Stent Design

Polymer-Free Biolimus A9-Coated Stent Demonstrates More Sustained Intimal Inhibition, Improved Healing, and Reduced Inflammation Compared With a Polymer-Coated Sirolimus-Eluting Cypher Stent in a Porcine Model

Summary: Drug-eluting stents (DES) still have late-stage disadvantages that might be attributable to the polymer. We hypothesized that polymer-free drug release may reduce late events and developed a newly designed polymer-free Biolimus A9-coated stent. The BioFreedom stent has 3 unique features. First, BioFreedom stents release the antiproliferative agent directly from a mechanically modified textured surface of the stent without the use of polymer. Second, Biolimus A9 is a highly lipophilic drug, which means it easily crosses the cell membrane to achieve therapeutic effects in its target tissue. Third, BioFreedom stents use asymmetrical coating on the outside surface of the stent. To test the hypotheses, we compared BioFreedom stents with a polymer-coated, sirolimus-eluting Cypher stent and a bare metal stent in an overstretched coronary mini-swine model. As a result, BioFreedom stents demonstrated equivalent early reduction of intimal proliferation with late efficacy compared with sirolimus-eluting Cypher stents. There appeared to be delayed healing and persistent inflammation in sirolimus-eluting Cypher stents compared with BioFreedom stents. The use of this new generation of polymer-free, drug-eluting stents versus traditional polymeric drug-eluting stents may be beneficial and should be examined in a randomized clinical trial.

Conclusions: The polymer-free Biolimus A9-coated stent demonstrates equivalent early and superior late reduction of intimal proliferation compared with sirolimus-eluting stents in a porcine model. After implantation of the BioFreedom stent, delayed arterial healing was minimal, and there was no increased inflammation at 180 days compared with sirolimus-eluting stent implantation. The use of polymer-free stents may have a potential long-term benefit over traditional polymeric-coated, drug-eluting stents.

Editor’s Comment: Although DES are more effective than bare metal stents in reducing the incidence of stent restenosis, rates of DES thrombosis are higher. Conventional DES include a polymer that serves as the vehicle for the antiproliferative drug, and pathological studies have raised concern that the polymer may enhance the risk for stent thrombosis. Accordingly, a DES without polymer, such as investigated in this study, might be safer. The polymer-free Biolimus A9 stent was at least as effective as the conventional sirolimus-eluting stent and had less inflammation. These results are encouraging; however, findings from the porcine model are not uniformly predictive of clinical outcomes in patients with coronary artery disease.1

Strut Coverage and Vessel Wall Response to a New-Generation Paclitaxel-Eluting Stent With an Ultrathin Biodegradable Abluminal Polymer: Optical Coherence Tomography Drug-Eluting Stent Investigation (OCTDESI)

Summary: Polymer-coated, drug-eluting stents have been associated with delayed healing, incomplete strut coverage, and an increased risk of stent thrombosis. It remains unknown whether a biodegradable abluminal coating that leaves a polymer-free bare metal stent after drug-eluting stent drug release can enhance strut coverage while preventing neointimal hyperplasia. This hypothesis was tested in the Optical Coherence Tomography Drug-Eluting Stent Investigation, a randomized pilot study comparing the conformal durable polymer TAXUS Liberté stent with a new generation paclitaxel-eluting stent with an ultrathin, biodegradable abluminal polymer designed to resorb in approximately 6 months (JACTAX). The efficacy of the stent was examined using optical coherence tomography, which can provide a high level of accuracy in evaluating minimal amounts of coverage after stent implantation, beyond what can be ascertained with angiography or intravascular ultrasound. The study found that the JACTAX stent, with 10-fold less drug and polymer load, did not result in improved strut coverage at 6 months but had antiproliferative effects similar to that achieved with the conventional TAXUS Liberté stent.

Conclusions: JACTAX paclitaxel-eluting stent, with an ultrathin microdot biodegradable abluminal polymer, did not result in improved strut coverage at 6 months compared with TAXUS Liberté.

Editor’s Comment: Limiting drug-eluting stent polymer to the abluminal surface of the stent and substituting a biodegradable polymer for a durable one may facilitate stent reendothelialization and potentially decrease the likelihood of stent thrombosis. Such technology was evaluated by OCT and clinical follow-up to 1 year. Unfortunately, no benefit was detected as compared with a conventional drug-eluting stent. Findings such as this, coupled with an apparent decline in the overall rates of stent thrombosis, may redirect future investigation of drug-eluting stent technology.2

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Paclitaxel-Coated Balloon Catheter Versus Paclitaxel-Coated Stent for the Treatment of Coronary In-Stent Restenosis

