Drug-eluting stents: insights into safety and indications

Walid Hassan

From the Department of Cardiovascular Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Correspondence and reprints: Walid Hassan, MD · Department of Cardiovascular Medicine, MBC 16, King Faisal Specialist Hospital and Research Centre · PO Box 3354, Riyadh 11211, Saudi Arabia · hassanw@kfshrc.edu.sa · Accepted for publication July 2007

Ann Saudi Med 2008; 28(2): 114-119

Currently, more than 4 million patients receive drug-eluting stents worldwide. Despite recent studies and editorials that have stirred controversy and generated tremendous publicity in the lay press related to the safety of drug-eluting stents for the treatment of coronary artery disease, enthusiasm for drug-eluting stents remains high. Drug-eluting stents decrease the need for repeat revascularization, but exhibit delayed endothelialization compared with bare metal stents. Adverse late vessel wall remodeling and inflammation have also been attributed to the drug/polymer coating.

Recent registry analysis data suggesting an increased risk of late or very late thrombosis with drug-eluting stents in routine clinical practice compared with previous clinical trial experience has led to concerns regarding the long-term safety of these devices. Clearly, there are many benefits to drug-eluting stents, which are an excellent and appropriate revascularization treatment for many patients with substantial reduction of restenosis compared with bare-metal stents. There is a need for understanding the benefits and risks of these devices in order to use them optimally and reduce likelihood of thrombosis. This review sheds some light on the risks and benefits of drug-eluting stents, and puts this treatment in perspective compared with alternative revascularization treatment options for obstructive coronary artery disease. The important take-home message is that the risks of drug-eluting stent thrombosis versus bare-metal stent thrombosis may have been overstated by some studies.

Drug-eluting stents have attracted considerable attention since their commercial approval more than 5 years ago when they were considered by some as one of the most important breakthroughs in the history of cardiovascular medicine. Different drug-eluting stents, with different drugs, different polymers, and different elution kinetics have been introduced. These drug-eluting stents behave differently with different cell cycle inhibition. In particular, drug elution kinetics and drug delivery homogeneity may play a role in the rate of vessel healing. The sirolimus-eluting stent (CYPHER, Cordis Corporation, USA) delivers the entire drug in the first 60 to 90 days. There is no drug left on the stent after this initial elution phase. In contrast, the slow-release, polymer-based paclitaxel-eluting stent (TAXUS, Boston Scientific, USA) elutes only about 10% of the active drug in the first 30 to 60 days. The remaining 90% of the taxol content on the stent is permanently sequestered, in the polymer. It is more likely that this large reservoir of taxol (nine times the initial therapeutic dose of eluted drug) is slowly eluted for months or years. This could contribute to late inflammation and intermittent endothelial cell loss.

Thrombosis Risk

Three recent clinical studies have raised a concern regarding the risk of stent thrombosis, and noncardiac death with drug-eluting stents. In the BASKET Late Trial, 1 bare-metal stents were compared with drug-eluting stents after clopidogrel had been discontinued at 6 months, with endpoints related to late stent thrombosis, death, and myocardial infarction (MI). There were no significant differences between bare-metal stents and drug-eluting stents, in the endpoints of death and MI. This study suggested a trend towards a higher rate of stent thrombosis with drug-eluting stents than bare-metal stents (2.6% vs. 1.3% at 18 months). However, there was major concern with the trial design.
All patients with major adverse cardiac events, including death, MI, target lesion revascularization, and stent thrombosis in the first 6 months after the initial stent implant were excluded from the analysis. Since the vast majority of adverse events with bare-metal stents occur in the first 6 months, this study design biased the results in favor of bare-metal stents. Indeed, patients with bare-metal stents who have no stent thrombosis, MI or clinical restenosis events at 6 months had a favorable long-term clinical outcome. Conversely, the rate of major adverse cardiac events with bare-metal stents in the first 6 to 9 months is significantly higher than with drug-eluting stents. It is this substantial reduction of major adverse cardiac events in the first 6 to 9 months that provides the rationale for drug-eluting stent use. A trial design that eliminates all of the adverse events that occur in the first 6 months after bare-metal stent implantation creates a biased result in an effort to show that bare-metal stents are as good as or better than drug-eluting stents.

