Restenosis has been called the Achilles heel of coronary stenting and is caused by a combination of factors, including neointimal proliferation, elastic recoil, reorganization of thrombus, remodeling, and inflammation. Long-term follow-up (>6 years) in patients with bare metal stents (BMS) shows that tissue proliferation reaches its peak at around 6 to 12 months and then regresses. This pattern fits with the observed increase in revascularization rates up to 1 year, after which a plateau occurs. After drug-eluting stent (DES) implantation, Carter et al showed a late catch-up of restenosis in sirolimus-eluting stents (SES) in porcine models. Although a 50% reduction of restenosis was observed at 30 days, restenosis rates for SES and BMS were equivalent at 6 months. A similar catch-up phenomenon was observed after implantation of paclitaxel-eluting stents (PES) and tacrolimus-eluting stents in porcine models. Conversely, in humans, there does not seem to be reason for concern about late catch-up for up to 4 years on both clinical and angiographic end points. However, several long-term DES studies showed that, in contrast to BMS, the neointima continued to grow up to 2 years as assessed by intravascular ultrasound. The discrepancy between porcine and clinical data is influenced by the temporal differences in arterial response in humans compared with animal models but also may be due to differences in species response to sirolimus and paclitaxel and physiological stimuli for neointimal formation.

Trading Restenosis for Thrombosis and Late Mortality?

The Problem of Restenosis

Restenosis has always been considered a benign and harmless entity. However, recent studies assessing the clinical presentation and long-term outcome of patients presenting with in-stent restenosis demonstrated worrying findings, leading some critics to ask whether restenosis had simply been traded for long-term issues like thrombosis and mortality. At least 10% of all cases of BMS in-stent restenosis presented with a myocardial infarction (MI); 0.7% died. Furthermore, long-term survival rates proved to be significantly lower in patients with binary restenosis. and many other new investigational agents like everolimus-, zotarolimus-, and tacrolimus-eluting stents have been tested extensively for their main purpose, namely their ability to reduce restenosis. Recent pooled data from the pivotal Cypher and TAXUS trials, evaluating the efficacy of both the SES and PES, proved that both DES are associated with a significantly lower rate of angiographic and clinical restenosis compared with BMS for up to 4 years in selected patients. Besides their superiority to BMS in reducing restenosis, DES also have been associated with several unintended consequences. First, DES proved to hamper the natural vascular healing process. A study of 48 matched DES-BMS postmortems (>30 days after stent implantation) revealed the following. First, re-endothelialization was observed in only 56% of the DES cases compared with 90% of the BMS cases, illustrated by significantly higher persistent fibrin depositions that reflect delayed healing caused by ongoing inflammation in the DES-treated lesions; and at least 61% of the DES cases showed signs of late stent thrombosis (ST) compared with only 8% of the BMS cases. Although these results may not accurately represent the fate of patients who receive DES and survive, they do show that the natural healing process after DES implantation is not as optimal as originally hypothesized. Second, stent underexpansion (minimum stent area <5.0 mm²), a factor linked to restenosis, proved to be significantly more frequent after DES implantation. Whereas stent underexpansion is observed in 20% of all restenotic BMS lesions, an incidence of 67% is reported in restenotic DES lesions. These data were confirmed by a recent intravascular ultrasound study concluding that the angiographic restenosis rate was highest in lesions with stent area <5.5 mm² and stent length >40 mm. In the BMS era, the theory of “the bigger, the better” was widely advertised and became an obsessive motto for the interventional cardiologist. Although a large final minimum lumen area was shown to be associated with lower repeated revascularization rates, the superior antirestenotic properties of DES groundlessly made optimal stent deployment less important. Nevertheless, this could be an explanation for the substantially higher rate of stent underexpansion in in-stent restenotic DES lesions. Third, DES implantation was associated with a significant impairment in endothelial function, which in turn has been
Stent Thrombosis

