CABG Versus Stent: Medicine's (not-so) New Great Debate
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Efficacy of Drug-Eluting Stents

The placement of drugs with anti-proliferative properties on coronary stents has provided a solution to the neointimal proliferation which characterized the restenosis process in patients who did not receive a durable result with a bare-metal stent (BMS). The additions of sirolimus, and its derivatives everolimus and zotarolimus, or paclitaxel to drug-eluting coronary stents (DES) has provided dramatic decreases in angiographic and clinical restenosis, and DES implantation is now the standard of care for a majority of patients undergoing percutaneous coronary interventions (PCI), especially in the United States.

Approved for clinical use in the United States in 2003, we now have more than forty randomized, double-blinded trials of drug-eluting stents in comparison with bare-metal stents in a variety of clinical scenarios, including acute coronary syndromes, angina, chronic total occlusion interventions, restenotic lesions and treatment of stenotic saphenous vein grafts. A common primary endpoint utilized in these trials is target lesion revascularization (TVR) which is the occurrence of revascularization (PCI or surgical) due to either restenosis or thrombosis at the site of the original treated stenosis. As the safety of drug-eluting stents has come into question, a more useful endpoint has been target vessel failure (TVF), defined as the occurrence of any of the following in the interval following the index procedure: death from cardiac causes, Q-wave or non-Q-wave myocardial infarction (MI), or revascularization of the target vessel by coronary artery bypass grafting (CABG) or PCI. MACCE rates refer to the combined endpoint of death, MI, stroke or repeat revascularization.

In most every clinical scenario, drug-eluting stents have been proven superior to non-drug-eluting stents. A 2007 metaanalysis by Stettler et al. of 38 trials with up to 4-years of follow-up showed a hazard ratio of 0.30 for sirolimus and 0.42 for paclitaxel-eluting stents when compared with bare-metal stents (1). This equates to a number needed to treat of 7 for sirolimus-eluting stent treated patients, or 8 for paclitaxel-eluting stents, to prevent one target vessel revascularization when compared with bare-metal stent PCI. A pooled analysis of 4-year follow-up of 4 initial trials of sirolimus and paclitaxel-eluting stents by Stone et al. showed similar findings with target vessel revascularization rates of 7.8% and 10.1% respectively as compared with rates of approximately 20-24% seen in the BMS stent control arms (2). The more clinically useful endpoint of target vessel failure, which includes myocardial infarctions or revascularizations in the same treated vessel, was 12.1% in sirolimus stent patients and 17.2% in paclitaxel stent patients versus 27.5% and 24.7% in the respective control arms. Differences in rates of clinical restenosis peaked at 1 year, and then remained stable during the remainder of the 4-year follow-up period, suggesting there is no late restenosis “catch-up” phenomenon with these two stent platforms.

Second generation stent platforms with the sirolimus derivatives everolimus and zotarolimus have also been shown to be efficacious with revascularization rates in the same range as first generation drug-eluting stents (3-5). Head-to-head trials of these stents have failed to generate definitive conclusions, however there is evidence from meta-analyses that sirolimus and its analogue everolimus may have improved efficiency over paclitaxel treated stents (1,5,6). While these differences are small, they are important to this discussion as one of the pivotal trials of CABG versus drug-eluting stents involved paclitaxel-eluting stents, which may not represent the best results that conventional coronary intervention has to offer.
Safety of Drug-Eluting Stents

The excitement the reduced rates of revascularization with drug-eluting stents has been muted by reports of increased stent thrombosis. This was unexpected by the interventional cardiology community as rates of stent thrombosis in the clinical trials of drug-eluting stents had been comparable to bare-metal stents (approximately 0.6-0.8%). Stent thrombosis is a serious complication that historically leads to Q-wave myocardial infarction and/or death in two-thirds of patients(7).

While initial reports of stent thrombosis were thought to be related to the learning curve with the new stent platforms, concern developed when a series of large multi-center registry reports and pooled analyses of published drug-eluting stent trial data showed increases in late drug-eluting stent thromboses (8-11). Prior to drug-eluting stents, stent thrombosis risk was thought to be confined to the first month after stent implantation. There are several plausible explanations for the increased risk of stent thrombosis. The decreased neointima which defines the lower restenosis risk with drug-eluting stents may magnify any mistakes made in stent deployment and may leave stent struts exposed for longer periods of time, increasing the potential for stent thrombosis. In addition, some patients may have delayed or impaired healing responses to drug-eluting stents and may be more prone to thrombosis, particularly when dual anti-platelet therapy with clopidogrel is discontinued.