One study that focused on total mortality analyzed 17 randomized clinical trials of bare-metal stents versus drug-eluting stents. This study found a higher total mortality rate in the sirolimus subgroup at a 2-year follow-up. Although the difference in total mortality was significant (P=.03), it was due to more noncardiac deaths in the sirolimus group (mainly from the RAVEL subgroup), primarily from concomitant comorbidities, including lung disease, cancer, and strokes. There were no differences between the drug-eluting stent and bare-metal stent groups in cardiac mortality, but there were no details provided as to the number of patients analyzed in each group. Others have suggested that these noncardiac deaths were somehow related to the drug-eluting stent implant. However, any relationship between 180 µg of sirolimus, eluted locally into a coronary artery over 60 to 90 days with fatal strokes, lung cancers, and chronic obstructive pulmonary disease, is difficult to explain.

Another study that has been given worldwide attention is a meta-analysis, presented at the World Congress of Cardiology in 2006, of data from selected CYPHER and TAXUS trials up to 2 years from implantation. The main conclusion from the analysis was that death and MI were higher for drug-eluting stents compared with bare-metal stents, and that this finding was significant for pooled CYPHER versus bare-metal stents studies, at a 2-year period. There are several questions about this analysis. First, it is unclear if all death or cardiac death was analyzed in TAXUS data set. The data sources used in the analysis were not well defined, and the sample sizes at different time points were not shown. The analysis appears to have used a summary of data from the literature instead of patient-level data.

Two independent academic cardiology research programs have critically analyzed the more complete, patient level data from more than 1600 patients from the same four randomized clinical trials of bare-metal stents versus CYPHER (SIRIUS, RAVEL, C-SIRIUS and E-SIRIUS trials), and follow-up data was obtained up to 4 years. These independent investigators were unable to confirm the risks of drug-eluting stents that were presented in the meta-analysis. In the four trials included in the meta-analysis, the total (definite and probable) stent thrombosis rates, using the ARC (Academic Research Consortium) definition, with 0 to 4 years of follow-up, were 1.8% (15/843 patients) in the bare-metal stent group and 1.5% (13/848 patients) in the CYPHER group (P=NS). At 4-years follow-up there was no significant differences in stent thrombosis, cardiac or noncardiac deaths, or MI. When a more complete set of data from 5007 patients from all 14 randomized clinical trials of bare-metal stents versus CYPHER were analyzed, none of the risks with drug-eluting stents could be identified that were presented in the BASKET Late report or the meta-analyses. The total stent thrombosis rate with a mean follow-up of about 24 months was 1.62% for bare-metal stents vs. 1.47% with CYPHER (P=NS). There were no statistically significant differences in death or MI after 1, 2, or 4 years of follow-up. Surprisingly, the researchers who reported concerns with drug-coated stents in 2006, found in 2007 that there was actually no difference in death rates, and that “drug-coated stents were safe after all.” This turnaround demonstrates how researchers can draw seemingly conflicting conclusions, based on small differences in the design or interpretation of studies, creating confusion for doctors and patients alike. Another study found that drug-coated stents were as

Acronyms for clinical trials related to drug-eluting stents.

| Acronyms | Description |
|----------|-------------|
| RAVEL    | Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent |
| SIRIUS   | SIrolesUS (coated stent) |
| C-SIRIUS | Canadian SIRIUS trial |
| E-SIRIUS | European SIRIUS trial |
| BASKET   | Basel Stent Kosten Effektivitats |
| ARTS     | Arterial Revascularization Therapy Study |
| PREVENT  | Project of Ex-vivo Vein Graft Engineering via Transfection |
safe as or safer than bare-metal stents when doctors used them ‘off-label.’ Interestingly, reported studies with angiographic confirmation on all late thrombosis events (>30 days) identified a very low incidence (only 0.16%-0.27%).