Summary: Drug-eluting stents are currently considered the best possible care in the treatment of in-stent restenosis. However, they include the presence of 2 layers of metal and may further reduce the flexibility of the vessel and limit the repeatability of the procedure. First-in-human trials with short-time local drug delivery using a paclitaxel-coated balloon catheter as compared with plain balloon angioplasty have shown beneficial effects in the treatment of coronary in-stent restenosis and in peripheral arteries. The PEPCAD (Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease) II trial compares the drug-coated SeQuent Please balloon with the approved and recognized drug-eluting Taxus Liberté stent. Angiographic late lumen loss was significantly lower with the coated balloon as compared with the drug-eluting stent. Furthermore, there was a trend toward a reduction of clinical events. Treatment of coronary in-stent restenosis with the paclitaxel-coated balloon was at least as efficacious and as well tolerated as the paclitaxel-eluting stent. For the treatment of in-stent restenosis, inhibition of re-restenosis does not require a second stent implantation.

Conclusions: Treatment of coronary in-stent restenosis with the paclitaxel-coated balloon was at least as efficacious and as well tolerated as the paclitaxel-eluting stent. For the treatment of in-stent restenosis, inhibition of re-restenosis does not require a second stent implantation.

Editor’s Comment: Contemporary revascularization options for in-stent restenosis in drug-eluting stents are limited. Current clinical practice favors a stent-in-stent procedure; however, this strategy leads to multiple layers of metal in the artery and may be associated with reduced efficacy of the eluted drug as well as side-branch occlusion. This study found that a paclitaxel-coated balloon decreased in-segment late lumen loss by approximately 55%, with a trend toward a decrease in adverse events. Although the study was underpowered to make definitive conclusions, it implies that paclitaxel-eluting balloons may have equal or greater efficacy than stent-in-stent procedures using paclitaxel-eluting stents for in-stent restenosis with an acceptable safety profile. The paclitaxel-coated balloon also has the potential to decrease the risk of stent thrombosis associated with restenting procedures. Further large-scale studies are warranted.3

Stent Thrombogenicity Early in High-Risk Interventional Settings Is Driven by Stent Design and Deployment and Protected by Polymer/Drug Coatings

Summary: Concern remains that stent thrombosis is a price paid for reducing restenosis, particularly with drug-eluting stents. Fear of clotting dictates procedural protocols, adjunctive medication, and device selection. We show that polymer/drug coatings reduce rather than increase thrombosis early after complex interventions and that stent design and deployment drive thrombogenicity. Thinner devices reduce clot formation, whereas coatings are protective, especially in malapposed and overlap scenarios. Indeed, thin polymer-coated devices exhibit low thrombogenicity even in the most complex settings. By defining clot relative to the flow regimes imposed by struts, our models further explain the lack of consensus in clinical trials that sought to correlate deployment and thrombosis. We show how well-apposed devices create flow separation upstream and downstream of struts and that clot potential tracks with these zones. As struts move off the wall, the flow-separation zones increase and then reduce as flow is restored beneath struts—clotting peaks and falls synchronous with flow alterations. With further displacement, strut-associated disturbances reemerge, eliciting a different pattern of thrombosis. When struts overlap, displaced struts impose a high-risk flow regime, and small changes in strut dimension or stent configuration elicit global changes in flow. Stent thrombosis differs with the nature of flow disruption, and clinical focus on design or deployment alone must give way to a broader context, considering their combined impact on flow. Given the inevitable variability in deployment, the choice of optimal design and/or antithrombotic therapies may now be dictated by these patterns of flow disruption.

Conclusions: Contrary to popular perception, drug/polymer coatings do not inherently increase acute stent clotting; they reduce thrombosis. However, strut dimensions and positioning relative to the vessel wall are critical factors in modulating stent thrombogenicity. Optimal stent geometries and surfaces, as demonstrated with thin stent struts, help reduce the potential for thrombosis despite complex stent configurations and variability in deployment.

Evaluation of the Second Generation of a Biodegradable Everolimus Drug-Eluting Vascular Scaffold for Treatment of De Novo Coronary Artery Stenosis: Six-Month Clinical and Imaging Outcomes

Summary: The first generation of the biodegradable everolimus drug-eluting vascular scaffold showed signs of shrinkage at 6 months, which largely contributed to late luminal loss. To maintain the mechanical integrity of the device up to 6 months, the scaffold design and manufacturing process of its polymer were modified. Forty-five patients successfully received a second-generation biodegradable everolimus drug-eluting vascular scaffold. One patient had postprocedural release of myocardial enzyme without Q-wave occurrence; 1 patient was treated 1 month later with a metallic drug-eluting stent. At the 6-month follow-up, quantitative coronary angiography disclosed 1 edge restenosis (in-segment binary restenosis, 2.4%). The backscattering of the polymeric struts did not decrease over time; the scaffold area was reduced by only 2.0% with intravascular ultrasound, and no change was noted with optical coherence tomography. The late lumen loss amounted to 0.19±0.18 mm, with a limited relative decrease in minimal luminal area of 5.4% on intravascular ultrasound. Optical coherence tomography showed at follow-up that 96.8% of the struts were covered and that malapposition was detected at follow-up in only 3 scaffolds. Mean neointimal growth measured by optical coherence tomography between and on top of the polymeric struts equaled 1.25 mm², or 16.6% of the scaffold area. A modified manufacturing process of the polymer and geometric changes in the polymeric platform have substantially improved the medium-term performance of the new generation of drug-eluting scaffold, making it comparable to that of current drug-eluting stents. The results constitute proof of concept that this device can adequately revascularize coronary vessels and prevent restenosis.

