Hybrid Coronary Revascularization in the Era of Drug-Eluting Stents

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Left internal mammary artery to left anterior descending coronary artery bypass grafting integrated with percutaneous coronary angioplasty (hybrid procedure) offers multivessel revascularization with minimal morbidity in high-risk patients. This is caused in part by the avoidance of cardiopulmonary bypass–related morbidity and manipulation of the aorta coupled with minimally invasive techniques. Hybrid revascularization is currently reserved for particularly high-risk patients or those with favorable anatomic variants however, largely because of the emergence of off-pump coronary artery bypass grafting, which permits more complete multivessel revascularization, with low morbidity in high-risk groups. The wider introduction of hybrid revascularization is limited chiefly by the high number of repeat interventions compared with off-pump coronary artery bypass grafting, which occurs because of the target vessel failure rate of percutaneous coronary intervention. Other demerits are the costs and logistic problems associated with performing two procedures with differing periprocedural management protocols. Recently, drug-eluting stents have reduced the need for repeat intervention after percutaneous coronary intervention, and this has raised the possibility that the results of hybrid revascularization may now equal or even better those of off-pump coronary artery bypass grafting. Although undoubtedly effective at reducing in-stent restenosis, drug-eluting stents will not address the issues of incomplete revascularization or the logistic problems associated with hybrid. Uncertainty regarding the long-term effectiveness of drug-eluting stents in many patients, as well as their high cost when compared with those of off-pump coronary artery bypass grafting surgery, also militates against the wider introduction of hybrid revascularization.

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nosis,” “RAVEL” (randomized study with the sirolimus-eluting, velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions), “SIRIUS” (sirolimus-eluting stent), “ASPECT” (Asian Paclitaxel-Eluting Stent Clinical Trial), “TAXUS” (feasibility study evaluating safety of the NIRx paclitaxel-coated, conformer coronary stent for the treatment of de novo coronary artery lesions), “RESEARCH” (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital), or “randomized controlled trial.” In addition, the reference lists from relevant articles, abstracts, and reviews were also searched for additional trials. Randomized controlled trials, noncontrolled prospective studies, and retrospective series, in which morbidity, mortality, angiographic patency, target lesion revascularization (TLR), major adverse cardiac events (MACE), or costs were reported, were selected for inclusion. Letters and editorials, publications in languages other than English, and duplicate publications were excluded. Individual case reports, pilot studies, and small retrospective studies were not considered when higher levels of evidence were available.

Results

Hybrid Revascularization

The results of published series of hybrid procedures are listed in Table 1. These series, although representing a
relatively small patient cohort, demonstrate low procedural morbidity, low mortality, and a short hospital stay with this technique. Other advantages are the low frequency of septic complications and use of homologous blood products, and virtual absence of neurologic injury. These are attributed to smaller incisions plus avoidance of CPB and manipulation of the aorta, which have proven to be particularly beneficial in the elderly and in those with poor ventricular function, renal impairment, morbid obesity, and chronic obstructive airways disease. Twenty-six percent of patients in one study had a Parsonnet predicted mortality of 20%, with an overall mortality in the series of 0 [8]. Zenati and colleagues [16] compared actual outcome to predicted risk-adjusted mortality in 20 high-risk patients undergoing minimally invasive coronary revascularization, including 7 patients who underwent hybrid procedures. This showed a 30-day mortality of 0 in a patient cohort with a predicted mortality of 26%. Furthermore, in this cohort the predicted stroke risk, calculated using the Multicenter Perioperative Stroke Index, was 22%, with an actual stroke frequency of 0.

Despite these excellent early results, hybrid revascularization still has a limited role in multivessel revascularization [8, 13]. Reiss and associates [13], in the largest series of hybrid procedures published to date, performed only 57 hybrid procedures during 4 years, compared with 239 OPCAB and 2,305 conventional CABG using CPB. This represented only 2.2% of the surgical workload. The failure of hybrid revascularization to enter widespread use has been attributed to the emergence of OPCAB surgery [13, 15], which combines many of the benefits of minimal invasiveness by avoiding CPB and, when necessary, aortic manipulation, while at the same time overcoming many of the limitations of hybrid revascularization by permitting unrestricted access to every vessel on the heart and uncompromising selection of the best sites for coronary anastomoses. Several large series have also highlighted excellent results after OPCAB in those patient groups thought to benefit most from hybrid procedures, notably the elderly [17], obese [18], diabetics [19], or those with poor left ventricular function [20]. The principal benefits of OPCAB compared with hybrid procedures relate to the need for repeat revascularization procedures associated with PCI, the limitations of the MIDCAB procedure, and the logistic issues associated with performing two procedures, involving two specialists, with different procedural protocols, particularly with respect to anticoagulation.

