Drug-eluting stents have been the most successful strategy for the prevention of restenosis after percutaneous coronary interventions (1). In line with this, the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus Eluting Stent versus Abciximab and Bare Metal Stent in Acute Myocardial Infarction) study showed a marked decrease in the need for reintervention with sirolimus-eluting stents (SES) as compared with bare-metal stents (BMS) even in the high-risk subset of patients with acute myocardial infarction (AMI) (2). Although the STRATEGY trial simultaneously evaluated the impact of another factor, glycoprotein IIb/IIIa inhibition with abciximab or tirofiban, this trial is now predominantly considered an SES versus BMS trial. In fact, there is no reason to believe that the type of glycoprotein IIb/IIIa inhibitor (3) had an important role in the difference in reintervention rates between the SES and BMS groups observed in the STRATEGY trial (2). In addition, the main 8-month results of the STRATEGY trial have been corroborated by a larger SES versus BMS trial in patients with AMI (4). Cardiologists have always been concerned with the sustainability of the initially positive results achieved with various drugs and devices. Thus, it is fully conceivable that the investigators of the STRATEGY trial were interested to know whether the advantages observed within 8 months of randomization with SES (2) are maintained beyond this time frame. In this issue of the Journal, Valgimigli et al. (5) assessed if the initial clinical benefit with SES is also demonstrable after 2 years. With this, they mark a second important achievement in their career: they were the first to evaluate SES in patients with AMI (2) and also become the first to report on this issue beyond 1 year (5).

The answer to the question posed at the beginning of this study is yes, the midterm benefit achieved with SES is maintained over 2 years. Indeed, the authors showed that SES continued to be associated with a significantly reduced risk of reintervention with a hazard ratio of 0.34 at 2 years (5), which is not different from that of 0.30 shown at 8 months (2). Also, the result regarding the composite of death and myocardial infarction was maintained between 8 months and 2 years: in both time points, SES did not impact significantly on the risk of death or myocardial infarction, with a hazard ratio of 0.77 at 2 years (5) versus 0.71 at 8 months (2).

Although the 2-year analysis of the STRATEGY trial clearly showed that the benefit achieved by SES at 8 months is sustained over 2 years, this analysis contributes less to the current discussion on the safety of drug-eluting stents. Current uncertainties are best illustrated in the figure included in a recent editorial presenting restenosis as the typical potential risk for BMS and thrombosis as the typical potential risk for drug-eluting stents (6). The 2-year report of the STRATEGY trial showed no significant differences in stent thromboses and mortality between SES and BMS, but, with only 2 stent thromboses and 22 death cases, this study has very limited power to help us eliminate existing concerns (5). In fact, no single SES versus BMS randomized trial has had sufficient power to assess this issue (7). Therefore, using single trials such as STRATEGY or a combination of a few of them as done in the recent past (8) may be misleading in the evaluation of long-term safety of drug-eluting stents. The 2-year results of the STRATEGY trial should be validated in the context of all available safety information from randomized SES versus BMS trials. Figure 1 presents a meta-analysis of stent thrombosis in 17 randomized trials including 5,606 patients who were randomly assigned to SES or BMS. Using the protocol-defined criteria for stent thrombosis as well as the longest available follow-up in each trial, there were 37 cases of stent thrombosis with SES and 38 with BMS, which corresponds to a pooled relative risk of 0.99 (95% confidence interval [CI] 0.61 to 1.61). These findings do not support the largely diffused concerns about a higher risk of stent thrombosis with SES compared with BMS. The basis of these concerns are not only pathological data on delayed healing with drug-eluting stents (9) but, most importantly, reports based on analyses of selected trials. In a recent analysis including only 4 SES versus

