Drug-eluting stents (DES) were introduced to address the major limitation of bare metal stents (BMS), namely exuberant neointimal hyperplasia leading to clinical restenosis, which occurred in up to 30% of patients. Sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES)—referred to as early generation DES—by means of controlled release of antiproliferative drugs had a major impact on restenosis, reducing the risk of repeat revascularization by 50% to 70% compared with BMS at 1 year.1 Although large-scale clinical trials and meta-analyses failed to show any difference in terms of death or myocardial infarction (MI) between DES and BMS, long-term follow-up of patients treated with early generation DES raised safety concerns because of a continuous risk of stent thrombosis (ST) during the very late phase (>1 year).2 This phenomenon was linked to delayed vascular healing of the stented segment, with evidence of inflammatory infiltrates, delayed reendothelization, and positive coronary remodeling.3 Therefore, a new generation of DES was developed to improve outcomes by reducing strut thickness; using more biocompatible, durable, or biodegradable polymer coatings; and reducing the drug load.

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The everolimus-eluting stent (EES) is the device with the largest amount of clinical information among newer-generation DES to date. Indeed, the safety and efficacy of EES has been compared with early generation devices in several randomized trials and registries.4–9 The superiority of EES over PES has been consistently shown as evidenced by a reduced risk of repeat revascularization, ST, and MI in favor of EES.4,5 Conversely, all individual trials directly comparing EES with SES failed to show any difference in clinical outcomes up to 2 years of follow-up.4–8 In this issue of *Circulation: Cardiovascular Interventions*, 2 new studies shed additional light on the impact of EES on clinical outcomes compared with other DES.10,11 Palmerini et al10 performed a meta-analysis of 11 randomized trials comparing EES with other DES in 16 775 patients and analyzed the risk of ST through 2 years. Five of the 11 included trials compared EES with PES (n=7133), another 5 compared EES with SES (n=7370), and 1 compared EES with newer-generation Resolute zotarolimus-eluting stents (R-ZES) (n=2292). The investigators observed a 62% relative and 0.6% absolute risk reduction in the device-specific end point of definite ST in favor of EES compared with the pooled sample of SES, PES, and R-ZES. In addition, a time-dependent analysis of the risk of ST shows that treatment effects in favor of EES were consistent during the first 30 days as well as beyond the early phase up to 2 years. These findings corroborate the results of a previous meta-analysis by Baber and colleagues,12 which described a lower risk of definite and probable ST with EES compared with other DES. Similarly, a marked risk reduction for very late ST with EES compared with SES and PES was observed in a large registry of 12 339 consecutive patients undergoing percutaneous revascularization with the unrestricted use of DES at 4 years follow-up.9 Moreover, Palmerini and colleagues11 recently published the results of a collaborative network meta-analysis and reported a lower risk of ST for EES compared with other DES as well as with BMS.

What is the clinical relevance of the present analysis? The study adds to the growing body of evidence attesting to the improved safety profile of newer-generation EES compared with early generation DES by extending the observation to 2 years of follow-up and providing insights on the more-specific end point of definite ST as opposed to the broader definition of definite and probable ST. Although there was no difference in the risk of early and late ST between early generation DES and BMS, both SES and PES have been associated with an increased risk of very late ST (ie, beyond 1 year), which resulted in uncertainty regarding the length of dual antiplatelet therapy and concerns of its discontinuation.14 It is noteworthy that EES appears to lower the risk of both early and very late ST compared with early generation DES, which by inference would also suggest a lower risk of early ST compared with BMS, a hypothesis that was recently supported by the findings of a network meta-analysis by the same group of investigators.13 Notwithstanding, as shown by the authors in the online-only Data Supplement Table V, the reduced risk of ST in favor of EES in the present study was mainly driven by differences vis-à-vis PES, whereas differences were less pronounced for the comparison of EES with SES. It is also pertinent to ask the question about whether the observed differences in ST translated into improved clinical outcomes. We therefore provide a random-effects meta-analysis for the end points of cardiac death and MI to complement the findings on ST by Palmerini and colleagues (Figure 1). Although there was a significant reduction in the risk of MI with EES compared with PES (Figure 1A), no such effect was observed for the comparison of EES and SES (Figure 1B).
Palmerini et al.\textsuperscript{10} For the comparison between EES and R-ZES, the recently published TWENTE trial was included. The analysis was Random-effects meta-analysis for the end points cardiac death and MI of the same randomized trials are included in the article by Stefanini and Windecker Is Stent Thrombosis No Longer an Issue? \textsuperscript{333}

Therefore, it is evident that risk differences in the propensity of ST differ substantially among various DES with differential effects on ischemic end points, important nuances that become camouflaged when EES are compared against a pool of various DES rather than head to head.

