Hybrid coronary revascularization: promising, but yet to take off

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Abstract: Hybrid coronary revascularization (HCR) combines arterial coronary artery bypass surgery (most commonly minimally invasive) and percutaneous coronary intervention in the treatment of a particular subset of multivessel coronary artery disease. It was first introduced in the mid-1990s, and aspired to bring together the "best of both worlds": the excellent patency rates and survival benefits associated with the durable left internal mammary artery graft to the left anterior descending artery alongside the good patency rates of drug-eluting stents, which outlive saphenous vein grafts to non-left anterior descending vessels. Although in theory this is a very attractive revascularization strategy, several years later, only one small randomized controlled trial comparing HCR with coronary artery bypass grafting has recently emerged in the medical literature, raising concerns regarding HCR’s role and generalizability. In the current review, we discuss HCR’s rationale, the current evidence behind it, its limitations and procedural challenges.

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Hybrid coronary revascularization (HCR) combines arterial coronary artery bypass surgery (most commonly minimally invasive) and percutaneous coronary intervention in the treatment of a particular subset of multivessel coronary artery disease. It was first introduced in the mid-1990s, and aspired to bring together the “best of both worlds”: the excellent patency rates and survival benefits associated with the durable left internal mammary artery graft to the left anterior descending artery alongside the good patency rates of drug-eluting stents, which outlive saphenous vein grafts to non-left anterior descending vessels. Although in theory this is a very attractive revascularization strategy, several years later, only one small randomized controlled trial comparing HCR with coronary artery bypass grafting has recently emerged in the medical literature, raising concerns regarding HCR’s role and generalizability. In the current review, we discuss HCR’s rationale, the current evidence behind it, its limitations and procedural challenges.

The rationale for HCR lies in the well-established survival benefit conferred by LIMA-to-LAD grafts (4–6) and the use of new stent platforms (7) featuring lower stent restenosis and thrombosis rates compared with venous graft stenosis and occlusion rates, respectively (8).

The survival benefit of a surgical LIMA-to-LAD graft. A unique conduit, the LIMA powerfully resists thrombosis and atherosclerosis (9). Consequently, the LIMA-LAD graft is associated with long-term patency rates reaching 98% at 10 years (10,11). Furthermore, a LIMA graft protects the native coronary tree from the deleterious effects of disease progression (9).
VEIN GRAFT PATENCY VERSUS STENT RESTATE- 
NOSIS AND THROMBOSIS: THE RATIONALE FOR 
COMPLETING THE REVASCULARIZATION WITH 
PCI. Unlike arterial conduits, veins were not 
designed to bear the load of systemic pressure; hence, venous grafts are more 
prone to atherosclerotic degeneration and progressive narrowing with high early and 
long-term failure rates. In the ex vivo PREVENT IV (Vein graft Engineering via 
Transfection IV) study (12), angiographic midterm (1 to 1.5 years) saphenous 
vein graft (SVG) failure, defined as stenosis ≥75%, stood as high as 46%, whereas reported graft occlusion rates in 
the literature range from 6.2% to 32% at 1 year (averaging ~20%) (13–17), 29% 
at 10 years, and 68% at 15 years (10) post-coronary 
artery bypass graft surgery (CABG).

Newer drug-eluting stent (DES) platforms with 
e.g., everolimus-eluting stents [EES] or zotarolimus-
eluting stents [ZES]) or without (bioreabsorbable 
polymer-based or polymer-free stents) durable poly-
mers show favorable outcomes, with 1-year target 
lesion revascularization (TLR) rates as low as 3% to 
3.25% (7) and midterm binary (≥50%) restenosis rates of 
2.3% for EES (8 months) (18) and 3.1% for the 
adhimilimus-eluting, polymer-free stent (6 months) 
(19). Even in high-risk patients and complex lesions, 
ZES and EES maintain very low 1-year TLR rates of 
4.4% and 4%, respectively (20). Thus, PCI and stent-
ing provide strong competition for SVG revascular-
ization because, unlike an LIMA-LAD graft, disease 
progression in the proximal native coronary segment 
occurs alongside SVG deterioration.