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From Deutsches Herzzentrum, Technische Universität, Munich, Germany. Dr. Kastrati has received lecture fees from Bristol-Myers Squibb, Cordis, GlaxoSmith-Kline, Lilly, Medtronic, Novartis, and Sanofi-Aventis; Dr. Schömig has received unrestricted grant support for the Department of Cardiology he chairs from Amersham/General Electric, Bayerische Forschungsstiftung, Bristol-Myers Squibb, Cordis, Cryocath, Guidant, Medtronic, Nycomed, and Schering.
BMS trials with a total of 15 protocol-defined stent thromboses, Stone et al. (10) described an excessive risk of stent thrombosis with SES after 1 year as illustrated by its occurrence in 5 patients with SES and none with BMS (p = 0.025). A possible selection bias and differences in the definition criteria of stent thrombosis across trials have contributed to these apparently controversial results. For example, in the 4 trials analyzed in the aforementioned analysis (10), patients undergoing reintervention were censored from further analysis of stent thrombosis. This led to the exclusion of 5 cases of stent thrombosis that had occurred among BMS patients after a reintervention (7). The following case from those 4 trials may illustrate par excellence the nonsense to which questionable definitions and post-hoc adjudication of events may lead. In a patient who received a BMS, stent thrombosis was not accounted for because it occurred after a reintervention for restenosis, which, in its turn, was not accounted for as a reintervention by the adjudication committee because of missing evidence of ischemia. Thus, 2 events that actually occurred do not appear in any of the previously published analyses.

Mortality certainly represents the most unbiased measure of drug-eluting stent safety. In the STRATEGY trial, there were 10 death cases in the SES group versus 12 death cases in the BMS group. These are small numbers, but the result is in line with the pooled result of the meta-analysis shown in Figure 2. There were 150 deaths in the SES group and 156 deaths in the BMS group, which corresponds to a pooled relative risk of 1.00 (95% CI 0.80 to 1.26). This is in full contrast with the 18% increase in the risk of death with drug-eluting stents reported recently from a registry study (11), providing the umpteenth testimony of how inaccurate registries might be for the comparative evaluation of 2 treatment strategies.

On-label use of SES is indicated in patients with symptomatic ischemic disease but without AMI for de novo lesions of length ≤30 mm in native coronary arteries with a reference vessel diameter between 2.5 and 3.5 mm. Therefore, the positive results shown in the STRATEGY trial should be seen in the context of a typical example of off-label use of SES. Of the 17 trials included in the analyses shown in Figures 1 and 2, only 4 addressed on-label use of SES, and the remaining 13 trials represented off-label indications. For on-label indications, SES was associated with relative risk of 1.04 (95% CI 0.75 to 1.46) for death and 1.60 (95% CI 0.53 to 4.82) for stent thrombosis; for off-label indications, SES was associated with a relative risk of 0.97 (95% CI 0.70 to 1.33) for death and 0.88 (95% CI 0.51 to 1.52) for stent thrombosis. Thus, there is no evidence at all that off-label use of SES is associated with compromised safety compared with BMS. This is very reassuring considering that off-label use often involves subsets (chronic occlusions, very long lesions, lesions in small vessels) that carry the highest risk for restenosis and may benefit the most from drug-eluting stents. These considerations may help to discourage the current trend to prevent off-label use of drug-eluting stents driven by some irreproducible findings coming exactly from on-label use of them.

The patients who received SES in the STRATEGY trial were treated with thienopyridines (ticlopidine or clopidogrel) for an average of 6 months after the procedure. Optimal duration of thienopyridine therapy after implantation of drug-eluting stents is not known. Although specific
studies on this topic are lacking, recent recommendations call for at least a 1-year duration (12).

In summary, drug-eluting stents are still a young technology with many unknowns, but also with a great potential for improvement. Initial optimism that claimed elimination of restenosis with drug-eluting stents is not supported by abundant evidence showing that restenosis is far from being completely defeated by current technology. However, emerging skepticism about late safety of drug-eluting stents is not justified by available evidence regarding long-term outcomes of patients treated with this therapy. The 2-year results of the STRATEGY trial are the most recent confirmation of this. Both unjustified optimism and skepticism may be equally harmful to patients with coronary artery disease. We should resist the temptation common to the lay media of prematurely proclaiming both the success and failure of a treatment strategy. Drug-eluting stents may have lost in brightness but not in real value.

Reprint requests and correspondence: Dr. Adnan Kastrati, Deutsches Herzzentrum, Lazarettstr. 36, 80636 Munich, Germany. E-mail: kastrati@dhm.mhn.de.

REFERENCES