In October 2006, the FDA initiated an advisory panel to look specifically at this issue. Prior to this meeting, 4-year follow-up data was presented at the TCT 2006 Scientific Sessions and subsequently published showing an increase in stent thrombosis after the originally reported one-year of clinical follow-up (12). This “very-late” stent thrombosis incidence was approximately 0.6-0.7%, bringing the overall rate of observed stent thrombosis to around 1.2-1.3% which was similar to the rates reported in large registries of drug-eluting stent patients. Once this increased risk was identified, cardiologists immediately modified the duration of therapy of aspirin and clopidogrel, based in part on an observational analysis from the Duke Cardiovascular Databank that suggested that prolonged therapy with the combination of aspirin and clopidogrel is protective against the increased risk of death and MI in patients receiving drug-eluting stents (13).

The magnitude of risk associated with drug-eluting stents has been difficult to ascertain, in part because the definitions of stent thrombosis have differed across trials as has the duration of therapy with clopidogrel. Another unexpected finding is that the increases in late stent thrombosis have not always translated into increased rates of death or MI, perhaps reflecting a balance between the risk of late thrombosis with DES and the morbidity associated with increased rates of restenosis with bare-metal stents. This observation is supported by the increased rates of stent thrombosis and MI seen in the bare-metal stents arms as the follow-up of these “control” patients has been extended.

In 2009, we now have extended follow-up and a series of pooled analyses and meta-analyses upon which to base conclusions. First, there is a slight increase in protocol-defined stent thrombosis in drug-eluting stents (1.2-1.3%) versus bare metal stents (0.6-0.8%). Second, more liberal definitions of clinical stent thrombosis have shown similar rates between stent groups (1.5-1.7%), suggesting clinical events in bare metal stent patients are likely underreported. Meta-analyses from Kastrati et al. and Schömig et al. showed no differences in rates of MI or death out to four years and the differences initially seen in observational analyses at 1-2 years have also disappeared in prolonged follow-up (14,15). This finding may be due to the increase in the duration of clopidogrel therapy or may also represent decreased MI and death as a result of decreased restenosis in the DES patient.

At this point in time, it appears the long term benefits of decreased restenosis offset the small initial increased risk of stent thrombosis. To optimally tilt the risk-benefit equation in favor of drug-eluting stents, prolonged duration of clopidogrel therapy is required. In the setting of this evolving information,
several professional societies have come together to issue a joint guideline statement on the duration of dual anti-platelet therapy in drug-eluting stent patients(16). In response to the dialogue at the FDA advisory meeting, industry has increased the follow-up of patients in DES clinical trials to 8 years and initiated large registries of drug-eluting stent patients which should additional information about the intermediate and long-term benefits of drug-eluting stents, define the risk period for stent thrombosis, and confirm the optimal duration of dual-anti-platelet therapy.

**New Guidelines for Dual Anti-Platelet Therapy after Drug-Eluting Stents**

- 1 month with Bare Metal Stent
- 12 months with Drug-Eluting Stent
- Consider Bare Metal Stent if:
  - Upcoming surgery
  - Bleeding risk precludes long-term therapy with aspirin and clopidogrel

**The Current Place of Drug-Eluting Stents in Coronary Revascularization**

While decisions about suitability percutaneous coronary revascularization are straightforward in most patients, many physicians continue to struggle with revascularization choices in patients with multi-vessel disease and/or diabetes. The rapid adoption of percutaneous coronary intervention in the cardiology community has, at times, out-paced the evidence supporting its use in certain clinical scenarios. While few would argue against an initial strategy of PCI in patients with single-vessel coronary artery disease, conflicting messages in fairly small randomized trials of patients with multi-vessel disease and/or diabetes mellitus have traditionally made decisions in these patients more difficult.

There have now been multiple randomized trials of percutaneous coronary intervention versus coronary artery bypass grafting (CABG) in patients with multi-vessel coronary artery disease, the past seven of which have included coronary artery stents in the percutaneous revascularization arm. As a whole, the results are fairly similar. While the balloon angioplasty trials showed increased mortality in PCI-treated patients, when the trials are viewed collectively, the frequency of death or myocardial infarction is similar with either strategy (17). Freedom from repeat revascularization procedures and relief from angina, however, is superior in the surgery arms. While none of these trials was large enough to provide enough definitive answers to allow generalization of this conclusion across all patient subgroups, this information has led to many physicians basing their choice of revascularization on the feasibility of PCI and cumulative risk of restenosis. A notable exception to this overall conclusion is patients with multi-vessel disease and diabetes mellitus. The Bypass Angioplasty Revascularization Investigation (BARI) study finding of decreased intermediate and long-term survival in diabetic patients with multi-vessel treated with PCI has remained consistent in other randomized trials of PCI versus CABG (18).