Pathologic studies of late stent thrombosis cases also suffer from potential sampling bias. These cases, however, do show endothelial cell disruption, some inflammation, and delayed healing. The more important question is whether these findings are relevant to the vast majority of patients who do not have restenosis or stent thrombosis 3 to 4 years after drug-eluting stent implantation, and 2 to 3 years after stopping clopidogrel.

Causes of stent thrombosis

Both early and late stent thrombosis are complex events with a multifactorial etiology. Lesion complexity, overlapping stents, long stent lengths, bifurcation lesions, stenting in acute MI, stent underdeployment, diabetes, renal failure, and premature discontinuation of antiplatelet agents are significant risk factors for stent thrombosis with both bare-metal stents and drug-eluting stents.

It is important to recognize that many of the major risk factors for stent thrombosis have been substantially amplified in the drug-eluting stents era by the use of these stents in complex lesions. Many of these uses are in clinical settings and lesion subsets that extend beyond approved indications, but still may be clinically reasonable, with overall risks that are as low as or lower than medical therapy, bare-metal stent use or bypass surgery. Nonetheless, this very aggressive use of drug-eluting stents, which is made possible by the very effective reduction of restenosis, may lead to higher risks of stent thrombosis.

Patient and physician noncompliance with guideline-based prescription of dual antiplatelet therapy also plays a significant role in drug-eluting stent thrombosis. A registry from Rotterdam showed that among patients who had a late stent thrombosis with drug-eluting stents (occurring after 30 days), only 26% of patients were still taking dual antiplatelet therapy, 51% were taking single antiplatelet therapy, and 23% were taking no antiplatelet medications. Importantly, as with bare-metal stents, premature discontinuation of dual antiplatelet therapy is the strongest risk factor in drug-eluting stent thrombosis.

The causes of very late stent thrombosis (i.e., after 1 year) are less certain. It is possible that the vessels still are not healed. Endothelialization of these devices after deployment in the coronary artery is delayed compared with bare-metal stents. Delayed hypersensitivity to the polymer/drug coating with intense local inflammatory cell infiltration and aneurysmal dilatation of the vessel wall has also been described, as has adverse late vessel wall remodeling associated with the development of incomplete drug-eluting stent apposition. In preclinical animal models, this delay in re-endothelialization, and the presence of inflammation appears more pronounced with the paclitaxel-eluting TAXUS stent than with sirolimus-eluting CYPHER stent. However, since stent thrombosis rates with TAXUS and CYPHER appear similar, these observations may not be relevant to clinical outcomes, particularly with longer duration thienopyridine prophylaxis. Whether vascular inflammatory reactions observed in a selected number of individuals are related to the drug delivery polymer is uncertain.

At present, patients who receive a drug-eluting stents implant are instructed to take clopidogrel for at least 6 months (as compared to 2 to 4 weeks after bare-metal stent implantation), and often indefinitely. By 6 to 12 months after a drug-eluting stents implant, most patients should have an intact endothelial cell layer.

Misconceptions about revascularization

Early thrombosis (within 30 days)

The concern about the use of drug-eluting stents is based on false assumptions related to the risks of stent thrombosis. The premise that bare-metal stents do not thrombose, or have a very low incidence of stent thrombosis, is misguided. The critical issue is the total incidence of stent thrombosis over the life of the implant. Even more relevant is the incidence of all major adverse cardiac events related to the target lesion over the life of the patient, beginning from the time of the index procedure onward.