**Repeat Revascularization**

The need for repeat revascularization after hybrid procedures is a reflection of the limitations of PCI: high reintervention rates that occur owing to incomplete revascularization at the time of the primary procedure as well as post angioplasty or in-stent restenosis [21]. Incomplete revascularization in the Bypass Angioplasty Revascularization Investigation (BARI) trial, which compared multivessel angioplasty with conventional CABG, occurred in 43% of patients in the PCI arm [22] owing to a large subgroup of patients for whom PCI was not suitable, notably chronically occluded, small, calcified, or tortuous vessels or long atherosclerotic lesions. Although in some hybrid series completeness of revascularization is as high as 100% [7, 10], in studies with broader inclusion criteria, completeness of revascularization occurred in as few as 68% of patients [8]. Revascularization of the left anterior descending coronary artery with the left internal mammary artery is associated with improved survival, freedom from cardiac events, and long-term patency compared with PCI and stenting [23–25]. The rationale for integrating this with PCI to the circumflex and right coronary arteries was that the results of PCI with stents, which have early restenosis rates in isolated short lesions as low as 30%, were comparable to the long-term survival of saphenous vein grafts [26]. Vein grafts, which have a patency of 60% at 10 years [27], are still used in the vast majority of CABG procedures despite the superior long-term patency of arterial grafts largely owing to their ready availability and the multivessel nature of the disease [27]. In the “real world,” stents have much higher restenosis rates, however, because the pattern of disease is often complex, involving bifurcations and sequential and long, diffuse, or calcified lesions, in which reocclosure rates can be as high as 60% [28]. This has been shown in randomized trials in which PCI and stenting is still associated with higher repeat revascularization rates compared with OPCAB or conventional CABG [29, 30]. After hybrid procedures restenosis of lesions originally treated with PCI is the most common cause of target vessel failure, TLR, or MACE, with TLR rates ranging from 12% to 14% at 18 to 24 months’ follow-up (Table 1). In contrast, in patients undergoing OPCAB surgery as part of the Beating Heart Against Cardioplegic Arrest Studies (BHACAS) trial, the TLR rate was 2% at a mean follow-up of more than 2 years (standard deviation, 9 months) [3]. Similarly, in patients randomized to OPCAB in the Octopus study [4], TLR rates were 3.5% at 1 year of follow-up, with 1-year graft patency in a randomized selection of OPCAB patients of 91%. In the Surgical Management of Arterial Revascularization Therapies (SMART) randomized trial of off-pump versus on-pump CABG [6], 1-year angiographic graft patency after OPCAB surgery was 94%. Hybrid revascularization, unlike OPCAB, has also not been shown to significantly reduce costs compared with conventional CABG [4–6, 31]. In a randomized trial of hybrid versus conventional CABG, although there was a trend toward a lower initial operative cost in the hybrid group ($8,100 ± $878 versus $9,700 ± $2,500), this difference was counterbalanced by the extra cost of percutaneous transluminal coronary angioplasty (total hybrid cost, $10,622 ± $1,329 versus conventional CABG cost, $9,699 ± $2,500; not significant). At 2 years the overall cost in the hybrid group had increased because of the need for repeat revascularization in 3 patients, although this was not significantly different from the cost of conventional CABG [31].
Table 2. Summary of Randomized Trials of Drug-Eluting Stents Versus Non-Drug-Eluting Stents