There are four modern era bare-metal stent versus CABG trials (ARTS, ERACI-II, MASS-II, and SoS) and a pooled analysis with 5-year follow-up was recently published(19). The primary endpoint of death, MI or stroke was similar between groups (16.7% vs. 16.9%), however repeat revascularization occurred much more frequently in the PCI group (29.0% vs.7.9%). In diabetics the mortality rates were not statistically different (12.4% vs. 7.7%, P=0.09), though clearly favoring CABG. The cumulative endpoint of death, MI, or stroke in diabetics, however, was not different (≈21%). Diabetics receiving PCI had a 3-fold higher incidence of repeat revascularization. Mortality in patients without diabetes was almost identical (≈8%) in both groups.

While three of these trials have failed to show a mortality advantage of CABG over PCI in long-term follow-up, the Stent or Surgery (SoS) Trial did show a survival advantage for CABG in recently published 6-year follow-up (20). This trial showed an early mortality advantage for CABG which was
magnified at 6 years (10.9% vs. 6.8%). This clear advantage is muted by the fact that there was a 2-fold excess of noncardiovascular death (25 vs. 11) in the PCI arm, which was mainly driven by deaths from cancer. Cardiovascular mortality was not statistically different between groups. Differences across these four stent versus surgery trials are hard to interpret as surgical mortality rates vary significantly (best in the SoS Trial) as do the rates of complete revascularization with PCI (72% in ARTS, 41-54% in the other three trials).

The results of these latest PCI versus CABG trials highlight several points. First, in non-diabetic patients, there is not a clear mortality penalty in patients receiving multi-vessel PCI with stents as an initial strategy. However, while an initial strategy of stenting may be defensible in terms of mortality, rates of revascularization are still approximately 20%, and patients are more likely to be angina-free with CABG. This point merits emphasis, as most revascularization procedures are performed for symptom relief and not for a mortality benefit. This difference should be taken in context, however, as the overwhelming majority of patients are now angina-free with either revascularization approach. Therefore, in non-diabetic patients at low risk for restenosis (discrete lesions in large vessels), a strategy of initial multi-vessel PCI seems reasonable.

Second, outcomes among diabetics with multi-vessel disease still favor surgery. While none of these studies are large enough to address mortality, rates of revascularization remain unacceptably high in diabetics treated with multi-vessel stenting. Five-year results of diabetic PCI patients in the ARTS trial are particularly sobering with 42.9% of patients requiring revascularization at 5 years compared with 10.4% of patients in which CABG was the initial treatment (21). Mortality in these studies, while underpowered, also favors CABG.

So what effect, if any, will the lower rates of restenosis seen with drug-eluting stents have on these results and will they push the outcomes of patients with multi-vessel disease in favor of PCI? The long-term benefits of CABG are dependent on graft patency, with the best outcomes seen in patients in whom one or both internal thoracic arteries are utilized, either alone or in combination with saphenous vein grafts. Unlike a coronary stent, which provides only a “spot”, lesion-specific treatment for atherosclerosis, a patent bypass graft placed distally in an epicardial coronary vessel provides protection against the lesion(s) for which the bypass graft was placed and future obstructive lesions in the segments proximal to the anastomosis. Most obstructive lesions occur in the proximal 6 cm of a coronary artery, a distance usually bypassed with a conventional coronary artery bypass graft (22).

The first potential answer to this question has been provided by ARTS II, a registry designed to enroll patients similar to those in ARTS I and treat them with sirolimus-eluting stents and compare outcomes with ARTS I CABG and bare-metal stent patients. This comparison is inherently unfair as CABG and PCI techniques and post-procedure care continue to improve, a point highlighted by the low 5-year mortality (7.6%) seen in the CABG arm of the ARTS trial. However, even while taken in context, the 3-year event rates in the drug-eluting stent group are promising (23). All-cause mortality was 5.0% compared with 5.2% in CABG patients and 7.1% in PCI patients in the original ARTS trial. Combined rates of death, stroke or MI in DES patients were lower than the ARTS-1 CABG population (9.4% vs. 13.5%) though rates of revascularization were still higher (21.4%) than ARTS-1 CABG patients (7.3%). Rates of death, MI or stroke in diabetics were similar in ARTS-2 patients and ARTS-1 CABG patients and rates of revascularization, though better than ARTS-1 patients, were still higher than ARTS-1 CABG patients. Stent thrombosis rates were higher than expected (definite or probable = 5.3%) likely due to the lack of knowledge about the requirement for prolonged anti-platelet therapy at the time this trial was conducted.

