CORONARY STENTS AND SURGERY: A DANGEROUS COMBINATION

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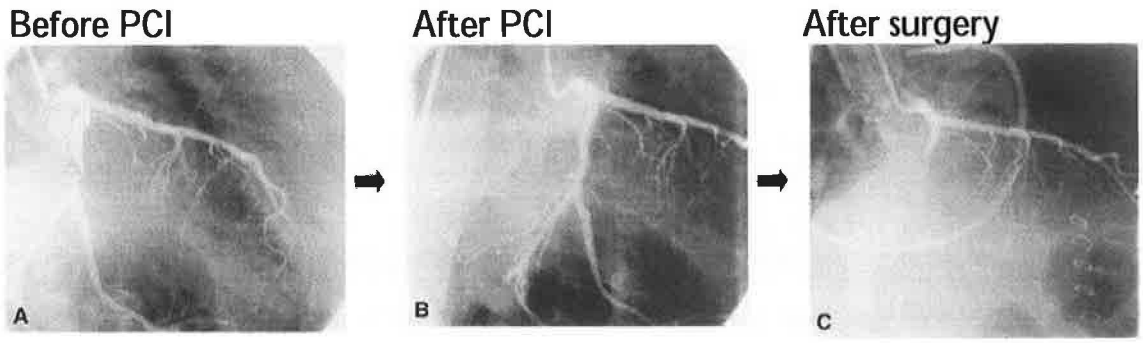

Figure 1. Excellent angiographic result (B) after stenting of a proximal circumflex lesion (A), followed by stent thrombosis (C) after non-cardiac surgery.

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Abbreviations

AMI = acute myocardial infarction

BMS = bare metal stent

CAD = coronary artery disease

CARP = Coronary Artery Revascularization Prophylaxis trial

DES = drug-eluting stent

IVUS = intravascular ultrasonography

PCI = percutaneous coronary intervention

PES = paclitaxel-eluting stent

SES = sirolimus-eluting stent

ST = stent thrombosis

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Coronary revascularization before non-cardiac surgery may decrease the peri- and post-operative risk in selected patients.[1] Stents are currently utilized in the majority of percutaneous coronary interventions (PCI) because they increase procedural success and decrease restenosis.[2] A rare but severe complication after coronary stent implantation is stent thrombosis (ST). Stent thrombosis is a highly morbid event; more than half of patients with stent thrombosis either die or suffer a Q-wave infarction.[3]

Stent thrombosis has been reported to be greatly increased in patients who undergo surgery (cardiac or non-cardiac) early after stent placement. Most of the information available on ST in the perioperative setting is based on studies of bare metal stents (BMS). There are limited data on the safety of drug-eluting stent (DES) placement shortly before surgery, even though the latter are currently used in >90% of PCI in the USA.[4] The goal of the current review is to summarize the known information on the incidence, risk factors, prevention, and treatment of perioperative coronary (bare metal or drug-eluting) ST.

1. Stent Thrombosis: risk factors and clinical implications

Stent thrombosis occurs in approximately 1% of patients who receive bare metal stents, usually in the first few days after implantation.[5] The frequency of DES stent thrombosis has been examined not only in randomized trials, which usually have narrow inclusion criteria, but also in much larger registries in which a far broader population of patients has been enrolled. Moreno et al did a meta-analysis of 10 DES trials and found similar rates of stent thrombosis in DES (0.58%) and BMS (0.54%) during a follow-up of 6-12 months.[6] In a US series of 2974 DES patients, stent thrombosis occurred in 1.27%.[7] ST occurred acutely (within 24 hours of placement) in 5 patients, subacutely (between 2 and 30 days) in 25 patients, and late (>30 days) in 8 patients. Iakovou reported that 14 of 2229 consecutive patients undergoing DES implantation in Italy and Germany developed subacute (0-30 days) stent thrombosis, and 15 (0.7%) developed late (>30 days) stent thrombosis.[3] In an Argentina series of 225 DES patients, stent thrombosis occurred in 3.1%.[8] Late (>1 month) stent thrombosis is rare and may be more frequent in patients receiving DES: between 6 and 18 months of follow-up in the BASKET trial, compared to BMS, DES patients had a higher incidence of cardiac death and myocardial infarction (4.9% vs. 1.3%, $p = 0.01$).

Stent thrombosis carries high mortality and morbidity: >50% of the patients either have a myocardial infarction or die.[5] Stent thrombosis is associated with (a) suboptimal angiographic result, [5,9-11] (b) specific coronary lesion subsets (such as small vessels[12-14] and bifurcations[3]), (c) high-risk patient groups (such as patients with diabetes, renal failure,[3] or acute coronary syndromes[15]) and (d) early cessation of dual antiplatelet therapy with aspirin and a thienopyridine.[3,16,17] Obtaining a good angiographic result, and administering dual antiplatelet therapy (currently aspirin and clopidogrel) are the cornerstones of stent thrombosis prevention.

2. Perioperative Myocardial Infarction

Acute myocardial infarction occurs in 1-4% of patients undergoing surgery.[18,19] The MI risk is proportionate to the presence and severity of coronary artery disease (CAD),[19] and also depends on the type of surgery, with vascular surgery having the highest risk.[18] Surgery may trigger MI by increasing sympathetic discharge[20] and by causing a prothrombotic state.[21] Treatment of perioperative MI may be challenging, since thrombolytics are usually contraindicated and percutaneous coronary intervention may carry increased bleeding risk. This is why medical therapy may be preferred, especially if the patient is hemodynamically stable.

Our review will focus on a special case of perioperative MI, ie MI occuring in patients who have undergone prior coronary stent implantation and develop perioperative stent thrombosis.