Conclusions: Modified manufacturing process of the polymer and geometric changes in the polymeric platform have substantially improved the medium-term performance of this new generation of drug-eluting scaffold to become comparable to those of current drug-eluting stents.
Editor’s Comment: Biodegradable stents are an attractive alternative to metallic stents because they provide the needed scaffolding during healing but are degraded over time, leaving the vessel to naturally remodel with return of vascular function and avoiding side branch occlusion, with improved imaging and rapid endothelialization, thus reducing late stent thrombosis. The initial biodegradable stent had a 24% decrease in lumen area due largely to vessel recoil. In addition, this new design demonstrated a low late loss, with 97% coverage with endothelium at 6 months. The stent performance is still less optimal than current metal stents and improvements in deliverability, and demonstration of equivalency or superiority to the new-third generation metallic drug-eluting stents is needed for wide spread acceptance.  

Outcomes

Previous Coronary Stent Implantation and Cardiac Events in Patients Undergoing Noncardiac Surgery

Summary: Patients treated with coronary stent implantation before undergoing noncardiac surgery appear to be at increased risk for adverse perioperative cardiac events. The period of risk and the influence of stent type on outcome remain to be determined in a large-scale multicenter study. To specifically address these issues, we performed a systematic, large-scale, retrospective cohort study in Scotland linking the national angioplasty registry with hospital admission data to examine outcomes in all patients treated with coronary stenting over a 4-year period who subsequently underwent noncardiac surgery (n=1953). Approximately 5% of patients underwent noncardiac surgery within 1 year of coronary stent implantation. Perioperative death and ischemic cardiac events were more common when surgery was performed within 6 weeks of stent implantation, especially when revascularization was performed after an acute coronary syndrome. For at least 2 years after coronary stent implantation, no difference in cardiac outcomes after noncardiac surgery was evident according to whether the initial stent was drug-eluting or bare metal. Our findings support current guideline recommendations that noncardiac surgery should be deferred for at least 4 to 6 weeks after implantation of a bare metal coronary stent. Although our findings suggest similar perioperative outcomes for patients treated with drug-eluting stents, further prospective large-scale studies are required before any change to the current guideline recommendations that noncardiac surgery be deferred for at least 6 to 12 months after drug-eluting stent implantation can be supported.

Conclusions: Patients undergoing noncardiac surgery after recent coronary stent implantation are at increased risk of perioperative myocardial ischemia, myocardial infarction, and death, particularly after an acute coronary syndrome. For at least 2 years after percutaneous coronary intervention, cardiac outcomes after noncardiac surgery are similar for both drug-eluting and bare metal stents.

Editor’s Comment: Just how to treat patients who require noncardiac surgery after stent implantation is an important clinical issue. Based on limited data, current guidelines recommend withholding such surgery for at least 4 to 6 weeks. In this large database analysis, death and ischemic events were more common if surgery was performed within 42 days of stent implantation, although other time points, such as 180 days, were not analyzed. Importantly, there was no excess in the incidence of adverse events between bare metal stents and drug-eluting stents.  

Very Long-Term (15 to 20 Years) Clinical and Angiographic Outcome After Coronary Bare Metal Stent Implantation

Summary: We previously reported that the long-term luminal response after coronary bare metal stenting is triphasic, with an early restenosis phase spanning the 6 months after the index procedure, an intermediate-term regression phase from 6 months to 3 years, and a late renarrowing phase beyond 4 years. However, the clinical significance of late luminal renarrowing remains unknown. Angiographic and clinical follow-up of the same cohort of 405 patients with successful Palmaz-Schatz stent placement was extended beyond 15 years. Clinical follow-up was completed in 98% of patients at 5 years and in 81% at 15 years. The incidence of death and cardiac death at 15 years was 48.4% and 20.6%, respectively. Paired long-term (4 to 10 years) and very long-term (>10 years) angiographic studies without intercurrent target lesion revascularization were performed in 55 lesions, and minimal luminal diameter further decreased from 1.88±0.50 mm to 1.60±0.73 mm (P<0.002). Late target lesion revascularization after initial stabilization of the stented segments occurred rarely within 4 years. Beyond 4 years, however, the incidence of late target lesion revascularization increased steadily from 3.3% at 4 years to 24.7% at 15 years. The incidence of definite very late stent thrombosis was low (1.5% at 15 years). Luminal renarrowing of the stented segment beyond 4 years was a progressive process extending beyond 10 years. The angiographic observation of late in-stent restenosis was clinically relevant because a corresponding progressive increase in the incidence of late target lesion revascularization was observed beyond 4 years and up to 15 to 20 years after bare metal stent implantation.