ST has emerged as an important safety concern after stent implantation, although the rates have decreased from \( \approx 20\% \) after Wall stent implantation in the early 1990s to 0.2% to 1.8% after the implantation of current-generation BMS and DES.\(^{28-36}\)

In an attempt to identify predictors of ST, several studies identified >15 patient- and procedure-related factors associated with early ST. Whereas in the early days the early pattern was hypothesized to be related mainly to technical aspects of stent implantation such as underexpansion and dissections, 2 recent large-scale registries showed that patient-related factors such as age, hypertension, smoking, renal failure, acute coronary syndrome at presentation, left ventricular function, and female gender also were independently associated with early ST.\(^{37,38}\)

Unfortunately, the lack of consistent data and the overall low number of events make it difficult to interpret these predictors. Conversely, the late form has been related to delayed endothelialization and a hypersensitivity reaction to the drug or polymer.\(^{39-41}\)

The most common predictors of late ST proved to be acute coronary syndrome at presentation, diabetes, and stent implantation of the left anterior descending coronary artery.\(^{37,38}\)

A worldwide controversy is currently ongoing as to whether (late) ST indeed occurs more frequently after DES implantation. Two meta-analyses showed early ST rates between 0.51% and 0.9% for patients treated with BMS.\(^{29,42}\)

Ong et al\(^{43}\) published a series of 2512 unselected patients who underwent stenting. Early ST proved to be equal in patients treated with BMS, SES, and PES and occurred in 1% to 1.5% of all patients, depending on the definition. The concerns for late ST (>30 days) after DES implantation originate from a report of a patient in the European SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions (E-SIRIUS) study, who developed late ST 18 months after SES implantation.\(^{40}\)

Because of the presence of polymer fragments surrounded by giant cells and eosinophils, the authors concluded that this might have been the cause of the thrombotic event rather than the drug itself, which is no longer present in the vessel wall after 60 days. Additionally, McFadden et al\(^{44}\) reported 4 cases of late ST when antiplatelet therapy was interrupted after elective implantation of either an SES (n = 2) or a PES (n = 2).

For on-label use, pooled analyses of the randomized Cypher and TAXUS family trials demonstrated identical ST rates of \( \approx 3.5\% \) (using the new Academic Research Consortium definitions\(^{45}\) that take not only angiographically proven ST but also MI in the target region and sudden unexplained death into consideration) in both selected BMS and DES patients up to 4 years.\(^{46}\)

However, a trend seems to arise toward a higher rate of late ST (between 30 and 365 days) in patients treated with BMS that is partially related to target lesion revascularization, reaching its peak at \( \approx 6 \) months, which is compensated for by a higher rate of very late (>1 year) ST in the DES patients not related to repeated interventions. An additional interesting finding from the meta-analyses of the Cypher and TAXUS trials was the association between intervening target lesion revascularization and ST.\(^{46}\)

In the Cypher trials, 6 of 15 cases (40%) of definite or probable ST in the BMS group occurred after repeated target lesion intervention. Conversely, in the SES group, 13 of 13 (100%) of the ST was primary, without intervening target lesion revascularization. In the randomized TAXUS trials, a similar pattern was observed; 5 of 18 cases (28%) of definite or probable ST occurred after intervening target lesion revascularization in the BMS group compared with 21 of 22 cases (95%) of primary ST in the PES group. Remarkably, in pooled patient-level data of the ENDEAVOR-I, II, and III trials, although limited to 2 to 3 years of follow-up, the occurrence of very late ST was 3 times lower after zotarolimus-eluting stent implantation than after BMS implantation, and ST after repeated intervention occurred in only 1 patient in both the DES and BMS groups.\(^{47}\)

Recently presented long-term follow-up data of 8146 patients treated with DES in 2 academic institutions showed that ST, observed in 152 patients, occurred at a steady rate of 0.6% per year between 30 days and 3 years of follow-up.\(^{38}\)

It is uncertain whether these rates exceed those of unselected patients treated with BMS after many years of follow-up. To settle this issue, extremely large-scale randomized observations comparing DES and BMS in all patients are needed. Unfortunately, the likelihood that in the present era these trials will actually be performed is low, and even if they were started, it would take at least another 3 to 4 years for valid conclusions about the long-term results to be drawn. For now, we need to rely on large-scale registries in which the BMS control groups often comprise lower-risk patients and lesions.

