Combining PCI and CABG: the Role of Hybrid Revascularization

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Abstract Hybrid coronary revascularization combines the benefits of both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in the treatment of multivessel coronary artery disease (CAD) by combining the benefits of the LIMA-to-LAD graft and drug eluting stent (DES) to non-LAD regions. Through this approach, a patient receives the long-term benefit of the LIMA graft and avoids the morbidity of a full sternotomy and saphenous vein grafts. Available data related to outcomes following hybrid revascularization is limited to small studies. In this review we seek to provide an overview of hybrid revascularization in the era of modern drug eluting stent technology, discuss appropriate patient selection, and comment on future trial design. Additionally, we review the recent literature pertaining to the hybrid approach.

Keywords Hybrid coronary revascularization · Coronary artery disease · Coronary artery bypass grafting · Percutaneous coronary intervention · Completion angiography · PCI · CABG

Introduction

Hybrid coronary revascularization is a treatment strategy for coronary artery disease (CAD), which offers an alternative

to either traditional coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) alone. With the goal being to reduce the risk of the procedure and maximize the benefit, hybrid therapy capitalizes on the strengths of each approach. Since first being described by Angelini and colleagues in 1996 [1], advances in both surgical and catheter based techniques have made hybrid therapy a more attractive option for the treatment of multi-vessel CAD. Using one of several minimally invasive techniques, the left anterior descending coronary artery is grafted with the left internal mammary (LIMA), and percutaneous intervention is applied to atherosclerotic disease in the left circumflex and right coronary arteries. In this approach, the well-established survival benefit of the LIMA graft [2] is capitalized upon and, being done with minimally invasive techniques, the increased morbidity of a full sternotomy is avoided. Additionally, the use of the LIMA graft confers benefit related to the relief of angina and long term patency. In addition to the requirement of a sternotomy for traditional CABG, another weakness has been the lower patency rates of saphenous vein grafts. Newer generation drug eluting stents have continued to improve long term patency following PCI, to rates similar to or even surpassing that of saphenous vein grafts [3–6].

CABG vs. PCI and the Role of HCR

Coronary revascularization has been shown to be superior to medical management in the setting of acute coronary syndrome. As an example, the reported median survival for patients with left main disease who undergo surgical revascularization is 13.3 years in comparison to 6.6 years for those managed medically [7]. Additionally, coronary revascularization may provide symptomatic relief in patients with angina, which may be especially important in patients with persistent angina despite medical therapy. To date, two

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dominant forms of coronary revascularization (i.e., coronary artery bypass grafting [CABG] and percutaneous coronary intervention [PCI]) have been established. Historically, CABG has been the preferential revascularization technique among specific subsets of patients, including those with diabetes, multi-vessel disease, systolic dysfunction, and left main disease. However, innovations in both stent design and minimally invasive operative techniques have the potential to change this balance. Hybrid revascularization combines the mortality benefit and higher rates of patency of the left internal mammary graft with the lower restenosis rates of DES in comparison to saphenous vein grafting for other coronary territories [8, 9•], all with a less invasive procedure than traditional CABG. While hybrid therapy has not been proven to be superior in any way to traditional CABG, multiple studies have suggested that it does not appear inferior [10–12, 13•, 14].

Within high risk subjects including diabetic patients with significant left coronary disease, revascularization via CABG utilizing a left internal mammary artery (LIMA) has been shown to have a substantial mortality benefit over PCI based revascularization strategies or medical management [15–17]. In comparison to the other revascularization approaches, LIMA has been shown to exceed 90 % patency at 10 years [15, 16, 18]. This high rate of success however, is not shared by saphenous vein grafts, which have reported failure rates up to 30 % at one year [19]. This was shown and confirmed in the 10 year outcome data from the Bypass Angioplasty Revascularization Investigation (BARI) trial [15]. Patients with a history of treated diabetes who were randomized to CABG with at least one arterial graft ($n=145$) had a 10 year survival of 64.3 % in comparison to 39.4 % for those who underwent CABG with vein grafts only ($n=33$) and 45.5 % in those who were randomized to PTCA ($n=63$). Among participants not treated for diabetes, there was no significant difference in 10 year survival for patients who underwent CABG with or without the use of arterial grafts (75.3 % vs. 77.8 %).