Conclusions: Luminal renarrowing of the stented segment beyond 4 years was a progressive process extending beyond 10 years. The angiographic observation of late in-stent restenosis was clinically relevant because a corresponding progressive increase in the incidence of late target lesion revascularization was observed beyond 4 years and up to 15 to 20 years after bare metal stent implantation.

Drug-Eluting or Bare Metal Stents for the Treatment of Saphenous Vein Graft Disease: A Bayesian Meta-Analysis

Summary: Observational studies and randomized trials have provided conflicting results regarding the potential benefits of drug-eluting stents (DES) for the treatment of saphenous vein graft (SVG) stenoses. Using bayesian meta-analysis, we tested whether DES compared with bare metal stents (BMS) in SVG interventions reduces death, myocardial infarction, target vessel revascularization (TVR), target lesion revascularization (TLR), or stent thrombosis. Bayesian methods, unlike standard methods, are able to provide inferences of direct clinical utility such as the probability that one intervention is better than another. We found no difference in mortality, myocardial infarction, or stent thrombosis with DES use compared with BMS. However, DES implantation significantly reduced major adverse cardiac events (death, myocardial infarction, and TVR), driven essentially by lower TVR rates. TLR was also significantly less frequent with DES implantation. This analysis suggests that DES implantation in SVG disease appears effective in reducing the need for repeat revascularization of SVG atherosclerotic lesions. DES are not associated with an important harm signal, but further data are needed.

Conclusions: In this study-level meta-analysis, the largest ever reported and the first using bayesian methods, the use of DES for the treatment of SVG disease reduces TVR and TLR procedures compared with BMS. Although there is no evidence to date to suggest increased rates of mortality, myocardial infarction, or stent thrombosis, further data are needed to address this safety issue.
Editor's Comment: SVG disease is one of the few lesion subsets for which inconclusive evidence exists regarding the efficacy and safety of DES compared with BMS. Available studies on DES for SVG disease individually are underpowered or nonrandomized. This meta-analysis performed using a bayesian approach to account for differences across studies provides strong support for the use of DES in SVG disease with clear superiority to BMS in terms of reducing TVR without a signal of harm.9

Impact of Angiographic Complete Revascularization After Drug-Eluting Stent Implantation or Coronary Artery Bypass Graft Surgery for Multivessel Coronary Artery Disease

Summary: The current guideline recommends complete revascularization (CR) with the use of percutaneous coronary intervention or coronary artery bypass grafting for stable patients with multivessel coronary disease because of its favorable long-term prognosis compared with the strategy of incomplete revascularization. However, in daily practice, CR is not always attempted because of hemodynamic instability, low ejection fraction, complex morphology, absence of objective ischemia, or preference for a minimally invasive procedure. In this regard, our study sought to investigate the benefit of CR with detailed angiographic analyses according to the Synergy Between PCI With Taxus and Cardiac Surgery classification for patients with multivessel disease undergoing percutaneous coronary intervention with drug-eluting stents or coronary artery bypass grafting. The major finding of our study was that CR, according to the varying definitions, did not improve clinical outcomes. Although the mechanism is not clear, the lack of association between CR and clinical prognosis may be closely related to the limitation of angiography to determine objective ischemia. In fact, recent clinical studies using fractional flow reserve, which is an invasive modality to determine objective ischemia in the tested epicardial coronary artery, demonstrated that the association between intermediate angiographic stenosis and functional ischemia is weak. Therefore, the strategy of angiographic CR might induce unnecessary procedures and subsequently fail to improve clinical outcome. Given this result and others with the use of invasive and noninvasive functional evaluations, an ischemia-guided procedure should be performed in treating patients with multivessel coronary disease.

Conclusions: Angiographic CR with drug-eluting stent implantation or coronary artery bypass grafting did not improve long-term clinical outcomes in patients with multivessel disease. This finding supports the strategy of ischemia-guided revascularization.