From ST to Hard Clinical End Points

Knowing that DES are able to reduce restenosis by \( \approx 70\% \), one could subsequently expect a long-term benefit in survival.\(^{48,49}\) Instead, concerns were raised about a higher rate of death and MI after DES implantation, and even cancer was hypothesized to occur more frequently in DES-treated patients.\(^{50,51}\)

Frightened by these detrimental findings, stent manufacturers put complete data sets of randomized trials with long-term patient-level–based follow-up at the disposal of independent researchers and statisticians for further analyses. After several intense scrutinizing exercises, long-term death and MI rates appeared to be similar in pooled analyses of the pivotal Cypher and TAXUS trials, including relatively low-risk patients.\(^{17,52}\)

In real-world registries in which the off-label DES use accounted for up to 60% of the population, the outcomes seem more at variance. Whereas the large DEScover and West Denmark registries and the 3-year follow-up of the
Rapamycin Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry showed equal survival rates between DES and BMS, a large-scale Swedish registry highlighted a significantly lower survival rate in the DES group compared with the BMS group at 2.4 years of follow-up.\textsuperscript{7,53–55} Of note, the BMS control groups in the above-mentioned registries comprised significantly less complex patients because of either the sequential nature of the cohorts or substantial selection bias favoring the BMS control groups. It remains disputed whether comprehensive regression and propensity analyses are able to completely account for these differences.

It is to be expected that, in the long term, higher rates of very late ST after DES implantation will put our DES-treated patients at higher risk for death and MI. Although DES have been shown to be safe up to 4 years for on-label use, the off-label long-term safety has not yet been determined, given the controversial findings of large real-world registries and the lack of properly powered randomized controlled trials.

**DES Use for Off-Label Indications**

Whereas DES seem to be not only safe and effective but also preferable to BMS for on-label use, a lack of dedicated research makes off-label use debatable. This issue was reviewed at a recent panel meeting of the US Food and Drug Administration on ST to which key opinion leaders from the entire world were invited.

**High-Risk Patient Subgroups**

Two of the most widely discussed indications for DES use are diabetes mellitus and acute MI. Although diabetic patients make up \(\approx 25\%\) of our current population, the most safe and effective device for this high-risk subgroup remains disputed.\textsuperscript{56} Patients with diabetes are known to have an accelerated and more aggressive form of atherosclerosis and tend to develop substantially higher rates of restenosis compared with nondiabetics.\textsuperscript{57–59} The latter finding can be explained by the smaller vessel size, longer lesion length, greater plaque burden, and a possibly different-acting restenotic cascade compared with patients without diabetes.\textsuperscript{60,61} To date, retrospective subset analyses in various randomized controlled trials and a select number of small single-center experiences reported that both SES and PES are effective in reducing restenosis and repeated revascularizations compared with BMS in diabetic patients for up to 1 year.\textsuperscript{59,62–64} However, in a randomized trial by Dibra et al.\textsuperscript{65} the extent of late loss and angiographic restenosis was greater in patients treated with PES than in patients with SES, although the difference in the clinical end points was not statistically significant.\textsuperscript{65} Conversely, the Strategic Transthoracic Evaluation of New Therapies (STENT) registry compared the outcome of 1680 diabetic patients treated with either SES or PES and showed no significant difference in each of the clinical end points at 9 months.\textsuperscript{66} These clinical findings were supported by recent results from a retrospective subgroup analysis of 702 diabetic patients from the RESEARCH and Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry.\textsuperscript{67,68} After propensity analysis, no significant differences in any of the clinical end points between SES and PES were noted after 2 years of follow-up. Finally, the Latin American Society of Interventional Cardiology (SOLACI) and the Taxus Express2 Stent versus Cypher Stent: What’s Your Real-World Experience? (TC-WYRE) registry showed even lower target vessel revascularization rates in diabetic patients treated with PES compared with those treated with SES.\textsuperscript{69,70}