Moreover, significant angiographic SVG stenosis 
occurs at least twice as frequently as binary in-stent 
restenosis using the latest technology platforms. However, ischemia-driven revascularization rates 
are considerably higher in stented patients with 
treated multivessel CAD (21). Furthermore, even 
though SVG occlusion occurs at a higher rate com-
pared with stent thrombosis (10), the clinical conse-
quences of the latter are more dramatic, as it is more 
frequently associated with major adverse clinical 
events (MACE) (22).

PATIENT SELECTION FOR HCR

The role of the heart team in guiding appropriate 
patient selection for HCR is crucial (23). In our view, 
an important anatomical feature favoring HCR should 
be plaque burden in the proximal LAD well charac-
terized by the SYNTAX (SYNergy Between PCI With 
TAXUS and Cardiac Surgery) score (24). The classic 
indication for HCR is multivessel CAD including: 1) a 
proximal complex LAD lesion with optimal distal 
artery anatomy amenable to LIMA-to-LAD grafting; 2) non-
LAD lesions amenable to PCI, in a patient with no 
contraindications to dual antiplatelet therapy (DAPT); 
and 3) a high likelihood of achieving “reasonable 
incomplete revascularization” (25,26) with such an 
approach.

Complex distal left main lesions are also ideal for 
HCR if the circumflex artery territory is amenable for 
PCI. HCR appears particularly appealing for patients with 
the aforementioned coronary anatomy and 
others considered too high risk for open cardiopul-
monary bypass surgery via midline sternotomy, 
including those with a high risk of deep sternal 
wound infection (e.g., diabetics, morbidly obese) (26), 
severely impaired left ventricular function, chronic 
kidney disease, significant carotid or neurological 
disease, severe aortic calcification, prior sternotomy, 
and lack of venous conduits. The 2011 American 
College of Cardiology Foundation/American Heart 
Association guidelines for CABG state that the “pri-
mary purpose of performing HCR is to decrease the 
morbidity rate of traditional CABG in high-risk pa-
tients” (27). Even in the more recent European Society of 
Cardiology/European Association for Cardio-
Thoracic Surgery guidelines on myocardial revascu-
larization (28), HCR has a Class IIb recommendation 
for specific patient subsets and only at experienced 
centers. The lack of several large randomized con-
trolled trials (RCTs) involving different risk groups, 
hinders the identification of an HCR target group. 
Consequently, physicians and surgeons do not 
embrace HCR in routine clinical practice. In a recent 
study from the Society of Thoracic Surgeons (STS) 
Adult Cardiac Surgery Database (29), HCR represented 
just 0.48% (n = 950 patients) of the total CABG volume 
(n = 198,622) between July 2011 and March 2013.

TECHNICAL ISSUES

1- VERSUS 2-STAGEd APPROACH. HCR can be 
performed either simultaneously or as a “2-staged” pro-
cedure. The former implies concurrent CABG and PCI 
in a single operative suite, with PCI following CABG 
within minutes. In the “2-staged” approach, the 
optimal order—PCI first versus CABG first—is debated 
because each approach has advantages and disad-
va n tages (Central Illustration). Currently, decisions 
should be guided by patient characteristics, operator 
skill/expertise, and available facilities.

A simultaneous approach is only feasible in 
hybrid suites featuring state-of-the-art surgical and
Interventional equipment. Often, CABG is performed first, allowing the interventional cardiologist to study the LIMA-LAD graft before PCI stent implantation. In cases of unsuccessful stent implantation, conventional CABG remains an option. Additionally, the simultaneous HCR approach can be cost effective by reducing hospital length of stay (30,31), the risk of lesion destabilization, and recurrent hospital admissions between staged procedures. An additional advantage: improved patient satisfaction (30), as it condenses revascularization into one patient encounter (27).

As for the limitations of this approach, 1 challenge is balancing the need for appropriate antiplatelet therapy, to avoid stent thrombosis, with surgical bleeding risk. Performing the LIMA-LAD anastomosis under DAPT can be difficult, particularly when a minimally invasive approach and video-assisted LIMA take-down are used. Furthermore, the response of DES to protamine administration at the end of CABG has not been fully investigated (32). When DAPT is not administered to reduce surgical bleeding risk, PCI becomes risky and is not recommended. Another challenging scenario for “1-stop” HCR is the patient with chronic kidney disease, who is exposed in a short period of time to the dual nephrotoxic insult of surgery and contrast media.