CABG vs. PCI: Role of Bare Metal and Drug-Eluting Stents

Initial studies compared revascularization strategies for multivessel disease using a percutaneous transluminal coronary angioplasty (PTCA) based technique in comparison to CABG surgery. Hoffman et al. performed a meta-analysis of 13 randomized trials incorporating a total of 7964 patients with coronary disease who were randomized to strategies of CABG versus PTCA [20]. They found patients randomized to CABG had lower five-year mortality, citing a 1.9 % absolute survival advantage ($p<0.02$), as well as less angina. As had been noted in the individual studies, patients

randomized to PTCA also had significantly more frequent revascularizations ($P<0.001$). Among patients who underwent placement of stents, however, the rate of revascularization was reduced by about half.

A subsequent meta-analysis of four trials (Arterial Revascularization Therapies Study, Stent or Surgery Trial, Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease 2, and Medicine, Angioplasty, or Surgery Study 2) compared revascularization strategies of PCI with bare metal stents (BMS) ($n=1518$) versus CABG ($n=1533$) [21]. The primary combined outcome of death, myocardial infarction, and stroke occurred in 8.7 % of patients randomized to multivessel PCI versus 9.1 % of patients randomized to CABG (hazard ratio 0.95, 95 % CI 0.74 – 1.2). As seen in prior studies, patients who underwent PCI with BMS required repeat revascularization procedures more frequently than those who had CABG (18 % vs 4.4 %, hazard ratio 4.4, 95 % CI 3.3–5.9). Additionally, a higher percentage of patients who had CABG were angina free compared to those who underwent multivessel PCI (82 % vs. 77 %, $P=0.002$).

There are increasing data supporting the use of drug eluting stents (DES) over bare metal stents in many clinical situations. A recent meta-analysis compared outcomes of patients who underwent revascularization using drug eluting stents ($n=18,538$) versus CABG ($n=15,740$) [22]. All-cause mortality at 12 months (4.5 % vs 4.0 %, $P=.92$) and 24 months (6.2 % vs 8.4 %, $P=.27$) were not significantly different. The 30-day rate of myocardial infarction was similar for each group as well (DES 1.4 % vs. CABG 2.0 %, $P=0.60$). Patients who underwent DES placement had significantly lower 30 day rates of stroke (0.4 vs. 1.7 %, $P<0.001$), major cardiac and cerebrovascular events (3.6 % vs. 5.5 %, $P<0.04$) and all-cause mortality (0.9 % vs. 2.3 %, $P<0.001$). In comparison to those who underwent PCI, patients who underwent CABG had a significantly lower incidence of post-procedural myocardial infarction (4.7 % vs. 5.5 %, $P=0.03$), rate of revascularization (4.1 % vs. 22.2 %, $P<0.001$), and 12-month major adverse cardiac and cerebrovascular events (10.5 % vs. 16.7 %, $P<0.001$). Outcomes were similar among the subset of patients with multi-vessel coronary disease. Thus it appears that there are advantages and disadvantages to a “complete” CABG or PCI approach, even when drug-eluting stents are used. Hybrid revascularization, on the other hand, may combine the benefits of both.

Patient Selection for Hybrid Revascularization

The patient population for whom hybrid therapy is optimal has not been well validated. In many patients for whom

CABG is not an option, a hybrid approach offers benefit beyond PCI or medical therapy alone. Specifically, this is a reasonable consideration in treating patients with at least two-vessel disease (both an LAD and a non-LAD target) who are suboptimal surgical candidates, in whom the non-LAD lesions are amenable to PCI (Fig. 1). Such scenarios may occur in patients who have a lack of suitable conduits, a severely calcified aorta, or a non-graftable coronary vessel for which PCI remains an option. Tortuosity of the LAD, or LAD lesion characteristics that may require complex PCI, may also make a LIMA graft a more attractive option than PCI alone [23]. Patients with comorbidities that are known to increase surgical mortality may especially benefit from the minimally invasive techniques of hybrid therapy. Such patients include those with significant non cardiac pathology, recent history of myocardial infarction, prior sternotomy,

poor left ventricular function (ejection fraction <0.40) [24], or severe extra-cardiac arteriopathy [25].