In assessments of the efficacy of both DES in diabetic patients, the different mechanisms of action of both drugs and the theory behind insulin resistance deserve some attention. Paclitaxel acts differently than the “limus” family drugs, which all inhibit the mTOR (mammalian target of rapamycin) gene. mTOR is dependent on the PI3 kinase pathway, which is degraded in patients with non–insulin-dependent diabetes mellitus.\textsuperscript{71} Whether these physiological differences will result in a significant long-term clinical difference between SES and PES remains to be determined.

A second high-risk subgroup in which the long-term safety and efficacy are not yet unanimously proven is the acute MI subset. A recent editorial incorporating a pooled analysis of the first retrospective subset analyses of MI patients treated with DES (mostly SES) concluded that the SES was safe and effective in reducing restenosis and repeated revascularizations in this high-risk subset.\textsuperscript{72} However, the number of patients included in these preliminary reports was small, and the studies were underpowered to definitively prove a beneficial effect of DES. Recently, the randomized Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty (TYPHOON) and randomized Sirolimus Stent Versus Bare Stent in Acute Myocardial Infarction (SESA MI) trial proved that SES were superior to BMS in reducing restenosis and repeated revascularization in patients presenting with acute MI.\textsuperscript{73,74} As a result of the negative findings of the Paclitaxel-Eluting Stent Versus Conventional Stent in Myocardial Infarction With ST-Segment Elevation (PASSION) trial and the nonsignificantly different repeated revascularization rates in the Helsinki Area Acute Myocardial Infarction Treatment Reevaluation: Should the Patient Get a Drug-Eluting or a Normal Stent? (HAAMU-stent) study, it is currently unclear whether this also holds for PES.\textsuperscript{75–77} We look forward to the results of the upcoming Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI) trial, which is designed to prove the efficacy of the PES in acute MI patients.

Of note, all the above-mentioned studies showed similar safety profiles (expressed by hard clinical end points like death, MI, and ST) for both DES and BMS in MI patients. However, this evidence goes no further than 1 year. Considering that very late ST was significantly more frequent after DES implantation (11 of 2278 cases) than after BMS implantation (1 of 2267)\textsuperscript{46} and knowing that acute MI proved to be among the strongest predictors of ST, we acknowledge that the long-term safety of DES in these patients remains debatable.\textsuperscript{35,36,38,78}
Off-Label Indications
A substantial amount of randomized controlled trials proved the efficacy of DES for off-label indications like chronic total occlusions, in-stent restenosis, small vessels, and bypass grafts. However, the primary end points of these trials were most often angiographic, and the follow-up is not reported beyond 1 year. Because of the limited number of patients in these trials, making them underpowered for assessing hard clinical end points, the long-term safety of DES for off-label indications needs to be determined on the basis of both pooled meta-analyses of these trials and real-world registries.

Duration of Antiplatelet Therapy
Currently, product labeling recommends 3 months of clopidogrel after SES implantation and 6 months after PES implantation, accompanied by lifelong administration of aspirin. Looking back on the rationale for these recommendations brings us to the First in Man (FIM) trial and the Randomized Study With the Velocity Balloon-Expandable SES in the Treatment of Patients With De Novo Native Coronary Artery Lesions (RAVEL) trial in which 2 months of ticlopidine or clopidogrel was mandated on the basis of the fact that the FIM was planned as a 60-day safety trial with concomitant ticlopidine use for 60 days. Although it would take another 2 years for the first concerns for late ST after DES implantation to be raised, clopidogrel prescription was prolonged to 3 and 6 months in the pivotal SIRIUS and TAXUS-I trials, respectively. Unfortunately, the rationale for this prolongation remains unclear.