3. Surgery after stent implantation

3.1 Bare Metal Stents (BMS)

The first paper that described the high risk of surgery early after stenting was published by Kaluza et al in 2000.[22] In a study of only 40 patients, these investigators reported that 8 of the 25 patients undergoing non-cardiac surgery within two weeks of BMS placement died (32%, 95% CI 15, 54). In contrast, none of the 15 patients who underwent surgery 15-39 days after stenting died. Six of the 8 deaths were due to acute myocardial infarction (AMI) and 2 were due to bleeding.[22] A total of 7 patents had AMI (which was either confirmed or likely related to stent thrombosis in all cases), and 6 of them died. Three of the 5 patients who were operated while taking ticlopidine died, 1 from bleeding and 2 from MI and bleeding.

Wilson et al reviewed a much larger population of 207 patients undergoing surgery within 2 months after bare metal stenting at the Mayo Clinic.[23] Only 8 patients (3.9%, 95% CI 1.7, 7.5) died or suffered an AMI or stent thrombosis.[23] In that study, all events occurred in the 168 patients who had surgery within the first six weeks after stent placement. The event rate ranged from 3.8-7.1%, much lower than the 32% mortality when surgery occurred in the two weeks after stent placement in the study by Kaluza and colleagues. In the Mayo study, no adverse events occurred in the 39 patients undergoing surgery 7-9 weeks after stenting.

Sharma et al analyzed the outcome of 27 patients who underwent non-cardiac surgery within 3 weeks following BMS implantation.[24] In 7 patients the thienopyridine was stopped for >5 days and 6 of those patients (86%) died. Death was sudden in 2 patients, due to a Q-wave MI in 3 patients, and due to cardiogenic shock in 1 patient. Stent thrombosis was demonstrated angiographically in 1 of the 6 patients. In contrast, only 1 of the 20 patients (5%) who underwent non-cardiac surgery within 3 weeks from

stent implantation and continued to take a thienopyridine had sudden death (P<0.001 for comparison between patients continued on a thienopyridine vs those not continued). Bleeding occurred with similar frequency in the 2 groups (44% in the 7 patients in whom the thienopyridine was stopped before surgery vs 25% in the 20 patients in whom the thienopyridine was continued through surgery). Sharma et al also reported on 20 patients who underwent surgery 3 weeks to 3 months post stenting (70% of those patients received a thienopyridine); only 1 of these 20 patients died, and 2 suffered a non-ST elevation myocardial infarction).

Reddy et al reported thrombotic events or major bleeding in 3 of 8 (38%) patients undergoing non-cardiac surgery within 14 days of BMS implantation, in 5 of 8 (63%) patients undergoing surgery between 15 to 42 days after stenting, and in 0 of 40 patients who underwent surgery >42 days after stenting.[25]

Finally, Vicenzi et al reported a high incidence of adverse cardiac events (43%) in 103 patients undergoing surgery after stent deployment, however stent thrombosis was documented in only 8 patients, and the time course of stent thrombosis, the type of stents used, and the administration of antiplatelet therapy in those patients were not provided in their report.[26]

The above BMS studies have appropriately increased attention to the potential risks of surgery early after stent implantation.

3.2. Drug-eluting stents (DES)

Even though there are no large studies, there are several case reports and case series of DES thrombosis both early and late after surgery.

3.2.1 Early DES perioperative stent thrombosis: <6 months post implantation

A patient underwent surgery for meniscopathy at the left knee 3 months after implantation of 2 paclitaxel-eluting stents in the circumflex and one bare metal stent in the right coronary artery. Aspirin and clopidogrel were stopped before surgery. Circumflex stent thrombosis occurred 2 hours after surgery and was treated with primary PCI.[27]

Another patient was found to have breast cancer after implantation of 2 sirolimus-eluting stents (LAD, circumflex), and one bare metal stent (OM). Clopidogrel and aspirin were stopped 10 weeks post stent implantation and the patient was started on enoxaparin, which was stopped the day before planned breast surgery. The following morning before surgery the patient developed LAD and circumflex stent thrombosis requiring emergency PCI.[28]

Similarly, a patient underwent sirolimus-stent implantation and then required surgery for cancer recurrence 77 days post stent implantation; stent thrombosis ensued.[29]

A 44-year-old woman developed stent thrombosis after hysterectomy done 2 weeks post sirolimus-eluting stent implantation, even though aspirin and clopidogrel were continued until the day before surgery.[30]

3.2.2 Late DES perioperative stent thrombosis: >6 months post implantation

Late stent thrombosis occurs more frequently with DES compared to BMS and has been a source of concern.

McFadden reported stent thrombosis occurring during the perioperative period in 3 patients after 343-442 days from implantation.[31] A 66-year-old man developed LAD paclitaxel-eluting stent thrombosis 343 days after stenting and 5 days after aspirin was discontinued for elective resection of bladder polyps. A 73-year-old man had LAD paclitaxel-eluting stent thrombosis 442 days after stenting after colon cancer resection; aspirin had been stopped one week earlier. A 62-year-old man had LAD sirolimus-eluting stent thrombosis 335 after stenting and 4 days after aspirin and clopidogrel were stopped in preparation for colonoscopy and polypectomy. This patient also had a bare metal stent in an obtuse marginal branch that was patent.

Two of the above patients were among seven of 2006 patients (0.35%) having late angiographic stent thrombosis in a large single-center series (one patient had thrombosis twice).[16] Three stent thromboses occurred with sirolimus-eluting stents (at 2, 25, and 26 months) and five with paclitaxel-eluting stents (at 6, 7, 8, 11, and 14.5 months). None of the patients developed late stent thrombosis while taking dual antiplatelet therapy (aspirin and clopidogrel): five patients were only on aspirin and 3 patients were on no antiplatelet therapy.

In a single center (Dallas VA Medical Center) series of 38 patients who underwent 41 major and 18 minor non-cardiac surgeries after a median of 9 months from successful DES implantation no major adverse cardiac event or death occurred during or after the 41 major (0%, 95% confidence intervals 0-9%), and the 18 minor non-cardiac surgeries (0%, 95% confidence intervals 0-19%).[32]

4. Treatment of coronary disease in patients who need surgery

Frequently patients with coronary artery disease are referred to cardiologists for preoperative clearance or optimization of their cardiac status prior to surgery. One of the main question about those patients is whether they need preoperative revascularization. As discussed below, the answer to this question for the vast majority of patients may be no.

