigators invoke the hypothesis that everolimus-eluting stents may be associated with lower rates of cardiac death or MI as well as very late stent thrombosis. Although the meta-analysis shows imprecise estimates of relative risk for cardiac mortality, rates of MI (relative risk 0.57, 95% CI 0.33 to 0.99, \( P = 0.04 \)) and the composite of cardiac death or MI (relative risk 0.61, 95% CI 0.37 to 1.02, \( P = 0.06 \)) appear indeed lower with everolimus-eluting stents than paclitaxel-eluting stents at 2 years (Figure). The findings are of a similar magnitude in both trials, with early and late MIs being less frequent with everolimus-eluting stents than with paclitaxel-eluting stents in both, SPIRIT II and SPIRIT III. Although a detailed angiographic analysis was not provided, a likely explanation of fewer periprocedural MIs may be related to improved stent design characteristics with the everolimus-eluting stent, such as reduced strut (81 versus 132 \( \mu \)m) and polymer thickness (7.8 versus 16.0 \( \mu \)m) and less polymer webbing resulting in less sidebranch compromise.\(^8\) The benefit of fewer early MIs is a welcome improvement with later-generation DES because some studies suggest a long-term prognostic impact of periprocedural myonecrosis.\(^13\) This advantage may prove particularly beneficial in the...
treatment of patients with acute coronary syndromes with a routine invasive strategy being more effective than a conservative treatment during long-term follow-up despite an increased risk of periprocedural MI.14

How can we explain the reduced risk of late MIs associated with everolimus-eluting stents in both SPIRIT II and III? A tempting explanation insinuated by Stone and colleagues8 is a trend toward less stent thrombosis with everolimus-eluting stents beyond 1 year. An experimental study in rabbit iliac arteries seems to support this notion by showing more rapid and complete endothelialization with everolimus-eluting stents than with sirolimus-eluting stents, paclitaxel-eluting stents, or zotarolimus-eluting stents.15 Moreover, everolimus-eluting stents implanted into atherosclerotic arteries of cholesterol-fed rabbits caused mammalian target of rapamycin–dependent clearance of macrophages thus potentially preventing penetration of the necrotic core through stent struts,16 a known mechanism of late stent thrombosis in humans.17 However, clinical evidence in support of these observations such as optical coherence tomography, endothelial function testing, or angioscopy is lacking. In addition, clopidogrel discontinuation and subsequent stent thrombosis among 360 patients who discontinued thienopyridines definitely beyond 6 months in the present study did not coincide but were temporally disconnected because the first stent thrombosis event was encountered 73 days after drug removal (range, 73 to 396 days), rendering alternative mechanisms of stent thrombosis more likely. More importantly, available clinical data do not permit the conclusion that a lower risk of very late stent thrombosis is associated with everolimus-eluting stents compared with paclitaxel-eluting stents. Event rates of overall and very late stent thrombosis are low and may be similar for everolimus-eluting stents and paclitaxel-eluting stents regardless of definition (per protocol or Academic Research Consortium definite and probable), with imprecise pooled estimates of relative risks (Figure).

Do alternative explanations exist for the lower incidence of late MIs with everolimus-eluting stents than with paclitaxel-eluting stents? The article does not explicitly specify whether myocardial infarction caused by secondary stent thrombosis (ie, thrombotic stent occlusion after intercurrent target lesion revascularization) was censored and excluded from the analysis. Although we consider censoring unlikely, it would not explain the observed differences in favor of everolimus-eluting stents. Censoring would have advantaged the stent with lower efficacy (paclitaxel-eluting stents) and camouflaged a trend toward less stent thrombosis with the more effective platform (everolimus-eluting stents). Another possibility is the play of chance. Because MI and cardiac death were secondary outcomes, the present study and also the pooled analysis are underpowered to definitively address the issue of whether everolimus-eluting stents are associated with a lower risk of cardiac death or MI. Finally, differences between groups in medical cointerventions may have led to lower rates of ischemic adverse events in patients allocated to everolimus-eluting stents unrelated to the stented segment.

Unsettled Issues
The long-term data of SPIRIT III provoke the following unsettled questions. First, how do the safety and efficacy of everolimus-eluting stents compare with the most widely studied limus analogue sirolimus? Even though it is unfortunate that no trial has addressed this question, available data indicate that everolimus-eluting stents are at least as safe and effective as sirolimus-eluting stents, although longer term follow-up and studies in more complex patients and lesions are still warranted. Nevertheless, everolimus-eluting stents are likely to replace sirolimus-eluting stents in routine clinical practice in light of their superior deliverability and ease of use. Second, are everolimus-eluting stents associated with a lower risk of cardiac death or MI compared with paclitaxel-eluting stents? Although the data are promising, only a large-scale randomized trial will be able to resolve this issue. The SPIRIT IV study with the primary end point of cardiac death, MI, or ischemia-driven target lesion revascularization at 12 months has completed enrollment of a total of 3690 patients. It will have >80% power to detect a relative-risk reduction of ~40%, as currently observed for the composite of cardiac death or MI for everolimus-eluting stents compared with paclitaxel-eluting stents (Figure) at a 2-sided α of 0.05. Third, is the risk of very late stent thrombosis lower with everolimus-eluting stents than paclitaxel-eluting stents and can thienopyridines be discontinued after 6 months? Although this question remains unresolved for the moment, a collaborative effort with pooling of data from multiple trials with long-term follow-up may allow insights into potential differences between various DES platforms.

For the time being, everolimus-eluting stents are superior to paclitaxel-eluting stents not only in terms of angiographic but also in terms of clinical efficacy. The lower rate of target lesion revascularization is robust, maintained throughout 2 years, and in line with the superior reduction in neointimal hyperplasia. If confirmed in future studies, the potential for a reduced risk of early and late MIs, as well as very late stent thrombosis in conjunction with potent restenosis reduction, is intriguing and may meaningfully improve outcomes with drug-eluting stents.

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Disclosures
Dr Windecker is consultant for Abbott, Biosensors, Biotronik, Boston Scientific, Medtronic, and Johnson and Johnson, and he receives lecture fees from Abbott, Biosensors, Biotronik, Boston Scientific, Medtronic, and Johnson and Johnson. Dr Jüni reports no conflicts.

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