It has been 5 years since the introduction of the first DES, and the optimal duration of dual antiplatelet therapy remains to be determined. In dedicated trials in the BMS era, the benefit of clopidogrel therapy proved to be apparent mainly in the first 1 to 6 months after stent implantation. The randomized Clopidogrel in Unstable Angina to Prevent Recurrent Events (PCI-CURE) trial proved that long-term administration of clopidogrel was associated with a 31% reduction in cardiovascular death or MI (P = 0.002) in patients presenting with a non–ST-segment elevation acute coronary syndrome. However, as supported by the findings of the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, which included only elective patients, the observed benefit was already achieved in the first month. No significant difference in death or MI between the clopidogrel- and placebo-treated groups was noted between 1 and 6 months. Given the lack of dedicated randomized trials in the DES era, we are forced to rely on indirect evidence indicating possibly severe consequences after the premature discontinuation of dual antiplatelet therapy. Currently, the Food and Drug Administration and the updated American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines recommend at least 12 months of clopidogrel in patients at low risk for bleeding. The currently available evidence supporting long-term clopidogrel use is controversial. On the one hand, recent large-scale registries demonstrated that 25% to 50% of all late ST events occurred in patients who were still on dual antiplatelet therapy. On the other hand, Eisenstein et al recently demonstrated a significant higher 2-year survival in patients remaining on dual antiplatelet therapy at 6 and 12 months compared with those who stopped clopidogrel. Unfortunately, the study does not report on the antiplatelet use at the time the 662 censored events in the first 6 months (156 of 1501 in the DES group versus 506 of 3165 in the BMS group) occurred. Finally, in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, which randomly assigned 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg/d) plus low-dose aspirin (75 to 162 mg/d) or placebo plus low-dose aspirin and followed them up for a median of 28 months, clopidogrel plus aspirin was not significantly superior to aspirin alone, and additional harm such as a significantly higher risk of bleeding could not be excluded.

Cost-Effectiveness
Although both SES and PES proved to be highly effective in reducing restenosis and the need for reinterventions, their cost-effectiveness is still debated. The cost-effectiveness analyses for both RAVEL and SIRIUS showed that SES were relatively cost-effective for simple lesions. Although the cost-effectiveness analyses of the RAVEL trial adjusted for the consequences of mandated angiographic follow-up, the results of economical analyses based on such trials should be interpreted with caution.

The Basel Stent Kosten Effektivitäts Trial (BASKET) analyzed the cost-effectiveness of both eluting stents combined compared with standard BMS in a real-world single-center setting. Total costs at 6 months were higher with DES (mean, €10,544; SD, €6849) than with BMS (mean, €9639; SD, €9067; P < 0.0001). At 6 months, the lower reintervention rates did not compensate for the higher initial costs. The incremental cost-effectiveness ratio of DES compared with BMS to avoid 1 major event was €18,311, and costs per quality-adjusted life-year gained exceeded €50,000. Subgroup analyses showed that DES were more cost-effective for elderly patients and specific high-risk subgroups like patients with 3-vessel disease, longer lesions, and type B lesions (the Figure). However, several methodological issues with this trial merit discussion. First, the analysis was based on 6-month clinical outcome, whereas we know from the randomized TAXUS and SIRIUS family trials that the Kaplan-Meier curves for target lesion revascularization for these DES compared with BMS continue to diverge up to 12 months. This would lead to a serious underestimation of their cost-effectiveness. In the simple incremental cost-effectiveness ratio equation, which expresses cost-effectiveness as change in cost divided by change in effect, the difference in cost would be overestimated, whereas the difference in effect would be underestimated.