4.1 No revascularization

According to the ACC/AHA guidelines, surgical revascularization is rarely done just to get the patient through surgery, but is most often done for its potential long-term benefits. Partly because of the lack of clinical studies, there has been significant disagreement even among cardiologists about the necessity of revascularization before elective surgery.[33]

Until recently, no randomized-controlled study had examined whether revascularization offers any benefit before non-cardiac surgery. A retrospective study of 1961 Coronary Artery Surgery Study (CASS) participants undergoing high-risk surgery, demonstrated that prior coronary artery bypass surgery was associated with fewer postoperative deaths (1.7% versus 3.3%, P=.03) and myocardial infarctions (0.8% versus 2.7%, P=.002) compared with medically managed coronary disease.[34]

In December 2004 the results of the first and only such trial, the Coronary Artery Revascularization Prophylaxis (CARP) trial were published.[35,36] A total of 510 stable patients with at least single vessel angiographic coronary artery disease (33% had 3-vessel disease, but patients with significant left main disease, unstable coronary syndromes, and severe cardiomyopathy were excluded) were randomized to revascularization vs no revascularization before undergoing major vascular surgery (33% abdominal aortic aneurysm repair and 67% lower extremity revascularization). Revascularization was accomplished with coronary bypass surgery in 41% and with PCI in 59%. Patients who underwent revascularization had similar incidence of postoperative AMI and long-term survival (mean follow-up was 27 months) with those who did not undergo revascularization. This could have been due to excellent perioperative management in both groups (86% received b-blockers and approximately half received statins), but nevertheless suggests that revascularization may not benefit patients undergoing non-cardiac surgery.

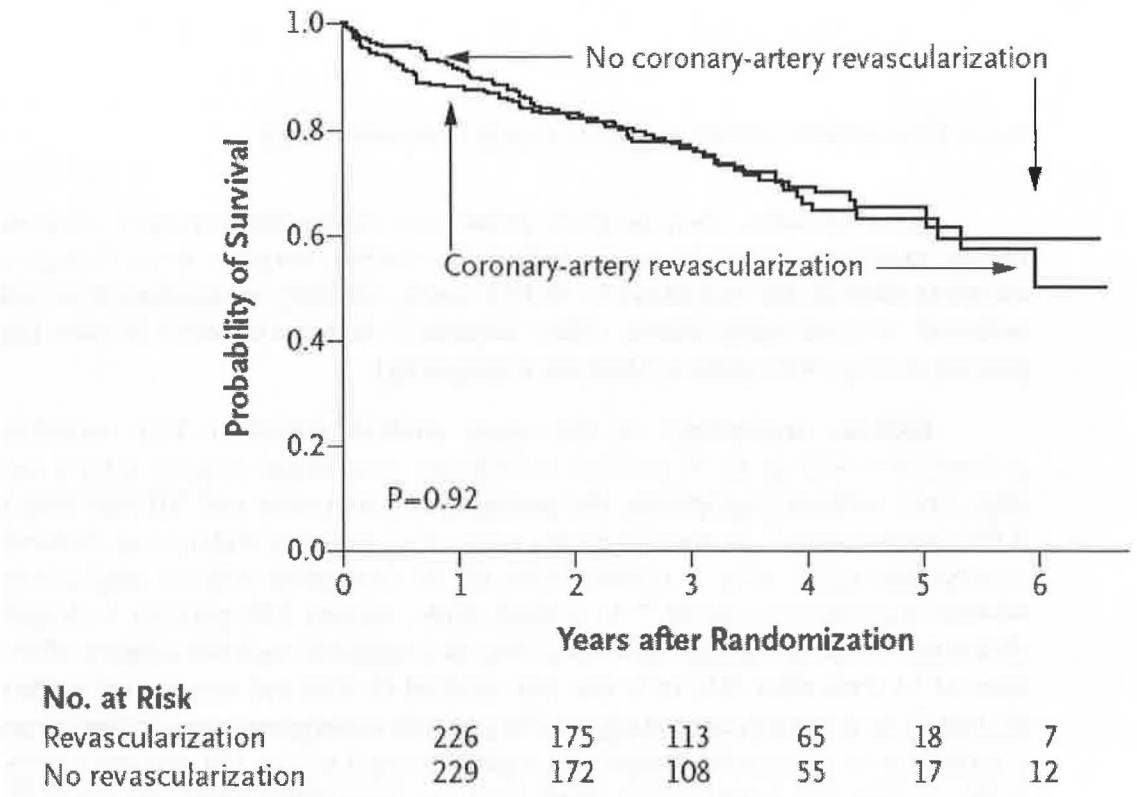

Figure 2. Long-term survival in the CARP trial.

Therefore, if a patient is known to require surgery in the near future, the first question to ask is whether the patient really needs revascularization. The CARP study results suggest that revascularization may not be necessary for a large number of those patients without unstable coronary syndromes or other very high risk features, such as severe arrhythmias, severe valvular disease, or severe myocardial or left main disease.

4.2 Revascularization

4.2.1 Revascularization without stents (balloon only)

Some patients, such as those presenting with acute coronary syndromes, may require coronary revascularization before non-cardiac surgery. Even though stents are currently used in the vast majority of PCI cases, coronary revascularization can also be achieved without using stents, either surgically (coronary artery bypass grafting) or percutaneously (with plain old balloon angioplasty).

Balloon angioplasty is the most studied non-stent PCI modality in the perioperative setting. In 50 patients undergoing non-cardiac surgery after a median of 9 days from balloon angioplasty, the postoperative mortality and MI rate was 1.9% and 5.6%, respectively.[37] In another study, none of 14 patients undergoing abdominal aortic aneurysmorrhaphy after a median time of 10 days after balloon angioplasty had an adverse postoperative event.[38] In a third study, among 194 patients undergoing aortic abdominal surgery, carotid endarterectomy or peripheral vascular surgery after a median time of 11 days after BA, only one patient died (0.5%) and one patient suffered an MI (0.5%).[39] In a retrospective study of 350 patients undergoing non-cardiac surgery within 2 months after successful balloon angioplasty only 3 of the 350 patients (0.9%, 95% CI 0.2% - 2.5%) had perioperative death (n=1) or myocardial infarction (n=2).[40] All three were among the 188 patients (1.6%, 95% CI 0.3%-4.6%) undergoing surgery within two weeks of balloon angioplasty. Target vessel revascularization is more likely to be needed after balloon angioplasty than after stenting, but the risk of arterial thrombosis is probably lower than the risk of patients who have received stents and undergo non-cardiac surgery.