To qualify for the hybrid procedure, patients must meet the requirements of both the catheter-based and surgical component of the operation. Ideal candidates have lesions in the right coronary and circumflex arteries amenable to stent implantation. Ideally, to receive maximum benefit from the hybrid approach, it is important that these non-LAD lesions, and the patient in general, qualify for drug eluting stents (DES). The patient should be properly screened for conditions that may interfere with the longer period of dual antiplatelet therapy required after DES placement. These would include high risk of bleeding, a history of medication non-adherence, or upcoming procedures, which may require cessation of antiplatelet agents. Patients with non-LAD disease that is not amenable to successful

Fig. 1 A proposed algorithm for considering revascularization approaches in patients with multivessel CAD. It should be noted that more evidence is needed prior to advocating hybrid therapy as a routine strategy

PCI (i.e., long lesions requiring multiple stents, small diameter vessels, lesions previously treated with PCI, or other more challenging lesions) are also less suitable for hybrid therapy [13•]. When the complexity of a lesion as a potential target for PCI is considered, local expertise may also be a factor in determining the appropriateness of hybrid therapy for a given patient. Relative contraindications for hybrid therapy include a non-graftable LAD, hemodynamic instability, prior thoracic surgery that may complicate access to the LIMA, and a large body mass index (>40). In addition, patients with coronary artery disease characteristics such as chronic total occlusions, bifurcation lesions, etc., generally should receive traditional open CABG [13•].

In an effort to identify which therapy would better address an individual patient's coronary disease, several investigators have sought to establish a system of stratification to predict clinical outcomes after interventions. In the landmark Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial, the SYNTAX Investigators reported on the predictive utility of a semi-quantitative angiographic scoring system that culminates in a SYNTAX score to characterize the coronary anatomy of patients with multi-vessel or complex CAD. An angiographic assessment is made of each lesion with a total cumulative score being calculated. They found that when patients were separated by SYNTAX score, there were no significant differences between CABG and PCI for those with low scores (0–22). Those with intermediate (23–32) to high (>33) scores who underwent PCI, however, had significantly higher incidences of MACCE at 36 months [26]. Although the SYNTAX score is useful in identifying patients at high risk following PCI, it does not identify patients at risk undergoing CABG, as the risk of bypass is determined by patient comorbidities. These risks are integrated in the European System for Cardiac Operative Risk Evaluation (EuroSCORE), in which clinical variables and a variety of risk factors such as age and renal function are considered in forming an additive score. The EuroSCORE is well validated in predicting event rates in the CABG group and is an independent predictor of MACCE following PCI as well. The EuroSCORE is insufficient for selection of CABG versus PCI, but is effective in identifying patients at high risk for mortality and poor outcome in either revascularization method [26]. We retrospectively analyzed the 30-day outcomes of 381 consecutive patients undergoing coronary bypass grafting ($n=301$) vs hybrid coronary revascularization ($n=80$) to identify patients best suited to hybrid therapy [9••]. After stratification of the groups by the SYNTAX score (≤ 32 vs ≥ 33) and the EuroSCORE (<5 vs ≥ 5), the composite endpoint (MACCE) and secondary endpoints (decline in renal function and bleeding) were determined. The 30-day rate of MACCE for hybrid vs CABG was similar in patients with low and intermediate SYNTAX

score (≤ 32). However, patients with high SYNTAX scores (>32) and EuroSCOREs (>5) experienced better outcomes with standard CABG than with hybrid therapy. As in previous studies, outcomes in the CABG group were not influenced by the SYNTAX score, and the EuroSCORE alone did not discern MACCE. Our findings demonstrate the effect of lesion complexity on PCI outcome, whereas the success of CABG is related to the quality of the distal targets and patients' suitability for major surgery, and not to the coronary lesions themselves. While the principal finding of this study was that hybrid revascularization is safe and feasible for many patients with multivessel CAD, these findings suggest that it should be considered only with caution in patients with high (≥ 33) SYNTAX scores, and even more so in those who also have a high (>5) EuroSCORE.

Even within the hybrid strategy, a patient's comorbidities or risk factors may indicate certain surgical approaches. Various minimally invasive techniques exist for the surgical portion of the procedure, and patient selection largely depends on the patient's candidacy for one of these. An example of one of the techniques used for the LIMA to LAD grafting is minimally invasive direct coronary artery bypass (MIDCAB). In this method, LIMA mobilization is performed through a sternal-sparing, limited (typically 5–6 cm) anterior or left thoracotomy incision and the LIMA-to-LAD anastomosis is subsequently completed by hand or by use of robotic manipulation of the beating heart [25, 27]. Patients benefit from the smaller incision and the avoidance of aortic manipulation and cardiopulmonary bypass, thereby reducing morbidity (i.e., adverse neurologic events, bleeding, infection, and pulmonary complications) and possibly improving outcomes (i.e., earlier hospital discharge and recovery) [28]. To demonstrate technique specific contraindications, adequate exposure during a MIDCAB is likely to require single lung ventilation, thereby making patients with severe pulmonary disease less optimal candidates.