When the heart team favors a 2-step procedure, the sequence of PCI and CABG should be guided by clinical presentation and coronary anatomy. In general, the American College of Cardiology Foundation/American Heart Association guidelines favor performing CABG first (27). This strategy...
allows angiographic visualization of the LIMA-LAD graft, facilitates full antiplatelet inhibition following CABG with no perioperative bleeding risk, and provides a protected anterior wall, lowering procedural risks during PCI of non-LAD vessels. On some occasions after minimally invasive LAD to LAD, patients become asymptomatic in the immediate post-operative period. In these cases, particularly when the residual non-LAD lesions are angiographically intermediate, optimal medical therapy and watchful waiting may be in the patients’ best interest (33).

The disadvantages of a CABG-first approach include the risk of ischemia of non-LAD territories during the LIMA-LAD grafting (although highly unlikely in stable patients) and the potential for a high-risk surgical reintervention following unsuccessful PCI. Although the PCI-first strategy overcomes these limitations, its disadvantages include a higher risk of stent thrombosis (with discontinuations of DAPT, administration of plasma/platelet products in case of surgical bleeding, and the inflammatory response to surgery), increased perioperative bleeding risk (with optimal platelet inhibition), and risk of adverse events in the LAD territory in the between-stages interval. A PCI-first approach does not allow angiographic validation of the “prognostic” LIMA-LAD graft and is not ideal in high-risk patients requiring extensive non-LAD percutaneous revascularization. However, a PCI-first approach is reasonable in patients presenting with acute coronary syndrome (ACS) who undergo non-LAD culprit lesion PCI followed by CABG of the LAD. If the lesions treated with PCI were the culprit ones, CABG can be delayed, allowing safe discontinuation of DAPT. A PCI-first approach also allows angiographic evaluation of the LIMA’s size.

ANTIPLATELET MANAGEMENT. One big challenge of HCR: balancing the risk of perioperative bleeding with that of stent thrombosis. In the majority of HCR registries following the “CABG-first” approach (33-35), CABG was performed on aspirin; a second antiplatelet agent was started >4 h post-bypass after ensuring that no bleeding complications had occurred. In the “PCI-first” approach, DAPT is typically commenced ahead of the PCI procedure and is continued uninterrupted during CABG (34). In most series of simultaneous HCR, patients are not premedicated with clopidogrel and undergo the LIMA-LAD graft taking only aspirin, followed by a single loading dose of clopidogrel 300 mg either when the LIMA-LAD graft is completed (36), just before its completion (37), or immediately post-PCI (30,38,39). Another approach involves a loading dose of clopidogrel at the induction of anesthesia (40) or intraoperatively (35), because maximal platelet inhibition occurs 4 to 24 h after administration (41,42), allowing the surgical step of simultaneous HCR to be performed with acceptable bleeding risk. In some registries, the exact timing and dose of antiplatelet therapy during the “2-step” and simultaneous HCR are not clearly described, highlighting the need for more robust clinical guidance (43,44). Newer antiplatelet agents like prasugrel, ticagrelor, or cangrelor (45) (an investigational agent with rapid onset and reversal) could prove to be safer alternatives for HCR; however, this remains an “evidence-free” zone.

THE INDIVIDUAL COMPONENTS OF HCR

THE LIMA-LAD ANASTOMOSIS. In most cases, the LIMA-LAD anastomosis can be performed using the minimally invasive approach, which aims to avoid cardiopulmonary bypass and the sternotomy incision. Minimally invasive direct coronary artery bypass grafting (MIDCAB) is performed on the beating heart through a small, left-sided thoracotomy in the 4th/5th interspace via direct visualization. To avoid the significant chest wall manipulation associated with MIDCAB and to improve post-operative pain control, thorascoscopic and robotic techniques have been developed. These include the endoscopic atraumatic coronary artery bypass (Endo-ACAB), which allows thorascoscopic/robotic LIMA identification and mobilization followed by a direct non-rib spreading thoracotomy permitting hand-sewn anastomosis on the beating heart (46), and the totally endoscopic coronary artery bypass grafting either on- or off-pump, in which the anastomosis is performed intracorporeally using a robot. The latter, although challenging, produces a reported clinical freedom from graft failure as high as 98.6% at 13 months in experienced hands (47).