Editor's Comment: In current clinical practice, it remains unclear whether or not a complete revascularization strategy, based on angiographic findings alone, will lead to similar clinical outcomes as when there is incomplete angiographic revascularization. This study showed that after 5 years, regardless of whether patients were revascularized by percutaneous coronary intervention or coronary artery bypass graft surgery, there was no significant difference in survival or clinical outcomes between patients with complete and incomplete angiographic revascularization. These observations reveal that clinical decision-making regarding complete or incomplete revascularization should not rely on angiographic findings alone and should include a functional assessment of ischemia to determine the optimal revascularization strategy.9

Restenosis and Stent Thrombosis

Late and Very Late Drug-Eluting Stent Malapposition: Serial 2-Year Quantitative Intravascular Ultrasound Analysis

Summary: The long-term natural history of acquired stent malapposition continues to be a subject of concern. Among 250 lesions in which intravascular ultrasound data were available at the time of implantation and at the 6-month and 2-year follow-up examinations, acquired stent malapposition was identified in 19 (7.6%) at 6 months and in an additional 13 at 2 years (5.2%). Malapposition areas and volumes were correlated with the increases in the external elastic membrane (positive remodeling) throughout the study period, both in the group that had malapposition at 6 months and in those who had malapposition at 2 years. Furthermore, those lesions with malapposition at 6 months continuously progressed. Thus, acquired stent malapposition appears to be an ongoing process and is related to progressive vascular remodeling. Determination of the incidence of acquired malapposition must take into account the duration of follow-up.

Conclusions: Expansive vascular remodeling may play a role in the development and dynamic progression of acquired drug-eluting stent malapposition, not only during the first 6 months after implantation but thereafter.

Editor's Comment: Malapposition may be observed after incomplete stent expansion at the time of percutaneous coronary intervention or, in the case of drug-eluting stents, during follow up (acquired malapposition), presumably due to the antiproliferative drug, the polymer, or the combination. Severe malapposition is clearly hazardous, but clinicians are uncertain about the prevalence and significance of milder malapposition. This investigation is unique in that a substantial number of patients had serial intravascular ultrasound over a period of 2 years. More than 1 of 10 patients had malapposition, and, importantly, the process causing malapposition remained active. Also, once present, malapposition did not resolve. Although 2 of 19 patients had cardiac death, the study is far too small to augment our understanding as to the consequences of acquired malapposition.10

Mechanisms of In-Stent Restenosis After Drug-Eluting Stent Implantation: Intravascular Ultrasound Analysis

Summary: We used intravascular ultrasound (IVUS) to (1) clarify the mechanisms of luminal loss after drug-eluting stent (DES) implantation and (2) classify morphological patterns of in-stent restenosis (ISR). Overall, 76 lesions had IVUS-defined ISR: 32 (42%) had stent underexpansion (minimal stent area [MSA] <5 mm²); and 71 (93%) had intimal hyperplasia (IH) area >50% of stent area. Total stent length negatively correlated with MSA (r = −0.613, P<0.001) as well as with stent area at the minimum lumen site (r = −0.436, P<0.001) but not with minimum lumen area (r = −0.084, P=0.472). Underexpansion was present at the minimum lumen site in 15 of 43 (35%) lesions with stent length >28 mm, even though there was significant IH in 34 (79%) lesions; conversely, in 32 of 33 (97%) lesions with stent length ≤28 mm, the minimum lumen site was not associated with stent underexpansion but significant IH. IVUS-defined focal ISR was the most common (47%) pattern of ISR. Compared with focal ISR, normalized vessel, stent, lumen, and plaque volumes were smaller in diffuse and multifocal than focal ISR, with no difference in IH extent. The current study demonstrated that IH was the dominant mechanism of ISR in most DES restenosis. Nevertheless, underexpansion associated with longer stent length remained an important preventable mechanism of ISR.

Conclusions: In most DES restenosis, IH was the dominant mechanism of ISR. Nevertheless, underexpansion associated with longer stent length remained an important preventable mechanism of ISR.

Editor's Comment: Although DES inhibit neointimal proliferation, ISR requiring revascularization still occurs. This investigation, using IVUS in symptomatic patients with angiographic restenosis, highlights the contribution of two predominant mechanisms of restenosis, IH and stent underexpansion. The implications are several, including the potential use of IVUS to optimize initial stent deployment in long lesion (>28 mm) and to guide ISR treatment according to mechanism...
of stent failure. Prospective studies are needed to test the effectiveness of an IVUS-guided approach for the treatment of DES ISR.11

**Difference of Tissue Characteristics Between Early and Very Late Restenosis Lesions After Bare Metal Stent Implantation: An Optical Coherence Tomography Study**

**Summary:** Recent reports have demonstrated that late restenosis occasionally was observed several years after bare metal stent implantation. However, the mechanisms of this late luminal narrowing have not been clarified. Optical coherence tomography, a high-resolution intravascular imaging modality, can serve as a useful adjunct to visualize microscopic structures of the coronary artery. We compared optical coherence tomography findings between very late and early restenotic tissue after bare metal stent implantation. Very late in-stent restenosis lesions demonstrated predominantly a heterogeneous pattern, whereas restenotic tissue in early in-stent restenosis lesions is predominantly homogeneous. These findings suggest different mechanisms between very late and early restenosis after bare metal stent implantation. Very late in-stent restenosis of bare metal stents may be a manifestation of atherosclerotic disease progression.