Second, the cost-effectiveness was based on the performance of “DES,” in this case a combined population of both SES and PES patients. Blending the outcomes of both stents may affect the accuracy of the cost-effectiveness for each
product. The 18-month cost-effectiveness results of BASKET are expected soon and should be much more informative.

As mentioned in BASKET, the possible cost-effectiveness of DES has to be driven by the ability to reduce the need for reinterventions because death and MI rates proved to be comparable. Ong et al evaluated the cost-effectiveness of SES in the RESEARCH study and concluded that the SES was not cost-effective at 1 or 2 years of follow-up compared with BMS. However, Ong et al concluded that the incremental cost-effectiveness ratio per target vessel revascularization avoided was €29,373 at 1 year and €22,267 at 2 years in the total cohort. On the basis of these results, the calculated maximum cost-effective price after 1 year of follow-up is €1336 per SES for all-comers or €1023 to achieve cost neutrality. It is clear that longer-term follow-up is needed to determine the number of reinterventions that could be avoided to make DES cost-effective. It is worth noting that an inherent trap exists when the incremental cost-effectiveness equation is applied for all new medical technologies that do not, for example, apply to pharmaceuticals. The incremental cost-effectiveness ratio will be heavily influenced by the costs of both the new and old technology. The more successful the new technology is, the more rapidly and farther the price of the old technology that it is replacing is likely to fall. Thus, although initially cost-effective, the new technology may no longer be so 1 or 2 years later according to this equation.

Conclusions

So far, DES have been proved to be safe and effective with significantly lower rates of repeated revascularization. The trend toward a higher incidence of very late ST in patients treated with DES does not seem to affect the long-term hard clinical end points like death and MI, at least for on-label use and assuming compliance with the antiplatelet regimen. Whether this restricted 4-year safety profile can be extended to 5 or even 10 years and to higher-risk patients remains to be determined, given the lack of dedicated trials sufficiently powered for clinical safety end points like death and MI. It is evident that DES are associated with adverse side effects like endothelial dysfunction and a severely disturbed vascular healing process. Future research has to demonstrate if, how, and when this will affect long-term safety and efficacy.

Although adherence to 6 months of clopidogrel in DES-treated patients seems crucial in preventing stent thrombotic events, dedicated large-scale randomized trials are needed to settle the pros and cons of prolonged dual antiplatelet therapy.

Disclosures

None.

References

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52. Spaulding C, Daemen J, Boersma E, Cutlip D, Serruys P. A pooled analysis of reported event rates from clinical trials. Paper presented at: Transcatheter Cardiovascular Therapeutics meeting; September 27–October 1, 2004; Washington, DC.


59. Sousa AG. Outcomes of Percutaneous interventions in diabetes treated with drug-eluting stents or bare metal stents: SOLACI Registry Results. Paper presented at: Transcatheter Cardiovascular Therapeutics meeting; September 27–October 1, 2004; Washington, DC.


69. Sousa AG. Outcomes of Percutaneous interventions in diabetes treated with drug-eluting stents or bare metal stents: SOLACI Registry Results. Paper presented at: Transcatheter Cardiovascular Therapeutics meeting; September 27–October 1, 2004; Washington, DC.


77. Tierala I. Comparison of paclitaxel-eluting with bare metal stents in acute myocardial infarction: the HAAMU-STENT study. Presented at: Transcatheter Cardiovascular Therapeutics meeting; October 22–27, 2006; Washington, DC.

78. de la Torre-Hernandez JM. Real world data on stent thrombosis: the Spanish ESTROFA Registry. Presented at: Transcatheter Cardiovascular Therapeutics meeting; October 22–27, 2006; Washington, DC.


87. Tierala I. Comparison of paclitaxel-eluting with bare metal stents in acute myocardial infarction: the HAAMU-STENT study. Presented at: Transcatheter Cardiovascular Therapeutics meeting; October 22–27, 2006; Washington, DC.


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Joost Daemen and Patrick W. Serruys

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