Other Technical Issues

Different strategies for hybrid therapy have been described in which revascularization is carried out in one visit to a hybrid operating suite, or the two procedures are conducted in a staged fashion in different locations separated by hours to days. Questions remain to be answered regarding the optimal order in which to conduct the procedures and advantages and disadvantages exist of each. Furthermore, questions remain related to the administration of antiplatelet therapy and its implications on timing of surgery. Small studies have reported reduction in length of hospital stay and more rapid return to work [10, 29], though overall cost advantage may be offset by the utilization of two relatively

expensive procedures [30]. Large, randomized controlled trials comparing outcomes following hybrid therapy vs CABG or multi-vessel PCI have not been performed.

The ideal hybrid program has available a hybrid operating suite providing the option for one stop revascularization with completion angiography. Our group has previously described the experience from within Vanderbilt Heart and Vascular Institute related to completion angiography [23]. Reported was a series of 366 consecutive patients who underwent CABG with (n=112) or without (n=254) concomitant PCI, with completion angiography performed in all patients. In this series, 796 grafts were evaluated prior to chest closure. Of these, 97 (12 %) demonstrated defects, which required minor adjustment of the graft (n=22, 2.8 %), intraoperative open-chest PCI (unplanned hybrid, n=48, 6 %) or traditional surgical revision (n=27, 3.4 %). These findings strongly support the argument that completion angiography should be routinely utilized, whether the patient is undergoing planned hybrid revascularization, or as a quality control measure following traditional CABG. In centers with hybrid operating suites, graft defects can be identified immediately and addressed with either surgical revision or percutaneous intervention. We are currently performing follow up of this patient cohort with the intention of providing longer-term data on what advantage may exist to immediate correction of graft defects.

Review of Recent Literature and Future Trial Design

While large, randomized trials comparing hybrid revascularization have not been performed, smaller series continue to be published (Table 1). Halkos et al. recently published what may be the largest series to date, in which 147 patients who underwent hybrid revascularization between 2003 and 2010 were compared in a 4:1 ratio to patients undergoing multi-vessel off-pump CABG [13•]. Over a median follow up of 3.2 years, both survival and observed rates of major adverse events were similar. There was a higher rate of repeated revascularization in the hybrid group (12.2 % vs 3.7 %, $p<0.001$). The authors concluded that HCR was a safe and effective therapy in appropriately selected patients with multivessel CAD. Bachinsky and colleagues reported a series of 25 patients who underwent one stop hybrid revascularization, specifically by robotic assisted takedown of the LIMA [10]. When compared to well matched, low to moderate risk patients undergoing standard CABG, they reported similar rates of MACE. They did find lower rates of in hospital post-operative blood transfusions, shorter hospital stay, and earlier return to work in the hybrid group. These advantages came at the expense of higher total hospital cost, due to higher procedural cost. Similarly, Rab and

colleagues reported on 22 patients with left main lesions who underwent minimally invasive LIMA to LAD grafting [11]. PCI of the LM, as well as other needed vessels was staged an average of 3 days later, following angiographic confirmation of LIMA patency. They reported no 30 day MACCE and at a mean of 38.8 month follow up, 21 of 22 patients were alive. The conclusion was that HCR represented a feasible alternative to CABG or PCI alone of an unprotected LM. In this series, PCI of the LM into the circumflex resulted in “jailing” of the LAD ostium in 18 of 22 patients. Considering that LAD perfusion was assured by the LIMA graft, no adverse effects were observed. This ability to avoid complex stenting techniques was felt to make the overall procedure both simpler and safer. Furthermore, the observation was made that LIMA grafting, as opposed to PCI, protects against future disease progression in the proximal segment of the LAD.

According to ClinicalTrials.gov, the Hybrid Revascularization Observational Study, funded by the National Heart Lung and Blood Institute, has recently been completed. The largest observational study to date, with planned enrollment of over 6000 patients, this study was intended to inform the design of a pivotal comparative effectiveness trial and more optimally identify the population for whom hybrid therapy may be the better option. Primary outcomes are a composite of death, stroke, MI, or repeat revascularization with follow up over 18 to 21 months. To date, no data from this study have been published. As noted previously, there are no large randomized controlled trials evaluating hybrid coronary revascularization. The numerous studies that have been published to date vary in the surgical and interventional techniques, as well as patient selection, anti platelet strategies and one-stop vs staged approaches.