**Conclusions:** The morphological characteristics of restenotic tissue in very late in-stent restenosis were different from those in early in-stent restenosis and similar to atherosclerotic plaque. In bare metal stents, progression of the atherosclerotic process within neointima after stent implantation may be associated with very late in-stent restenosis.

**Editor's Comment:** This study used high-resolution intracoronary imaging with optical coherence tomography to examine plaque morphology in areas of luminal narrowing within bare metal stents. The observed difference in tissue type according to time from stenting, with findings consistent with atherosclerosis in lesions with very late in-stent restenosis, is novel. The development of plaques with the potential for rapid growth or rupture may explain the rare but observed occurrence of very late stent thrombosis in bare metal stents. The clinical implications of this imaging finding deserve further study.12

**Predicting Restenosis of Drug-Eluting Stents Placed in Real-World Clinical Practice: Derivation and Validation of a Risk Model From the EVENT Registry**

**Summary:** Prediction of restenosis after percutaneous coronary intervention (PCI) remains challenging because existing risk assessment algorithms were developed before widespread adoption of drug-eluting stents (DES). Identifying patients at high risk of DES restenosis would provide clinicians with an opportunity to select therapeutic options best tailored for the individual patient (eg, choosing medical therapy or bypass surgery versus PCI, number of lesions to revascularize, and type of stent to implant). We therefore used a large multicenter registry of contemporary PCI to identify predictors of clinically driven target lesion revascularization (TLR) among 8829 DES patients treated in “real-world” clinical practice between 2004 and 2007. We then constructed a risk score for TLR and tested the model for predictive accuracy in a separate population. At 1-year follow-up, TLR occurred in 4.2% of patients. Using multivariable logistic regression, we identified 6 predictors of TLR at 1 year: age <60, prior PCI, unprotected left main PCI, saphenous vein graft PCI, minimum stent diameter ≤2.5 mm, and total stent length ≥40 mm. There was a >3-fold difference in TLR rates between the lowest risk category (score = 0; TLR rate, 2.2%) and the highest risk category (score ≥5; TLR rate, 7.5%). In conclusion, the overall incidence of clinically driven TLR remains low (<5%) among unselected patients receiving DES in routine clinical practice. A simple risk model incorporating 6 readily available clinical and angiographic variables helps provide important patient-centered estimation of risk for clinical restenosis in the 12 months after DES placement—particularly for those individuals at low (~2%) and modestly elevated (>7%) risk of TLR.

**Conclusions:** The overall incidence of TLR remains low among unselected patients receiving DES in routine clinical practice. A simple risk model incorporating 6 readily available clinical and angiographic variables helps identify individuals at extremely low (<2%) and modestly increased (>7%) risk of TLR after DES implantation.

**Editor's Comment:** The ability to estimate the need for clinically driven TLR for restenosis after PCI with DES has several potential applications. Despite overall very low rates of TLR, this study demonstrated that a risk model incorporating 6 variables provided discrimination of risk. Awareness of TLR risk may influence the recommended mode of revascularization; however, low TLR rates in even the highest-risk patients suggest that PCI with DES is probably suitable in the majority of patients. Validated risk models as described in this study can be used to risk-adjust PCI outcomes in quality improvement programs.13

**Frequency and Predictors of Stent Thrombosis After Percutaneous Coronary Intervention in Acute Myocardial Infarction**

**Summary:** The prospective, multicenter, randomized Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial included 3602 patients with ST-segment elevation–myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) who were randomly assigned to heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy. Stents were implanted in 3202 patients, including 2261 who received drug-eluting stents and 861 who received only bare metal stents. Definite or probable stent thrombosis within 2 years occurred in 4.4% of patients, including 0.9% acute events, 1.6% subacute events, 1.0% late events, and 1.1% very late events. The 2-year cumulative rates of stent thrombosis were similar with both drug-eluting stents and bare metal stents, as well as in patients randomly assigned to bivalirudin monotherapy versus heparin plus glycoprotein IIb/IIIa inhibitor. Acute stent thrombosis occurred more frequently in patients assigned to bivalirudin compared with heparin plus a glycoprotein IIb/IIIa inhibitor, whereas stent thrombosis after 24 hours occurred less frequently in patients with bivalirudin compared with heparin plus a glycoprotein IIb/IIIa inhibitor. Prerandomization heparin and a 600-mg clopidogrel loading dose were independent predictors of reduced acute and subacute stent thrombosis, respectively. Optimizing adjunct pharmacology, including early antithrombin therapy and preloading with a potent antiplatelet therapy, may further reduce stent thrombosis in STEMI, thereby improving event-free survival in these high-risk patients.

**Conclusions:** Stent thrombosis is not uncommon within the first 2 years after primary PCI in STEMI and occurs with similar frequency in patients receiving drug-eluting stents versus bare metal stents and bivalirudin alone versus heparin plus a glycoprotein inhibitor. Optimizing adjunct pharmacology, including early antithrombin therapy preloading with a potent antiplatelet therapy, may further reduce stent thrombosis in STEMI.