There are several trials of drug-eluting stents vs. CABG ongoing, and this past year saw the presentation of the 1-year results from the SYNTAX trial (24). The SYNTAX trial was designed to enroll 1800
patients with 3-vessel coronary disease with or without left main involvement, in whom agreement for eligibility was obtained from a cardiologist, cardiac surgeon and study coordinator. Enrolled patients received a SYNTAX score which factors in not only the amount of disease and involvement of the left main artery, but also factors like calcification, tortuosity, bifurcation involvement, presence of thrombus, and chronic total occlusions. All of these factors can impact on the success of PCI or CABG, and the SYNTAX score is meant to be an anatomic risk score.

Patients randomized to PCI received paclitaxel-eluting stents (mean 4.6 stents/patient) and received dual anti-platelet therapy (aspirin + clopidogrel or ticlopidine) for 6 months. Patients treated with CABG received a mean of 2.8 grafts with >95% of patients receiving an arterial conduit to the LAD. The primary endpoint of major adverse cardiac events (MACCE = death, MI, stroke, revascularization) at 1 year occurred in 12.1% of CABG patients vs. 17.8% of PCI patients (p=0.002) and PCI failed to meet the noninferiority standard when compared with CABG. Rates of death, MI, or stroke were almost identical in both groups (7.7% CABG, 7.6% PCI). Repeat revascularization was required in 13.7% of PCI patients vs. 5.9% of CABG patients. Rates of death, MI, or stroke were similar in both diabetic and nondiabetic patients, though rates of repeat revascularization in diabetics receiving PCI were markedly higher than CABG patients.

With these mixed 1-year results, both cardiac surgeons and interventional cardiologists will cling to parts of the SYNTAX analysis to argue their supremacy. Surgeons will highlight that the differences in 1 year MACCE rates are significant and may be even more discrepant over time. While not statistically significant, 1-year mortality favored CABG (4.3 vs. 3.6%).

Interventional cardiologists will argue that since rates of death, MI or stroke are similar between patients, there is no penalty for PCI as an initial strategy, and CABG can reserved for those who fail a PCI strategy. They will point out the higher rate of stroke in CABG patients (2.2 vs. 0.6%, p=0.003) and that the rates of death and MI are not statistically different. Also arguing in favor of PCI is that the rate of symptomatic graft occlusion or stent thrombosis was virtually identical (3.4%, 3.3%), highlighting the limitations of graft patency in complex patients.

While both sides can make valid arguments using these results, the truth may lie somewhere in the middle ground, particularly when the results as viewed by the SYNTAX scores. Patients with low SYNTAX scores, and likely the most suitable for PCI, had comparable MACCE rates (PCI 13.5% vs. CABG 14.4%) while patients with high SYNTAX scores clearly benefited most from the protection a distally placed bypass graft has to offer (PCI MACCE 23.3% vs. CABG 10.7%).

Conclusions

In most patients who receive CABG rather than multi-vessel PCI, the clinical benefit is confined to angina relief and freedom from further revascularization. With improved rates of restenosis with drug-eluting stents, the fundamental question now becomes: Is a drug-eluting stent better than a coronary artery graft? The high bar for patency and durability established by internal mammary artery grafts to the left anterior descending coronary artery will be difficult to surpass with any percutaneous strategy, however, in some patients with disease requiring placement of supplemental saphenous vein grafts, it is possible that patency rates of native vessel obstructions treated with drug-eluting stents could exceed that of those treated with saphenous vein grafts. To identify these circumstances, physicians will be required to predict not only the risk of restenosis, but also which patients are at high risk for disease progression and would benefit from the protective effect of a saphenous vein graft.

In diabetic patients, the questions will be more complex. While the reduction in restenosis rates in diabetics with drug-eluting stents is significant, diabetics are also more prone to progression of
atherosclerosis. Currently, the available early data still favors CABG as an initial strategy in diabetics. It will take careful scrutiny of the long-term results of trials of optimally treated drug-eluting stent and CABG patients to reach a consensus on the best treatments for individual patients.

References