The ideal study design will be a multi centered, randomized controlled trial comparing hybrid revascularization to CABG. A design in which hybrid revascularization is compared directly to multi-vessel PCI will essentially be comparing the well-established advantage of the LIMA graft to LAD stenting, which is largely a non-contested issue. The hybrid vs CABG design will allow a true comparison of non LAD PCI to saphenous vein grafting, as well as allow for observations of what decrease in morbidity may be observed by avoiding a sternotomy. Additionally, we submit that the design will incorporate both staged and one stop procedures. Completion angiography should be an integral part as this is one of the advantages offered by the hybrid approach. Centers included in the trial should have surgeons experienced in minimally invasive techniques, as the technical expertise required could directly affect the outcome. As has been discussed extensively, a strong collaboration between the interventional cardiology and cardiovascular surgery departments is imperative to an individual programs success.

Table 1 Summary of published hybrid revascularization studies

Author	Year	Method	n	Mortality (%)	PTCA/PCI restenosis (% per patient)	Mean/median follow-up (month)	MACCE-free survival (%)
Angelini et al. [1]	1996	MidCAB/PTCA/PCI	6	0	n/r	n/r	n/a
Lloyd et al. [31]	1999	MidCAB/PTCA	18	0	6	18	89
Lewis et al. [32]	1999	MidCAB/PTCA/PCI	14	0	0	1.44	93
Zenati et al. [33]	1999	MidCAB/PCI	31	0	10	11	90
Wittwer et al. [34]	1999	MidCAB/PTCA/PCI	35	0	7	11	87
Isomura et al. [35]	2000	MidCAB/PTCA	37	0	n/r	24	92
De Canniere et al. [29]	2001	MidCAB/PTCA	20	0	5	24	95
Presbitero et al. [36]	2001	MidCAB/PTCA	42	2	14	18	83
Cisowski et al. [37]	2002	MidCAB/PTCA	50	0	10	12	87
Stahl et al. [38]	2002	MidCAB/PTCA	54	0	n/r	12	87
Riess et al. [39]	2002	MidCAB/PTCA	57	0	24	24	n/r
Lee et al. [40]	2004	TECAB/PCI	6	0	16	12	n/r
Davidavicius et al. [41]	2005	TECAB/PCI	20	0	0	19	100
Kiaii et al. [42]	2005	TECAB/PCI	1	0	0	6	100
Us et al. [43]	2006	MidCAB/PCI	17	0	18	21	87
Katz et al. [44]	2006	TECAB/PCI	10 BMS 17 DES	0	30 BMS 24 DES	3	67
Vassiliades et al. [45]	2006	TECAB/PCI	47 DES	0	6.6	7	90
Gilard et al. [46]	2007	MidCAB/PCI	70 DES	1.4	1.4	33	97
Kon et al. [47]	2008	MidCAB/PCI	15 DES	0	3	12	93
Bonatti et al. [48]	2008	TECAB/PCI	5 DES	0	0	6	100
Reicher et al. [49]	2008	MidCAB/PCI	13 DES	0	8	14	86
Holzhey et al. [50]	2008	TECAB/PCI	117	1.9	4.2	12	86
Zhao et al. [23]	2009	Transsternal CABG/PCI	87 DES 1 BMS 8 Both	2.6	11 BMS 5 DES	42	88
Halkos et al. [13•]	2011	EndoACAB	147 DES	0.7	3.4	38.4	86
Hu et al. [51]	2011	MidCAB/PCI	104	0	1.9 (n/r)	18	99
Rab et al. [11]	2012	MidCAB/PCI	22 DES	4.5	0	38.8	95
Leacche et al. [9••]	2012	MidCAB/PCI	80	5	N/A	1	91
Bachinsky et al. [10]	2012	Robotic MidCAB/PCI	25 (17 DES)	0	0	1	100
Fedakar et al. [12]	2012	OPCABG/PTCA/PCI	11*	0	0	0.5	100

MACCE: any death, stroke, MI, and/or revascularization/restenosis

*Unknown type of stent

Conclusions

Combined surgical and percutaneous coronary revascularization is a valuable option for management of multivessel disease in centers with hybrid capabilities. The optimum approach utilizes a minimally invasive surgical technique for LIMA to LAD anastomosis in conjunction with percutaneous coronary intervention employing newer generation drug

eluting stents for suitable lesions in non-LAD vessels. A number of selection factors including: Distal LM or proximal LAD disease, diabetes, systolic dysfunction, surgical risk, and coronary anatomy; may be important in deciding which patients may be candidates for a hybrid approach. Further studies are needed to better define the impact of a hybrid approach on patient outcome and to determine the patient population for whom this strategy may be best suited.

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