Bare-metal stents have a substantial risk of both acute, subacute and late stent thrombosis. In one study involving bare-metal stents in a single lesion using a single stent, the 30-day stent thrombosis risk for these simple lesions was 2%. In another study looking at bare-metal stents versus heparin-coated stents, the 30-day stent thrombosis rate with bare-metal stents was at least 2.5%. Other trials with bare-metal stents also suggest a 1.5% to 3% incidence of stent thrombosis, in real-world stenting, and with a rare follow-up past 1 year. Thus, even with relatively short-term follow-up, in both simple and more complex lesions, the rate of bare-metal stent thrombosis is higher than most physicians perceive.

In the ARTS 1 trial comparing bare-metal stents versus coronary artery bypass grafting (CABG) for multivessel disease (2.8 stents and 47.6 mm mean...
stent length per patient), the 30-day stent thrombosis rate with bare-metal stents was 2.8%.” In the ARTS 2 Trial, using an average of 3.7 CYPHER implants (mean stent length, 72.5 mm) per patient, the 30-day stent thrombosis rate with CYPHER was 0.9%.29 This was significantly lower than the bare-metal stents early thrombosis risk (P<.009), despite a much higher-risk case mix in the patients treated with CYPHER stent in ARTS 2.

Late thrombosis (after 30 days)  
The premise that bare-metal stents do not thrombose after 30 days is also incorrect. Less attention has been directed to this issue in the era of bare-metal stents. However, in the two large published registries26,27 evaluating late bare-metal stents thrombosis (30 to 240-270 days), the late bare-metal stents thrombosis rates were 0.75% and 0.64%. When added to the early stent thrombosis rates in these studies the overall stent thrombosis with bare-metal stents with less than 1 year follow up was at least 2%. In one study looking at treatment of bare-metal stent thrombosis, approximately one-third of bare-metal stent thrombosis occurred late, with some cases observed up to 600 days after bare-metal stent implantation.28

In the pooled analysis of CYPHER versus bare-metal stents from 12 randomized clinical trials, the 30-day to 1-year rate of stent thrombosis was 0.62% for the bare-metal stents and 0.29% for CYPHER.7,8 A recent meta-analysis looking at both CYPHER and TAXUS showed no difference in late stent thrombosis out to 1 year vs. bare-metal stents.30 In the DEScover Registry, which enrolled 6906 real-world patients, the 1-year stent thrombosis rates were 0.8% for bare-metal stents, 0.8% for TAXUS, and 0.5% for CYPHER, despite substantially higher risk lesions treated in the drug-eluting stent subgroups.31 Finally, the one-year stent thrombosis rate with CYPHER in 15 157 patients in the e-CYPHER registry was very low (0.88%) in complex real-world cases.13

Thus, bare-metal stents definitely do thrombose after 30 days, due to incomplete endothelial cell regrowth, stent under-expansion, and critical restenosis with superimposed thrombus. Although the mechanism(s) of late stent thrombosis with bare-metal stents may differ from drug-eluting stents, the overall incidence appears to be at least 1%, over a 30-day to 2-year follow-up, and not clearly lower than with drug-eluting stents.

Restenosis is not totally benign  
Restenosis of bare-metal stents is neither rare, nor benign. The concept that we are trading a low incidence and low-risk restenosis event for a morbid late thrombosis event, thereby justifying the use of bare-metal stents rather than drug-eluting stents, ignores a number of very important points. First, restenosis of bare-metal stents is not benign. In one large study from the Cleveland Clinic, 36% of bare-metal stent restenosis cases presented with acute coronary syndromes requiring urgent hospitalization.32 Approximately 25% of these patients presented with either non-Q wave or an ST-elevation MI. Assuming a 30% bare-metal stent restenosis rate; there is a 5% to 7% risk of acute MI risk related directly to severe restenosis of a bare-metal stent.