<table>
<thead>
<tr>
<th></th>
<th>DES/control</th>
<th>MR/control</th>
<th>ASPECT [40]</th>
<th>TAXUS-1 [38]</th>
<th>TAXUS-2 [39]</th>
<th>SIRIUS [37]</th>
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<tbody>
<tr>
<td><strong>Sirolimus</strong></td>
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<td>RADEL [36]</td>
<td>238</td>
<td>61</td>
<td>177</td>
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<tr>
<td>Mean Vessel Length (mm)</td>
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<td>10.9</td>
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<tr>
<td>Mean Vessel Diameter (mm)</td>
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<td>2.9</td>
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<td>Overall Diabetics (%)</td>
<td>16</td>
<td>18</td>
<td>20</td>
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<tr>
<td>6-Month Outcome (%) TLR</td>
<td>0/26</td>
<td>0/7</td>
<td>3.3/3.4/3.4</td>
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<tr>
<td>1-Year Outcome (%) TLR</td>
<td>3/27</td>
<td>0/10</td>
<td>7.8/20.6</td>
<td></td>
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<tr>
<td>MACE</td>
<td>0/26</td>
<td>0/10</td>
<td>8.3/12.1/16.9</td>
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<tr>
<td>Restenosis*</td>
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<td>7/19</td>
<td>6.6/20.6/45.8</td>
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<tr>
<td>Mean Vessel Diameter (mm)</td>
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<tr>
<td>Overall Diabetics (%)</td>
<td>18</td>
<td>12</td>
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<tr>
<td>6-Month Outcome (%) TLR</td>
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<tr>
<td>Restenosis*</td>
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<td>10/21</td>
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* Calculated on a patient basis (more than one reintervention occurred in some patients).

Table adapted from: ASPECT [40], DES vs. control; RADEL [36], DES vs. control; TAXUS-1, TAXUS-2 = feasibility study evaluating safety of the NIRx paclitaxel (new intravascular rigid flex) coated conformer, coronary stent for the treatment of de novo coronary artery lesions; DES/control = coronary artery bypass grafting in hybrid procedures in particular, offers the prospect of minimally invasive revascularization with excellent long-term outcomes. Summaries of the results of several landmark clinical trials of DES versus non-DES.
are listed in Table 2. Sirolimus (rapamycin), a macrolide antibiotic with potent immunosuppressive and antiproliferative effects on vascular smooth muscle cells, was the first agent to be evaluated in clinical trials. The multicenter, double-blind RAVEL study evaluated the efficacy of the sirolimus-eluting Bx velocity stent (Cypher; Cordis, a Johnson & Johnson Company, Miami, FL), and reported reductions in stent restenosis from 26.6% to 0% at 210 days’ follow-up [36]. The larger US multicenter SIRIUS study also reported a reduction in target vessel failure (defined as a composite of deaths from cardiac causes, myocardial infarction, and repeat revascularization) from 21% in control patients to 8.6% in the sirolimus group, with a TLR rate of 16% and 4% in control patients and sirolimus groups, respectively [37]. Follow-up in both the RAVEL and SIRIUS studies reported almost complete abolition of in-stent neointima formation [37, 41, 42]. Paclitaxel, a taxane with antimiotic properties, has also shown remarkable efficacy in clinical trials. Restenosis rates of 0% to 4% at 6 and 12 months compared with 11% to 27% in control patients have been reported in the TAXUS I (feasibility study evaluating safety of the NIRx paclitaxel coated conformer coronary stent for the treatment of de novo coronary lesions) [38] and ASPECT (Asian Paclitaxel-Eluting Stent Clinical Trial) studies [40]. Similar advantages in terms of lower TLR rates and MACE have been subsequently reported in the larger TAXUS II study [39]. In TAXUS I and II, MACE were reduced from 10% to 21% in control patients to 3% to 10% in the paclitaxel groups at 1 year [38, 39]. In the smaller TAXUS III study, paclitaxel-eluting stents were shown to be effective for the treatment of in-stent stenosis [43].

The potential for these stents to increase the numbers of hybrid procedures is limited by several factors. First, the applicability of these studies to PCI practice in the real world is unclear. The RAVEL, SIRIUS, TAXUS, and ASPECT trials assessed the efficacy of DES in a highly selected group of patients, and none published the numbers of patients who were initially considered for inclusion. Day-to-day clinical practice often involves more-complex patients than were included in these trials. There were no implantations in left mainstem disease, or vessels with chronic total arterial occlusion, ostial stenosis, in-stent restenosis, bifurcation lesions, or bypass grafts, or in patients after acute myocardial infarction [36]. The effectiveness of DES on completeness of revascularization and restenosis in these high-risk subgroups remains to be seen. The stented lesions in these studies were predominantly short lesions in large vessels, features associated with low restenosis rates with non-DES [44–46]. Whereas a 2.5-× 20-mm stent would be expected to have an angiographic restenosis rate of approximately 32%, a 4-× 8-mm stent would have an angiographic restenosis rate of 2% [28]. In the RAVEL study only 18% of vessels were less than 2.5 mm, and mean lesion length was small (9.6 mm) [36], with similar observations in the SIRIUS and TAXUS trials. Another consideration is that diabetics, who constitute 20% of the PCI population, still have higher restenosis rates with DES. In the SIRIUS study the 6-month in-segment restenosis rate in diabetics was 17.6% with a target lesion revascularization rate of 6.9%, rising to 10.5% in lesions less than 2.5 mm in diameter [37]. Multiple stents, including multivessel stenting, further increase the likelihood of restenosis as a result of the cumulative increase in restenosis risk. There is some evidence from the RESEARCH registry that DES are efficacious in high-risk subgroups in the real world [47]. The RESEARCH registry is a single-center registry that permits comparison of a recent cohort of patients in whom DES have been used without restriction with a historic control group treated before the introduction of DES. They have shown significant reductions in TLR, 5.1% versus 10.9%, and MACE, 9.7% versus 14.8%, in DES and control groups, respectively, at 1 year [47]. These benefits were observed despite a higher proportion of patients within the DES cohort having multivessel disease, multiple stents, bifurcation stenting, and type C lesions. It is noteworthy, however, that in a separate analysis of the same data set de novo in-stent restenosis within DES was associated with cases that were described as “technically complex” [48].