These data suggest that balloon angioplasty may be safer than stenting prior to noncardiac surgery, if an adequate result can be achieved, in patients undergoing non-cardiac surgery early (within 4-6 weeks) after revascularization, at which time even a bare metal stent has not yet been reendothelialized. However, balloon angioplasty may result in a suboptimal angiographic result, and coronary stent placement is needed in 10-25% of patients who achieve an adequate initial result.

According to the 2002 ACC/AHA guidelines on perioperative cardiovascular care "there is uncertainty regarding how much time should pass before non-cardiac surgery is performed" for patients who had balloon angioplasty.[1] Delaying non-cardiac surgery for > 6-8 weeks was discouraged, because of increased risk for restenosis resulting in perioperative ischemia or MI. However, performing non-cardiac surgery too early after the PCI may also be risky, since acute or subacute closure following balloon angioplasty usually occurs within hours or few days after the procedure. Accordingly, delaying surgery "for at least a week after balloon angioplasty to allow for healing of the vessel injury at the balloon treatment site has theoretical benefits".

4.2.2 Revascularization with bare metal stents

Sometimes stenting cannot be avoided during PCI, either because of the complexity of the lesion or because of a suboptimal balloon angioplasty result. Choice of the type of stent to be used depends heavily on the timing of surgery:

If surgery needs to be performed within 6 months of revascularization, then implantation of a bare metal stent may be preferable to implantation of a DES, since BMS endothelialize more rapidly and may therefore carry a lower risk of stent thrombosis. If restenosis, which is 3-4 times more likely to occur after BMS than DES, does develop, it almost always does so more than 2-3 months after stent placement, at which point the patient will have already undergone the surgical procedure. At that time, a DES can be placed within the BMS, which is the best treatment for in-stent restenosis.

4.2.3 Revasculatization with covered stents

Several covered stents are currently commercially available, such as heparin-coated and antiproliferative drug-eluting stents.

Heparin-coated stents could be an attractive option in patients known to need surgery. In one study of 200 patients the 1-month risk of heparin-coated stent thrombosis was low (1%) even though only aspirin without clopidogrel was used.[41] Yet, the randomized and non-randomized trials, though underpowered, have not indicated a reduction in stent thrombosis with either commercially available form of heparin stent coating compared with BMS placement.[42,43]

If surgery can be delayed until after 6 months, then a DES can be used, keeping in mind that there may remain a risk for stent thrombosis even >1 year after DES implantation, which is believed (though not proven) to be greater than with BMS.[31] It would seem important, though it is not proven, to use a sirolimus eluting stent (which requires at least 3 months of clopidogrel after placement to prevent stent thrombosis in patient not undergoing surgery[44]) than a paclitaxel-eluting stent (which requires at least 6 months of clopidogrel)[45], although little is known about the safety and risk of stent thrombosis shortly after a 3 and 6 months duration of clopidogrel in sirolimus-eluting, or paclitaxel-eluting stents, respectively.

In the future new stent types will likely be available that hold the promise of minimizing the risk of stent thrombosis, such as bioabsorbable stents[46] (magnesium oxide [47] and poly-l lactic acid stents[48]), or antibody-coated stents[49] that can attract endothelial progenitor cells and re-endothelialize more rapidly.

Regardless of the type of stent used, every effort should be made to obtain optimal stent deployment, which could help reduce the risk of stent thrombosis.[9,10] Overlap of drug-eluting stents should be avoided, since overlap areas may have

significantly delayed endothelialization.[50,51] Finally, patients who undergo surgery after stent implantation will also need further management as discussed in chapter 5.

5. Approach to the patient who underwent stent implantation and now needs unplanned surgery

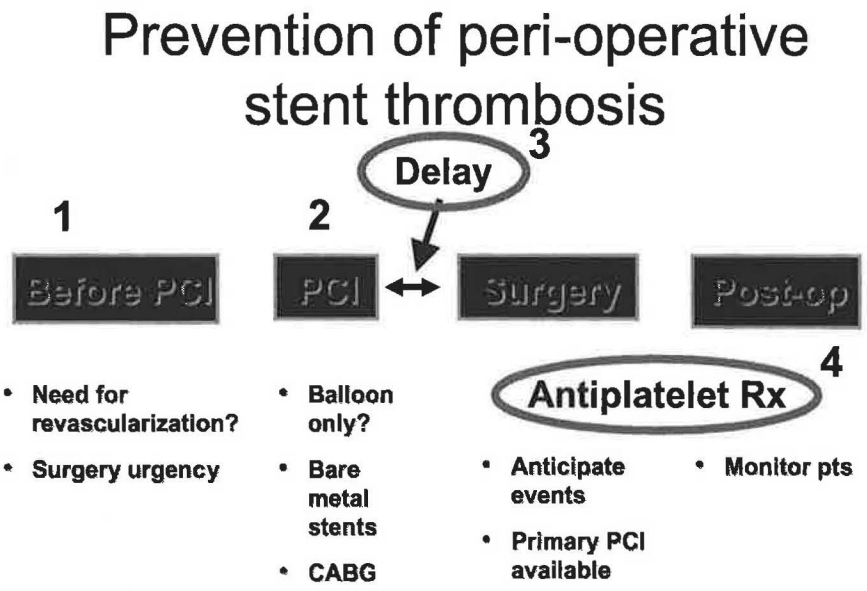

Figure 3: strategies to prevent peri-operative stent thrombosis: (1) do not revascularize, (2) revascularize but do not stent, (3) delay surgery, and (4) continue or minimize interruption of aspirin and clopidogrel in the perioperative period.