Palmerini et al.\textsuperscript{10} also included newer-generation R-ZES as a comparator in the meta-analysis. However, the analysis was limited to a single trial, the large-scale RESOLUTE All Comers (Randomized, Two-arm, Non-inferiority Study Comparing Endeavor-Resolute Stent With Abbot Xience-V Stent) trial (N=2292),\textsuperscript{15} which was powered to detect differences between EES and R-ZES for a composite clinical end point of cardiac death, target vessel MI, and ischemia-driven target lesion revascularization but not for ST, which occurred infrequently, particularly during the late phase (ie, >30 days up to 2 years: 5 versus 10 definite or probable ST events). Moreover, in the meantime, the randomized TWENTE (Real-World Endeavor Resolute Versus Xience V Drug-Eluting Stent Study: Head-to-Head Comparison of Clinical Outcome After Implantation of Second Generation Drug-Eluting Stents in a Real World Scenario) trial was included. The analysis was performed with STATA 12.1 (StataCorp) statistical software. BASKET-PROVE indicates Basel Stent Cost-effectiveness Trial-Prospective Comparison of Clinical Outcome After Implantation of Endeavor-Resolute Stent With Abbot Xience-V Stent).
Generation Drug-Eluting Stents in a Real World Scenario) trial was reported, which randomly assigned 1361 patients to R-ZES or EES with no significant differences in terms of definite or probable ST (6 versus 8 events) and definite ST (4 versus 0 events) at 1 year.16 Both RESOLUTE All Comers and TWENTE showed comparable risks of cardiac death and MI with R-ZES and EES as summarized in an updated meta-analysis for the comparison of R-ZES and EES, including the RESOLUTE All Comers and TWENTE trials (Figure 1C). In view of the very low rates of late ST in both trials, the limited duration of follow-up, and the similar results in terms of overall ischemic end points between R-ZES and EES, it is misleading to include R-ZES in a pooled analysis with early generation PES and SES, insinuating a similar risk profile of these devices. Rather, available evidence suggests that clinical outcome of EES and R-ZES is comparable among a wide range of patients studied within the framework of the RESOLUTE All Comers and TWENTE randomized trials, and potential differences in rates of ST require further study as well as long-term follow-up of the 2 trials.

The study by Park et al,11 also in this issue of Circulation: Cardiovascular Interventions, compared EES with SES in a large-scale, multicenter, prospective Korean registry of 6166 patients (IRIS-DES [Evaluation of the First, Second, and New Drug-Eluting Stents in Routine Clinical Practice]). At 2 years (median follow-up, 1.3 years), the authors observed no significant differences between EES and SES with respect to the primary composite end point of death, MI, and target vessel revascularization as well as to its individual components. As for ST, the authors found exceedingly low rates with respect to both definite (0.25%) and definite or probable (0.35%) ST, with no difference between the 2 stent types up to 2 years of follow-up. How can we resolve the seemingly different outcomes in the meta-analysis by Palmerini and colleagues? First, the 2 studies differ with respect to the methodology: The meta-analysis by Palmerini and colleagues summarizes available evidence from randomized controlled trials, whereas Park and colleagues report the results of a registry without random stent allocation, which is open to various sources of bias. In addition, the studied patient population differs widely with the unrestricted use of DES in a registry of consecutive patients, whereas the meta-analysis included patients according to predefined inclusion and exclusion criteria. Along this line, the randomized trials analyzed by Palmerini and colleagues investigated multiethnic populations, whereas Park and colleagues included patients recruited in South Korea. In this context, it is noteworthy that the propensity of ST has been shown to be lower among the Asian population than among other populations.17,18 This might be due to differences in the pharmacogenetic response to antiplatelet therapy as well as to procedural factors such as the systematic use of intravascular ultrasound guidance and postdilatation with noncompliant balloons.17,18

However, both the studies of Palmerini et al and Park et al underscore the very low risk of ST and overall excellent clinical outcomes achieved in today’s clinical practice. If any differences with respect to ST may still emerge among currently available DES, they need to be carefully evaluated in the context of overall clinical outcomes, including death and MI. It is worth mentioning that other newer-generation devices are available beyond EES. One of these is the Food and Drug Administration-approved R-ZES included in the study by Palmerini and colleagues. In addition, several newer-generation DES currently not approved by the Food and Drug Administration have promising results with respect to the risk of ST. In particular, DES with biodegradable polymer coatings have been recently shown to reduce the risk of ST compared with early generation SES during long-term follow-up, with a direct impact on the risk of cardiac death and MI.19,20 Therefore, the lower propensity for ST, particularly during the very late phase beyond the interruption of dual antiplatelet therapy, appears to be not limited to newer-generation EES but may equally apply to several other newer-generation DES as shown in Figure 2. Indeed, one may argue that very late ST—the principal limitation of early generation DES—is no longer an issue with the use of newer-generation DES, which may have important implications for the duration of dual antiplatelet therapy. For the time being, EES constitutes the newer-generation DES with the most extensive and robust clinical evidence of improved outcomes over early generation DES and should therefore serve as benchmark for any new device in view of its excellent safety and efficacy profile.

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Giulio G. Stefanini and Stephan Windecker

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