Second, animal and clinical studies have suggested that DES may be associated with late restenosis or thrombosis. Thrombosis has been attributed to the inhibition of endothelial regeneration by high local drug concentrations, which is undesirable, in addition to the intended inhibition of neointima formation. This results in persistently high levels of thrombogenic fibrin and few vascular smooth muscle cells around exposed stent struts [49]. An additional problem noted with sirolimus-eluting stents in the RAVEL study [42] was a higher rate of malapposition in patients with eluting stents (21%) versus control patients (4%). This may represent expansive remodeling around the stent, possibly related to apoptosis. Thrombus formation between the stent and vessel wall may propagate and lead to stent thrombosis. Late thrombosis leading to myocardial infarction has been reported with both rapamycin-eluting [49] and paclitaxel-eluting [50] stents. Late restenosis is also a possibility, as has been seen after brachytherapy, in which a delayed restenotic response occurs despite impressive early results [51]. Diminished late efficacy may be caused by a steady reduction in local tissue levels of the drug. In sirolimus-eluting stents 63% of the initial dose is eluted by 14 days; at this time arterial wall tissue levels are at a maximum (approximately 160 μg) and are reduced 50% by 28 days [52]. A recent study of 15 patients treated for in-stent restenosis with QuaDS stents (Quanam Medical Corporation, Santa Clara, CA) containing the paclitaxel derivative 7-hexanoyltaxol (QP2 or taxen) has unequivocally demonstrated late restenosis [53]. Although at 6 months there was minimal in-stent neointimal hyperplasia (late loss, 0.47 ± 1.01 mm), at 12 months there was an aggressive increase in neointimal growth (late loss, 1.36 ± 0.94 mm), resulting in a dramatic 61.5% rate of restenosis. Some series do report continued inhibition of neointima formation at up to 2 years after sirolimus-eluting stent implantation [54, 55]. These were short stents (18 mm) placed in large arteries (3 to 3.5 mm) in small numbers of low-risk patients, however.
A final concern is the high cost of stenting multiple vessels with DES. Cypher, the first DES on the market, costs approximately five times more than a conventional stent, and would therefore negate any initial cost saving associated with lower TLR rates after PCI, particularly if multiple stents are used to treat several vessels or complex lesions. Gunn and colleagues [28] calculated that despite some cost savings associated with lower restenosis rates, the use of DES would increase overall stent budgets by 256%.

Conclusions

Hybrid procedures currently occupy a select niche in particularly high-risk patients or those with favorable anatomic variants. It remains attractive in situations such as redo procedures, in patients with significant comorbidity, and in those with severe aortic or mitral ring calcification in whom moving or elevating the heart during revascularization of the posterior coronary vessels might result in injury of the calcified ascending aorta or the mitral annulus. Other patients who may benefit are those with prior chest wall irradiation in which median sternotomy is relatively contraindicated. In the general- ity, however, OPCAB permits superior levels of revascularization with lower MACE and fewer TLR and similar benefits in terms of low morbidity in high-risk patients. Although undoubtedly effective at reducing in-stent restenosis, DES will not address the issues of incomplete revascularization or logistic problems associated with hybrid procedures. Uncertainty regarding the long-term effectiveness of DES in many patients as well as their high cost, when compared with OPCAB surgery, may also limit the wider introduction of hybrid procedures.

References