There is a remarkable (approximately 70%-80%) reduction of major adverse cardiac events (predominantly repeat revascularization) with drug-eluting stents versus bare-metal stents. Both the TAXUS and CYPHER products substantially reduce the need for repeat target lesion reintervention, with a reduction of the costs, risks and pain and suffering related to repeat interventions for restenosis.4,6 Forty to fifty percent of bare-metal stent restenosis presents with vessel occlusion or diffuse proliferative in-stent restenosis. These patients often do poorly after repeat intervention with drug-eluting stents, bare-metal stents, percutaneous transluminal coronary angioplasty (PTCA), brachytherapy, or CABG. Restenosis of bare-metal stents is not benign, and has significant associated major adverse cardiac events, financial and emotional costs, and mortality.

Bypass surgery is not totally benign and grafts do close  
If drug-eluting stents are imperfect, perhaps coronary bypass surgery offers a safer and more durable revascularization result. This may drive more referrals to bypass surgery, since bypass grafts are often considered a gold standard, when it comes to predictable coronary revascularization. There is an assumption that bypass graft patency is grossly superior to bare-metal stents, and even drug-eluting stents, but this is not true either. Two recent studies in the New England Journal of Medicine15 and Circulation,39 reported angiographic follow-up data at 12 months to assess the patency rates of radial artery grafts, internal mammary artery grafts (IM), and saphenous vein grafts (SVGs). In these two studies the one-year (angiographic) patency rates of SVGs were 85% and 59%, respectively. That is, 15% to 41% of SVGs were completely occluded at 12 months. The arterial conduits were better. However, 14.2% of the radial artery grafts and 6% to 7% of the IM grafts were completely occluded or nonfunctional at 12 months. These results are also consistent with the PREVENT IV study with 3000 patients, which demonstrated a 40%
failure rate at 1-year angiographic follow-up. In addition, other studies have described a 2% to 3% major stroke rate and a 10% to 20% incidence of permanent cognitive impairment after CABG. These results suggest that, like PTCA, bare-metal stents, and drug-eluting stents, CABG surgery is not perfect either.

**Patient Selection/Challenges**

Proper patient selection should involve an assessment of the balance between restenosis risk and thrombosis risk (and the consequences of restenosis and thrombosis). Many factors, such as diabetes, long lesions, small vessels, chronic kidney disease and lesions in SVGs, have been identified that portend a higher risk of restenosis and may shift the benefit:risks ratio in favor of drug-eluting stents. These subgroups may also have a higher risk of very late thrombosis. It is important for the clinician to consider the risk:benefit ratio for each individual patient.

Consideration must be given to the patient’s ability to comply with long-term dual antiplatelet therapy. Social, medical, and financial barriers to proper adherence must be considered before a drug-eluting stent is selected for implantation, and in particular, the likelihood of future bleeding risk or need for surgical/invasive procedures should be carefully assessed. Drug-eluting stent implantation should be avoided if there is any doubt that the patient can comply with prolonged dual antiplatelet therapy.

Patients with previously implanted drug-eluting stents who are currently taking dual antiplatelet therapy present a significant management challenge to the cardiologist or primary care provider when a situation arises that requires cessation or interruption of antiplatelet therapy (for example, when elective or urgent surgery is required). There are no existing studies that examine alternative management strategies. Each practitioner must therefore rely on personal knowledge of the individual patient, the specific reason(s) for antiplatelet therapy discontinuation and other relevant factors in making the recommendation for how to manage the situation. Unlike available recommendations for alternative anti-coagulant bridging strategies when warfarin therapy must be temporarily discontinued, there are no existing data or recommendations for the practitioner to minimize the risk of stent thrombosis when anti-platelet therapy must be stopped. Discussion of the risks and benefits with the surgeon or other practitioner should be undertaken to determine if the procedure could be performed with reasonable safety without discontinuation of antiplatelet agents. In the patient considered at high risk for stent thrombosis involving a large area of myocardium, short-acting intravenous glycoprotein IIb/IIIa inhibitors have been empirically suggested prior to and after surgery for platelet inhibition during the period when the patient is unprotected between clopidogrel discontinuation to re-initiation. However, the safety and efficacy of this practice has not been formally studied. Similarly, there are no data to support bridging with low molecular weight heparin.