5.1 Delay surgery

As described in section 3, the earlier surgery occurs after stenting, the higher the risk for stent thrombosis. This applies to both bare metal[22-25] and drug eluting stents[32].

The 2002 ACC/AHA guidelines on perioperative cardiovascular care state that if (bare metal) stenting is performed prior to non-cardiac surgery, the latter should be "delayed for at least 2 and ideally 4 weeks, to allow for at least partial endothelialization of the stent".[1] However, a histologic study found that 12 weeks were required for complete endothelialization of the stent to coccur.[52] Thus, although stent thrombosis usually occurs within the first 2 weeks in patients receiving bare metal stents, this has been observed among patients not exposed to the prothrombotic state induced by non-cardiac surgery. The lack of complete endothelial coverage of a BMS may still pose a risk of stent thrombosis in a patient undergoing surgery.

The delay needed from DES implantation to surgery remains empiric: 3 months for sirolimus-eluting stent and 6 months for paclitaxel-eluting stent.

5.2 Antiplatelet therapy

The required duration of thienopyridine is 3 months for the sirolimus-eluting stent and 6 months for the paclitaxel-eluting stent. Those recommendations are based on the duration of time that the thienopyridine was required in the pivotal trials. However, in neither the pivotal trials nor in subsequent randomized trials comparing these stents to BMS was the actual duration of time that clopidogrel was administered known. The CREDO trial had been published long before these trials and many physicians chose to continue clopidogrel in their patients longer than the duration required in these protocols.[53] Therefore, the true time required to prevent late stent thrombosis among patients receiving these DES is unknown. Furthermore, the pivotal trials excluded patients with bifurcation lesions, in whom the stent would cross a side branch, and in patients with acute MI, patients undergoing PCI of a aortocoronary bypass graft, and patients with occluded vessels. These groups of patients appear to be at increased risk of stent thrombosis, and the risk may be increased even further if clopidogrel is not administered for a period longer than the recommended 3 or 6 months, particularly if the patient undergoes a surgical procedure shortly after stent placement.

Antiplatelet administration strategies to minimize perioperative stent thrombosis include:

- Option A: Continue dual antiplatelet therapy during and after surgery
- Option B: Discontinue clopidogrel but "bridge" the patient to surgery using a short-acting antiplatelet agent, such as a glycoprotein IIb/IIIa inhibitor or an antithrombin, such as a low-molecular weight heparin – then restart clopidogrel as soon as possible after surgery
- Option C: Discontinue clopidogrel before surgery and restart it as soon as possible after surgery

Options A and B would be most appropriate for patients early after stent implantation (4-6 weeks after BMS, 3 months after SES and 6 months after PES, even though increasing durations of antiplatelet therapies are currently used for DES[4]), whereas option C would be best for patients late after stent implantation. These recommendations are empiric, but are mechanistically sound and the consequences of perioperative stent thrombosis are severe.

Option A. Continue dual antiplatelet Rx during surgery

This is undoubtedly the safest option to prevent stent thrombosis. Surgeons that are particularly concerned about the risk of perioperative bleeding would need to be consulted and weigh the risk of bleeding with that particular operation in their hands,against the risks and benefits of continuing dual antiplatelet therapy through the

surgical period. When surgeons are informed that the risk of bleeding is higher but that stent thrombosis, when it occurs, leads to death or an MI in over 50% of patients, and that the available data suggest an increased risk of stent thrombosis in patient undergoing surgery shortly after stent placement (7-38%), they will often be persuaded that the risk of thrombosis outweighs the risk of bleeding. This option would not be appropriate for patients in whom bleeding could have catastrophic consequences, such as neurosurgery patients.

Option B. Stop clopidogrel and "bridge" the patient with a short acting antiplatelet or antithrombotic agent

Thienopyridines cause irreversible platelet inactivation, and need to be discontinued for 5-7 days to allow production of new platelets that will replace the inhibited platelets and will allow return to normal platelet function. If surgery is needed early after stenting and clopidogrel needs to be stopped, then it may be appropriate to "bridge" the patient to surgery using a short acting antiplatelet agent or an antithrombin.[54]

Glycoprotein IIb/IIIa inhibitors, mostly the shorter acting eptifibatide and tirofiban, have been advocated for use in this setting.[55] Alternatively, unfractionated heparin, a low-molecular weight heparin, or a direct thrombin inhibitor may be used to bridge the patients until surgery is needed. No data exist about the relative benefits of an intravenous glycoprotein IIb/IIIa inhibitor compared to an anticoagulant.

Option C. Stop clopidogrel and restart after surgery

This is the simplest and most cost-effective strategy, and may be sufficient when the stent is believed to have been fully endothelialized and the risk of stent thrombosis no longer exists. However, there appears to be variability in the rate at which DES are re-endothelialized, and the risk of stent thrombosis may persist in some patients for many months or longer. Indeed, data suggest that there may be a greater frequency of late stent thrombosis (thrombosis occurring more than one year after stent placement) and this may be particularly true following the prothrombotic state induced by surgery.[31]

If the surgical procedure can be perfromed while the patient is on aspirin and clopidogrel, discontinuing them before surgery should be avoided. If it cannot, both aspirin and clopidogrel ought be administered as early as possible in the post-operative period with a loading dose to speed the onset of action. Postoperative stent thrombosis often occurs several days after surgery and could potentially be prevented by early re-initiation of clopidogrel. In the study by Kaluza 3 of the 6 MIs occurred during the first postoperative day, and the remaining 3 on postoperative days 6, 7, and 11.[22] In the study by Wilson, the adverse event rate was stable during the first 6 postoperative weeks.[23] Postoperative events occurred between day 1 and 17 in the study by Sharma, but the timing was not specified, as it was not presented in the study by Redding, Preliminary studies suggest that re-initiation of clopidogrel in the early postoperative period is safe.[56]