**Editor's Comment:** There is an increased risk of stent thrombosis when stents are implanted during PCI for STEMI as compared with PCI procedures performed electively. This observation has raised concern about the type of stent (bare metal versus drug-eluting) that should be implanted in STEMI PCI. This study found that when implanted in patients pretreated with a loading dose of 600 mg clopidogrel, drug-eluting stents do not appear to increase the rate of stent thrombosis in STEMI patients. Thus, the presence of STEMI should not influence stent selection. Although bivalirudin monotherapy was shown to decrease the risk of access site bleeding, this benefit may occur at the cost of an increased risk of acute stent thrombosis.14
Optical Coherence Tomographic Analysis of In-Stent Neoatherosclerosis After Drug-Eluting Stent Implantation

Summary: We report the findings from optical coherence tomography (OCT) of in-stent neatherosclerosis as a cause of drug-eluting stent failure. OCT was performed in a total of 50 lesions with angiographic in-stent restenosis (30 stable and 20 unstable angina). OCT-defined thin-cap fibroatheroma (TCFA)-containing neointima, thrombi, and neointimal rupture were identified in lesions with significant intimal hyperplasia (>50% of stent area). Median follow-up time was 32 months. Overall, 26 lesions (52%) had in-stent TCFA-containing neointima, and 29 (58%) had neointimal rupture. Patients presenting with unstable angina showed a thinner fibrous cap (55 μm [interquartile range, 42 to 105] versus 100 μm [interquartile range, 60 to 205], \( P = 0.006 \)) and higher incidence of TCFA-containing neointima (75% versus 37%, \( P = 0.008 \)), intimal rupture (75% versus 47%, \( P = 0.044 \)), thrombi (80% versus 43%, \( P = 0.010 \)), and red thrombi (30% versus 3%, \( P = 0.012 \)) than those presenting with stable angina. Fibrous cap thickness negatively correlated with follow-up time (\( r = -0.318, P = 0.024 \)). Compared with stenting <20 months after implantation (the best cutoff to predict TCFA-containing neointima), stenting 20 months after implantation had a higher incidence of TCFA-containing neointima (69% versus 33%, \( P = 0.012 \)) and red thrombi (27% versus 0%, \( P = 0.007 \)). Postintervention creatine kinase-MB was significantly higher in intimal rupture versus no intimal rupture (\( P = 0.025 \)). The rate of agreement between grayscale intravascular ultrasound and OCT for detecting intimal rupture was 50% and for detecting thrombus was 44%. In the virtual histology intravascular ultrasound subgroup (n = 32), the agreement between virtual histology intravascular ultrasound and OCT for identifying TCFA-containing neointima was 78%. Thus, in-stent neoatherosclerosis may be an important mechanism of drug-eluting stent failure, especially late after implantation.

Conclusions: In-stent neatherosclerosis may be an important mechanism of drug-eluting stent failure, especially late after implantation.

Editor’s Comment: Neointimal formation associated with drug-eluting stent in-stent restenosis and device failure has remained incompletely described, owing to the resolution limitations associated with conventional intravascular imaging modalities. In this study, the authors use OCT imaging to demonstrate the presence of at least 1 OCT-defined TCFA in 52% of lesions. The implication of this study is that drug-eluting stent in-stent restenosis has a complex phenotype that shares characteristics with de novo atherosclerosis. It also indicates that intravascular imaging techniques with advanced resolution, such as OCT, are required to delineate the composition of these in-stent neointima. Future longitudinal studies will be needed to follow the progression of these neointima and determine the effectiveness of therapies to limit their progression.

Technical Considerations

In Vitro and Human Studies of a 4F Double-Coaxial Technique (“Mother-Child” Configuration) to Facilitate Stent Implantation in Resistant Coronary Vessels

Summary: Small-sized 6F guiding catheters are now commonly used as the standard in percutaneous coronary intervention. When treating severely calcified and/or tortuous lesions, however, stent delivery is often difficult with a 6F guiding catheter because of limited backup support. A 4F child guiding catheter that can be inserted into 6F or larger conventional guiding catheters has been recently developed. The use of the 4F child catheter in combination with a 6F mother-guiding catheter (the so-called mother-child technique) may improve the delivery of coronary stents in treating complex coronary lesions. In the present study, quantitative measurements using a coronary tree model showed improved backup force and deliverability of the 4-in-6 mother-child guiding systems. We demonstrated the successful application of this system in treating complex coronary lesions in which conventional techniques had been unsuccessful for stent delivery. The 4F mother-child system may be a viable alternative to conventional techniques in treating complex coronary lesions.