**Conclusions**

The purpose of this review of stent safety and indication is to provide some counterpoint to some of the attention surrounding issues of late drug-eluting stent thrombosis. The important take-home message is that the risks of drug-eluting stent thrombosis versus bare-metal stent thrombosis may have been overstated by some studies. Late stent thrombosis does occur with both bare-metal stents and drug-eluting stents, and may or may not be modestly higher with drug-eluting stents. The time course of very late drug-eluting stents thrombosis, suggests that persistent plaque ruptures and disease progression in the target vessel may cause some, or many of these events. The implantation of bare-metal stents as an alternative to drug-eluting stents will be associated with incremental morbidity, particularly in higher risk lesion and patient subsets. Yet, bare-metal stents can be recommended for one particular subgroup of patients who cannot take prolonged dual antiplatelet therapy for various reasons such as anticipated poor compliance, inability to afford medications, need for noncardiac surgery, and increased risk for bleeding complications.

There is still much to be learned about the biology of drug-eluting stents. However, there is no question that this technology provides tremendous benefit to the vast majority of patients compared with prior revascularization strategies. Clinicians and scientists should work on improving antiplatelet regimens and developing newer generation of biocompatible drug-eluting stents, which have biodegradable polymers or are polymer-free to minimize the risks of stent thrombosis.
DRUG-ELUTING STENTS