5.3 Education and team approach

In view of the rapidly changing PCI techniques there is a need for continuous education, especially of non-cardiologists, about the unique risks that coronary stent implantation can create in the perioperative setting. The need to delay elective surgery after stent implantation cannot be overemphasized. In a survey of 2,167 Canadian anesthesiologists in March, 2003 (996 responded), 63% were not aware of literature about the appropriate length of time between the insertion of a stent and a subsequent surgical procedure and 32.6% recommended a 0-2 weeks waiting time, which is insufficient for bare metal stents, let alone DES.[57]

Anesthesiologists and surgeons should be alerted to the high-risk of stent thrombosis in patients who have received coronary stents.[58] They should:

1. determine the type of stents (bare metal vs sirolimus vs paclitaxel eluting stent) and the date of implantation
2. consult with an interventional cardiologist and, whenever possible, with the patients cardiologist
3. have a team of anesthesiologists, cardiologists, and surgeons make any decisions about the cessation of antiplatelet therapy, the timing of surgery, and the peri-operative management
4. perform surgery in centers with 24-hour interventional cardiology coverage to promptly treat stent thrombosis should it occur.

6. Treatment of perioperative stent thrombosis

Stent thrombosis will manifest as ST-elevation acute myocardial infarction and is best treated with early reperfusion. Thrombolytic administration in the peri-operative period may carry prohibitive bleeding risk. Primary PCI is therefore the treatment of choice, yet it also carries increased risk of bleeding since antithrombin and antiplatelet agents need to be administered during the procedure. In a retrospective analysis of 48 patients with acute myocardial infarction occurring within 1 week from surgery, survival with an early invasive strategy was 65%, which is encouraging in these very high risk patients.[59] Only one patient had significant bleeding at the operative site. If bleeding at the surgical site could have catastrophic consequences (such as after neurosurgical procedures) then medical therapy would be preferable.

7. Conclusions

In summary, perioperative coronary stent thrombosis is a catastrophic complication. If non-cardiac surgery is planned within 2-3 months, coronary stent implantation with a drug eluting stent should be avoided. Balloon angioplasty might be preferred if surgery is to be performed within weeks and an adequate angioplasty result can be achieved. Otherwise, a bare metal rather than a drug-eluting stent should be placed. A paclitaxel-eluting stent which requires not 3 but at least 6 months of dual antiplatelet therapy should not be used. Awareness, prevention, and early treatment of perioperative stent thrombosis are best achieved by collaboration between surgeons, anesthesiologists, and cardiologists.

8. References

1. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, Fleisher LA, Froehlich JB, Gusberg RJ, Leppo JA, Ryan T, Schlant RC, Winters WL, Jr., Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Jacobs AK, Hiratzka LF, Russell RO, Smith SC, Jr. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery---executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation*. 2002;105:1257-67.
2. Al Suwaidi J, Berger PB, Holmes DR, Jr. Coronary artery stents. *Jama*. 2000;284:1828-36.
3. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *Jama*. 2005;293:2126-30.
4. Holmes DR, Jr. Antiplatelet therapy after percutaneous coronary intervention. *Cerebrovasc Dis*. 2006;21 Suppl 1:25-34.
5. Cutlip DE, Baim DS, Ho KK, Popma JJ, Lansky AJ, Cohen DJ, Carrozza JP, Jr., Chauhan MS, Rodriguez O, Kuntz RE. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation*. 2001;103:1967-71.
6. Moreno R, Fernandez C, Hernandez R, Alfonso F, Angiolillo DJ, Sabate M, Escaned J, Banuelos C, Fernandez-Ortiz A, Macaya C. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. *J Am Coll Cardiol*. 2005;45:954-9.
7. Kuchulakanti PK, Chu WW, Torguson R, Ohlmann P, Rha SW, Clavijo LC, Kim SW, Bui A, Gevorkian N, Xue Z, Smith K, Fournadjieva J, Suddath WO, Satler LF, Pichard AD, Kent KM, Waksman R. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. *Circulation*. 2006;113:1108-13.
8. Rodriguez AE, Mieres J, Fernandez-Pereira C, Vigo CF, Rodriguez-Alemparte M, Berrocal D, Grinfeld L, Palacios I. Coronary stent thrombosis in the current drug-eluting stent era: insights from the ERACI III trial. *J Am Coll Cardiol*. 2006;47:205-7.