Conclusions: With the superior trackability of the 4F child catheter and with increased backup support of the mother-child system, the 4F mother-child system provided >90% success rate for lesions in which conventional techniques had failed. The 4F mother-child system may become a viable alternative to conventional techniques in treating complex coronary lesions.

Editor’s Comment: The mother and child technique with a 4-in-6 system provides an alternative approach to stent delivery in complex lesions. The ability to increase backup support without the use of a larger, 7F or 8 F, guiding catheter is an important advantage of the technique in cases done through the radial approach or in patients at high risk for access site complications. Operators adopting this technique must be cognizant of the potential for stent dislodgment and the limitations of the system with respect to device compatibility within the 4F catheter.

Randomized Comparison of Final Kissing Balloon Dilatation Versus No Final Kissing Balloon Dilatation in Patients With Coronary Bifurcation Lesions Treated With Main Vessel Stenting: The Nordic-Baltic Bifurcation Study III

Summary: The 1-stent bifurcation stenting approach with stenting of the main vessel and optional side branch stenting using drug-eluting stents is the preferred strategy to treat coronary bifurcation lesions. It is unknown whether a successful main vessel stenting procedure should be finalized by a simultaneous kissing balloon dilatation (FKBD). In the present study, 477 patients with successful main vessel stenting were randomly assigned to FKBD versus no FKBD. The 6-month rates of major adverse cardiac events (cardiac death, non-procedure-related index lesion myocardial infarction, target lesion revascularization, or stent thrombosis) were similar and low in the study groups. FKBD reduced angiographic side-branch (re)stenosis, especially in patients with true bifurcation lesions. The simple no-FKBD procedures resulted in reduced use of contrast media and shorter procedure and fluoroscopy times. FKBD may be recommended in genuine bifurcation lesions treated with main-vessel stenting but may be avoided in bifurcations without side branch stenosis. Long-term data on stent thrombosis are needed.

Conclusions: Main-vessel stenting strategies with and without FKBD were associated with similar clinical outcomes. FKBD reduced angiographic side-branch (re)stenosis, especially in patients with true bifurcation lesions. The simple no-FKBD procedures resulted in reduced use of contrast media and shorter procedure and fluoroscopy times. Long-term data on stent thrombosis are needed.

Editor’s Comment: Bifurcation lesions are common, and percutaneous coronary intervention is technically challenging and results in worse outcomes. Randomized trials have demonstrated that a simple technique using 1 stent with provisional stenting of the side branch is preferred and results in lower rates of periprocedural myocardial infarction, less contrast, and shorter procedure times. It has also been common to perform a final kissing balloon to optimally dilate both vessels and avoid plaque shift. This study evaluated the outcomes after a final kissing balloon or not and found that major adverse cardiac events were not different between the groups at 6 months. However, in those with true bifurcation lesions, restenosis was better in the side branch when final kissing balloon inflation was done. These results suggest that selective use of FKBD is the best strategy to use when significant disease exists in the side branch and plaque shift would be expected to cause significantly greater restenosis.
Randomized Trial of Simple Versus Complex Drug-Eluting Stenting for Bifurcation Lesions: The British Bifurcation Coronary Study: Old, New, and Evolving Strategies

Summary: Treatment of bifurcation coronary lesions generates much debate. The British Bifurcation Coronary Study: Old, New, and Evolving Strategies study recruited 500 patients with coronary bifurcation lesions and randomly allocated them to either a simple strategy (main-vessel stenting with or without kissing balloon dilatation/T stenting) or a complex strategy (complete lesion coverage with either crush or cutout stenting plus mandatory kissing balloon dilatation). Clinical follow-up of these 2 groups to 9 months showed an 8% major adverse event rate in the simple group versus a 15% major adverse event rate in the complex group. This difference was largely driven by periprocedural myocardial infarction. The study therefore suggests that the usual strategy for the majority of bifurcation lesions should be the simple provisional strategy and that more complex strategies should be reserved for more complex anatomies, involving perhaps large side branches with significant length ostial side-branch disease.

Conclusions: When coronary bifurcation lesions are treated, a systematic 2-stent technique results in higher rates of in-hospital and 9-month major adverse cardiovascular events. This difference is largely driven by periprocedural myocardial infarction. Procedure duration is longer, and x-ray dose is higher. The provisional technique should remain the preferred strategy in the majority of cases.

Editor’s Comment: Bifurcation lesions continue to be a technical challenge and in many studies are associated with worse long-term outcomes, including restenosis. A simple single-stent technique is easier, but long-term advantages have been mixed. This study randomly assigned patients to a simple or complex strategy. Unlike prior studies, the vast majority were true bifurcation lesions. Outcomes were superior in the simple group, and this was largely due to a reduction in periprocedural myocardial infarction. This trial supports the findings of the Nordic Bifurcation Study, and together they provide strong evidence for a simple approach with bailout stenting for the side branch only when flow is severely reduced.18

References