REFERENCES

1. Pflister M, Brunner-La Rocca HP, Buser PT, et al for the BASKET-LATE Investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents. An observational study of drug-eluting versus bare-metal stents. Am Coll Cardiol 2006; 48: 2594-2599.
2. Camenzúd E. Safety of drug-eluting stents: A meta-analysis of 1st generation DES programs. Oral Presentation at World Cardiology Congress 2006, Barcelona, Spain, 2006; 27: 2784-2784.
3. Nordmann AJ, Brièl M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: A meta-analysis. Eur Heart J 2006; 27: 1721-1728.
4. Morice MC, Serruys PW, Sousa E, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002; 346: 1737-1743.
5. Fitzerald PJ, Holmes DR, O’Shaughnessy C, et al, for the SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003; 349: 1315-1323.
6. Stone GW, Ellis SG, Cox DA, et al, for the TAXUS IV Investigators. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: The TAXUS-IV trial. Circulation 2004; 109: 1942-1947.
7. CYPHER(r) stent: Evaluation of benefits and risks. Available from: www.cordis.com/actives/crdus/en_US/html/cordis/downloads/155_5056_1_ARC_Overview.pdf. [AUTHOR: This is a URL for a Powerpoint presentation. Can you provide published references instead?]
8. Cutlip DE. Stent thrombosis after drug-eluting stenting: Impact of a new standard definition on clinical trial results. Available from: www.tctmd.com/csporta/a ttp://tctmd.com/tct20067-rnfpb=true&_p ageLabel=TCT2006BContent&h Con=1462381&articleId=18&contentId=78. [AUTHOR: This link does not work. Can you provide another citation, maybe Mauri et al. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 2007;356:1020-9?]
9. Marroquin OC, Selez F, Mulukutla SR, et al. A comparison of bare-metal and drug-eluting stents for off-label indications. N Engl J Med 2008; 358(4):342-52.
10. Sandhu G, Doyle B, Singh, et al. Frequency, etiology, treatment, and outcomes of drug-eluting stent thrombosis during one year of follow-up. Am J Cardiol 2007; 99(4): 465-9.
11. Ong AT, McFadden EP, Regar E, et al. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. J Am Coll Cardiol 2005; 45: 2088-2092.
12. Kuchulakanti PK, Chu WW, Torgenson R, et al. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. Circulation 2006; 113: 1108-1113.
13. Urban P, Gershlick AH, Guagliumi G, et al. Safety of coronary sirolimus-eluting stents in daily clinical practice: one-year follow-up of the e-Cypher registry. Circulation 2006; 113: 1434-1441.
14. Joner M, Fini AV, Farb A, et al. Pathology of drug-eluting stents in humans: Delayed healing and late thrombotic risk. J Am Coll Cardiol 2006; 48: 193-202.
15. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: A pooled analysis of multicenter coronary stent trials. Circulation 2001; 106: 1753-1755.
16. Cheneau E, Leborne L, Mintz GS, et al. Predictors of subacute stent thrombosis: Results of a systematic ultrasound study. Circulation 2003; 108: 43-47.
17. Fujii K, Carlier SG, Mintz GS, et al. Stent under-expansion and residual segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation. J Am Coll Cardiol 2005; 45: 995-998.
18. Finn AV, Kolodgie FD, Hamek J, et al. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. Circulation 2005; 112(2): 270-8.
19. Wenaweser P. Late coronary stent thrombosis of DESs in routine clinical practice. Oral Presentation at the World Cardiology Congress 2006, Barcelona, Spain, 2006.
20. Sousa JE, Serruys PW, Costa MA. New frontiers in cardiology: drug-eluting stents: Part I. Circulation 2003; 107: 2274-2279.
21. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent should we be cautious?. Circulation 2004; 109: 701-705.
22. Ako J, Morino Y, Honda Y, et al. Late incomplete stent apposition after sirolimus-eluting stent implantation: a serial intravascular ultrasound analysis. J Am Coll Cardiol 2005; 46: 1002-1005.
23. Tanischu M, Kurz HJ, Lasala JM. Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. Circulation 2001; 104: 539-543.
24. Gupta V, Aravamudhan BR, Baskerville S, et al. Reduction of subacute stent thrombosis (SAT) using heparin-coated stents in a large-scale, real world registry. J Invasive Cardiol 2004; 16: 304-310.
25. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001; 344: 1117-1124.
26. Wang F, Stouffer GA, Waxman S, Urytak BF. Late coronary stent thrombosis: Early vs. late stent thrombosis in the stent era. Catheter Cardiovasc Interv 2002; 59: 142-147.
27. Heiler L, Sheflrell KC, Hug K. Late stent thrombosis in the absence of prior brachytherapy. Catheter Cardiovasc Interv 2003; 53: 23-28.
28. Wenaweser P, Rey C, Eberl FR, et al. Stent thrombosis following bare-metal stent implantation: Success of emergency percutaneous coronary intervention and predictors of adverse outcome. Eur Heart J 2005; 26: 1180-1187.
29. Serruys PW, Ong AT, Morice MC, et al. Arterial revascularization therapies study. Il. Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. EuroInterv 2005; 147-156.
30. Moreno R, Fernandez C, Hernandez R, et al. Drug-eluting stent thrombosis. Results from a pooled analysis including 10 randomized studies. J Am Coll Cardiol 2005; 45: 954-959.
31. Williams DO, Abbott D, Kip KE, for the DEScov er Investigators. Outcomes of 6906 patients undergoing percutaneous coronary intervention in the era of drug-eluting stents. Report of the DEScove r registry. Circulation 2006; 114: 2154-2162.
32. Chen MS,John JM,Chew DP,Lee DS, Ellis SG,Shah DT. Bare metal stent restenosis is not a benign entity. Am Heart J 2006; 151: 1296-1294.
33. Desai N, Cohen EA, Naylor D, et al. A randomized comparison of radial artery and saphenous vein coronary bypass grafts. N Engl J Med 2004; 351(22): 2302-9.
34. Widimsky P, Straka Z, Strops P, et al. One-year coronary bypass graft patency: A randomized comparison between off-pump and on-pump surgery angiographic results of the PRAGUE-4 Trial. Circulation 2004;110: 3418-3423.
35. PREVENT IV Investigators. Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery-PREVENT IV: A randomized controlled trial. JAMA 2005; 294: 2446-2454.