9. Cheneau E, Leborgne L, Mintz GS, Kotani J, Pichard AD, Satler LF, Canos D, Castagna M, Weissman NJ, Waksman R. Predictors of subacute stent thrombosis: results of a systematic intravascular ultrasound study. *Circulation*. 2003;108:43-7.
10. Fujii K, Carlier SG, Mintz GS, Yang YM, Moussa I, Weisz G, Dangas G, Mehran R, Lansky AJ, Kreps EM, Collins M, Stone GW, Moses JW, Leon MB. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol*. 2005;45:995-8.
11. Regar E, Lemos PA, Saia F, Degertekin M, Tanabe K, Lee CH, Arampatzis CA, Hoye A, Sianos G, de Feyter P, van der Giessen WJ, Smits PC, van Domburg RT, Serruys PW. Incidence of thrombotic stent occlusion during the first three months after sirolimus-eluting stent implantation in 500 consecutive patients. *Am J Cardiol*. 2004;93:1271-5.
12. Hausleiter J, Kastrati A, Mehilli J, Schuhlen H, Pache J, Dotzer F, Dirschinger J, Schomig A. Predictive factors for early cardiac events and angiographic restenosis after coronary stent placement in small coronary arteries. *J Am Coll Cardiol*. 2002;40:882-9.
13. Mehilli J, Dibra A, Kastrati A, Pache J, Dirschinger J, Schomig A. Randomized trial of paclitaxel- and sirolimus-eluting stents in small coronary vessels. *Eur Heart J*. 2006;27:260-6.
14. Ardissino D, Cavallini C, Bramucci E, Indolfi C, Marzocchi A, Manari A, Angeloni G, Carosio G, Bonizzoni E, Colusso S, Repetto M, Merlini PA. Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. *Jama*. 2004;292:2727-34.
15. Clarkson PB, Halim M, Ray KK, Doshi S, Been M, Singh H, Shiu MF. Coronary artery stenting in unstable angina pectoris: a comparison with stable angina pectoris. *Heart*. 1999;81:393-7.
16. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol*. 2005;45:2088-92.
17. Ong AT, Hoye A, Aoki J, van Mieghem CA, Rodriguez Granillo GA, Sonnenschein K, Regar E, McFadden EP, Sianos G, van der Giessen WJ, de Jaegere PP, de Feyter P, van Domburg RT, Serruys PW. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. *J Am Coll Cardiol*. 2005;45:947-53.
18. Ashton CM, Petersen NJ, Wray NP, Kiefe CI, Dunn JK, Wu L, Thomas JM. The Incidence of Perioperative Myocardial Infarction in Men Undergoing Noncardiac Surgery. *Ann Intern Med*. 1993;118:504-510.
19. Eagle KA, Rihal CS, Mickel MC, Holmes DR, Foster ED, Gersh BJ, Investigators ftC, Program UoMHC. Cardiac Risk of Noncardiac Surgery : Influence of Coronary Disease and Type of Surgery in 3368 Operations. *Circulation*. 1997;96:1882-1887.
20. Sametz, Metzler, Gries, Porta, Sadjak, Supanz, Juan. Perioperative catecholamine changes in cardiac risk patients. *European Journal of Clinical Investigation*. 1999;29:582-587.
21. Sautter RD, Myers WO, Ray JF, 3rd, Wenzel FJ. Relationship of fibrinolytic system to postoperative thrombotic phenomena. *Arch Surg*. 1973;107:292-6.
22. Kaluza GL, Joseph J, Lee JR, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol*. 2000;35:1288-94.
23. Wilson SH, Fasseas P, Orford JL, Lennon RJ, Horlocker T, Charnoff NE, Melby S, Berger PB. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. *J Am Coll Cardiol*. 2003;42:234-40.

24. Sharma AK, Ajani AE, Hamwi SM, Maniar P, Lakhani SV, Waksman R, Lindsay J. Major noncardiac surgery following coronary stenting: when is it safe to operate? *Catheter Cardiovasc Interv.* 2004;63:141-5.
25. Reddy PR, Vaitkus PT. Risks of noncardiac surgery after coronary stenting. *Am J Cardiol.* 2005;95:755-7.
26. Vicenzi MN, Meislitzer T, Heitzinger B, Halaj M, Fleisher LA, Metzler H. Coronary artery stenting and non-cardiac surgery--a prospective outcome study *Br. J. Anaesth.* 2006;96:686-693.
27. Auer J, Berent R, Weber T, Eber B. Risk of noncardiac surgery in the months following placement of a drug-eluting coronary stent. *J Am Coll Cardiol.* 2004;43:713; author reply 714-5.
28. Fleron MH, Dupuis M, Mottet P, Le Feuvre C, Godet G. [Non cardiac surgery in patient with coronary stenting: think sirolimus now!]. *Ann Fr Anesth Reanim.* 2003;22:733-5.
29. Aoudia-Mentfakh R, Raoux F, Collet JP, Fleron MH, Drobinski G, Metzger JP, Le Feuvre C. [Thrombosis caused by active rapamycin stents]. *Arch Mal Coeur Vaiss.* 2004;97:165-7.
30. Murphy JT, Fahy BG. Thrombosis of sirolimus-eluting coronary stent in the postanesthesia care unit. *Anesth Analg.* 2005;101:971-3.
31. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet.* 2004;364:1519-21.
32. Compton P, Zankar A, Adesanya A, Banerjee S, Brilakis E. Risk of Non-Cardiac Surgery After Coronary Drug-Eluting Stent Implantation. *Am J Cardiol.* 2006:in press.
33. Pierpont GL, Moritz TE, Goldman S, Krupski WC, Littooy F, Ward HB, McFalls EO. Disparate opinions regarding indications for coronary artery revascularization before elective vascular surgery. *Am J Cardiol.* 2004;94:1124-8.
34. Eagle KA, Rihal CS, Mickel MC, Holmes DR, Foster ED, Gersh BJ. Cardiac risk of noncardiac surgery: influence of coronary disease and type of surgery in 3368 operations. CASS Investigators and University of Michigan Heart Care Program. Coronary Artery Surgery Study. *Circulation.* 1997;96:1882-7.
35. McFalls EO, Ward HB, Krupski WC, Goldman S, Littooy F, Eagle K, Nyman JA, Moritz T, McNabb S, Henderson WG. Prophylactic coronary artery revascularization for elective vascular surgery: study design. Veterans Affairs Cooperative Study Group on Coronary Artery Revascularization Prophylaxis for Elective Vascular Surgery. *Control Clin Trials.* 1999;20:297-308.
36. McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, Pierpont G, Santilli S, Rapp J, Hattler B, Shunk K, Jaenicke C, Thottapurathu L, Ellis N, Reda DJ, Henderson WG. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med.* 2004;351:2795-804.
37. Huber KC, Evans MA, Bresnahan JF, Gibbons RJ, Holmes DR, Jr. Outcome of noncardiac operations in patients with severe coronary artery disease successfully treated preoperatively with coronary angioplasty. *Mayo Clin Proc.* 1992;67:15-21.
38. Elmore JR, Hallett JW, Jr., Gibbons RJ, Naessens JM, Bower TC, Cherry KJ, Gloviczki P, Pairolero PC. Myocardial revascularization before abdominal aortic aneurysmorrhaphy: effect of coronary angioplasty. *Mayo Clin Proc.* 1993;68:637-41.
39. Gottlieb A, Banoub M, Sprung J, Levy PJ, Beven M, Mascha EJ. Perioperative cardiovascular morbidity in patients with coronary artery disease undergoing vascular surgery after percutaneous transluminal coronary angioplasty. *J Cardiothorac Vasc Anesth.* 1998;12:501-6.

40. Brilakis ES, Orford JL, Fasseas P, Wilson SH, Melby S, Lennon RJ, Berger PB. Outcome of patients undergoing balloon angioplasty in the two months prior to noncardiac surgery. *Am J Cardiol.* 2005;96:512-4.
41. Mehran R, Aymong ED, Ashby DT, Fischell T, Whitworth H, Jr, Siegel R, Thomas W, Wong SC, Narasimaiah R, Lansky AJ, Leon MB. Safety of an Aspirin-Alone Regimen After Intracoronary Stenting With a Heparin-Coated Stent: Final Results of the HOPE (HEPACOAT and an Antithrombotic Regimen of Aspirin Alone) Study. *Circulation.* 2003;108:1078-1083.
42. Mehran R, Nikolsky E, Camenzind E, Zelizko M, Kranjec I, Seabra-Gomes R, Negoita M, Slack S, Lotan C. An Internet-based registry examining the efficacy of heparin coating in patients undergoing coronary stent implantation. *Am Heart J.* 2005;150:1171-6.
43. Wohrle J, Al-Khayer E, Grotzinger U, Schindler C, Kochs M, Hombach V, Hoher M. Comparison of the heparin coated vs the uncoated Jostent(R)--no influence on restenosis or clinical outcome. *Eur Heart J.* 2001;22:1808-1816.
44. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med.* 2002;346:1773-80.
45. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med.* 2004;350:221-31.
46. Waksman R. Biodegradable stents: they do their job and disappear. *J Invasive Cardiol.* 2006;18:70-4.
47. Di Mario C, Griffiths H, Goktekin O, Peeters N, Verbist J, Bosiers M, Deloose K, Heublein B, Rohde R, Kasese V, Ilsley C, Erbel R. Drug-eluting bioabsorbable magnesium stent. *J Interv Cardiol.* 2004;17:391-5.
48. Tamai H, Igaki K, Kyo E, Kosuga K, Kawashima A, Matsui S, Komori H, Tsuji T, Motohara S, Uehata H. Initial and 6-month results of biodegradable poly-l-lactic acid coronary stents in humans. *Circulation.* 2000;102:399-404.
49. Aoki J, Serruys PW, van Beusekom H, Ong AT, McFadden EP, Sianos G, van der Giessen WJ, Regar E, de Feyter PJ, Davis HR, Rowland S, Kutryk MJ. Endothelial progenitor cell capture by stents coated with antibody against CD34: the HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man) Registry. *J Am Coll Cardiol.* 2005;45:1574-9.
50. Finn AV, Kolodgie FD, Harnek J, Guerrero LJ, Acampado E, Tefera K, Skorija K, Weber DK, Gold HK, Virmani R. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation.* 2005;112:270-8.
51. Chu WW, Kuchulakanti PK, Torguson R, Wang B, Clavijo LC, Suddath WO, Pichard AD, Satler LF, Kent KM, Waksman R. Impact of overlapping drug-eluting stents in patients undergoing percutaneous coronary intervention. *Catheter Cardiovasc Interv.* 2006;67:595-9.
52. Grewe PH, Deneke T, Machraoui A, Barmeyer J, Muller KM. Acute and chronic tissue response to coronary stent implantation: pathologic findings in human specimen. *J Am Coll Cardiol.* 2000;35:157-63.
53. Steinhubl SR, Berger PB, Mann III JT, Fry ETA, DeLago A, Wilmer C, Topol EJ, for the CREDO Investigators. Early and Sustained Dual Oral Antiplatelet Therapy Following Percutaneous Coronary Intervention: A Randomized Controlled Trial. *JAMA.* 2002;288:2411-2420.

54. Auerbach A, Goldman L. Assessing and reducing the cardiac risk of noncardiac surgery. *Circulation*. 2006;113:1361-76.
55. Jaffe R, Halon DA, Carmeli J, Lewis BS. Prolonged intravenous eptifibatide infusion for prevention of coronary stent thrombosis. *Int J Cardiol*. 2006.
56. Halkos ME, Cooper WA, Petersen R, Puskas JD, Lattouf OM, Craver JM, Guyton RA. Early Administration of Clopidogrel Is Safe After Off-Pump Coronary Artery Bypass Surgery. *The Annals of Thoracic Surgery*. 2006;81:815-819.
57. Patterson L, Hunter D, Mann A. Appropriate waiting time for noncardiac surgery following coronary stent insertion: views of Canadian anesthesiologists [corrected]. *Can J Anaesth*. 2005;52:440-1.
58. Dupuis JY, Labinaz M. Noncardiac surgery in patients with coronary artery stent: what should the anesthesiologist know? *Can J Anaesth*. 2005;52:356-61.
59. Berger PB, Bellot V, Bell MR, Horlocker TT, Rihal CS, Hallett JW, Dalzell C, Melby SJ, Charnoff NE, HolmesJr. DR. An immediate invasive strategy for the treatment of acute myocardial infarction early after noncardiac surgery. *The American Journal of Cardiology*. 2001;87:1100-1102.

9. Biographical Sketch

Emmanouil S. Brilakis, M.D., MSc, PhD received his medical degree from the University of Athens Medical School. He served in the Greek Army and then completed training in Internal Medicine, Cardiovascular Diseases, and Interventional Cardiology at the Mayo Clinic. He is currently assistant professor of Medicine at the University of Texas Southwestern Medical School and director of the cardiac catheterization laboratory at the Dallas VA Medical Center.

Apart from perioperative management of coronary stents, his research interests include:

(1) interventional cardiology clinical trials (designed and currently performing the SOS – Stenting Of Saphenous vein grafts multicenter randomized controlled trial of Taxus™ vs. Express™ stents in saphenous vein graft lesions)

(2) physiologic assessment of coronary artery lesions (intravascular ultrasonography and fractional flow reserve measurements)

(3) clinical evaluation of novel cardioprotective agents, such as darbepoetin

(4) assessment of novel atherosclerosis risk factors, such as lipoprotein-associated phospholipase A2