WHICH TYPE OF STENT TO IMPLANT? Without question, modern PCI should be performed with second- or third-generation DES (7,48,49). Irrespective of DES choice, it is essential that DAPT be continued for at least 6 months (50,51). Fully biodegradable DES are an interesting new development (52,53), but long-term follow-up data, especially in complex lesions, are needed before we consider them a replacement for current metallic DES.

THE EVIDENCE ON HCR

Since the first report in 1996 (1), there have been multiple publications on single-center experiences...
<table>
<thead>
<tr>
<th>First Author, Year (Ref. #)</th>
<th>Registry Recruitment</th>
<th>HCR/Total Assessed (N = 998)*</th>
<th>Age, yrs</th>
<th>Male, %</th>
<th>Diabetes, %</th>
<th>LVEF, %</th>
<th>ACS, %</th>
<th>Timing</th>
<th>SYNTAX Score</th>
<th>Risk Score</th>
<th>Surgical Technique</th>
<th>Conversion to Open</th>
<th>Angiographic Type/Location of PCI Lesions</th>
<th>DES/BMS</th>
<th>Type of DES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams et al., 2013 (37)</td>
<td>2004–2012</td>
<td>94–96</td>
<td>64 ± 12</td>
<td>72.9</td>
<td>N/A</td>
<td>N/A</td>
<td>38 (UA)</td>
<td>1-stop</td>
<td>N/A</td>
<td>N/A</td>
<td>MIDCAB Da Vinci-OP</td>
<td>2</td>
<td>N/A</td>
<td>95/10 stents</td>
<td>91 PES 3 SES 1 ZES</td>
</tr>
<tr>
<td>Halkos et al., 2013 (33)</td>
<td>2003–2012</td>
<td>269–300</td>
<td>64.12 ± 12.1</td>
<td>68.3</td>
<td>36.7</td>
<td>54.7 ± 69.2</td>
<td>34 (MI)</td>
<td>21 1-stop</td>
<td>92 CABG 1st</td>
<td>1.6 ± 2.1 (S)</td>
<td>&lt;2,009 Endo-ACAB &gt;2,009 MIDCAB Da Vinci-OP</td>
<td>6</td>
<td>N/A</td>
<td>232/28 patients</td>
<td>4 POBA 3 Unknown</td>
</tr>
<tr>
<td>Repossini et al., 2014 (43)</td>
<td>2004–2011</td>
<td>166</td>
<td>65.8 ± 10.3</td>
<td>90.4</td>
<td>24.1</td>
<td>9.6 (EF &lt;30%)</td>
<td>58.4</td>
<td>60 CABG 1st</td>
<td>29.3 ± 7.37</td>
<td>3.49 ± 4.77 (EII)</td>
<td>4.69 ± 3.77 (S)</td>
<td>MIDCAB-OP</td>
<td>4</td>
<td>N/A</td>
<td>57/109 patients</td>
</tr>
<tr>
<td>Bonatti et al., 2012 (35)</td>
<td>2004–2011</td>
<td>140–162</td>
<td>61 (31–85)</td>
<td>79.3</td>
<td>28.6</td>
<td>60 (20–79)</td>
<td>43.6 (MI)</td>
<td>28 1-stop</td>
<td>74 CABG 1st</td>
<td>22 (0–13) (Add E)</td>
<td>0.5 (0.2–9.9) (S)</td>
<td>Robotic TECAB On &amp; off pump</td>
<td>22</td>
<td>N/A</td>
<td>98/34 patients</td>
</tr>
<tr>
<td>Rab et al., 2012 (57)</td>
<td>N/A</td>
<td>22</td>
<td>61.0 ± 13.7</td>
<td>59.1</td>
<td>27.3</td>
<td>54.8 ± 8.8</td>
<td>N/A</td>
<td>22 CABG 1st</td>
<td>22.3 ± 10.0</td>
<td>1.6 ± 1.9 (S)</td>
<td>MIDCAB Da Vinci-OP</td>
<td>NA</td>
<td>NA</td>
<td>21/1 patients</td>
<td>N/A</td>
</tr>
<tr>
<td>Bonaros et al., 2011 (61)</td>
<td>2001–2009</td>
<td>130</td>
<td>58 (41–75)</td>
<td>77</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>21 1-stop</td>
<td>97 CABG 1st</td>
<td>12 PCI 1st</td>
<td>NA</td>
<td>13</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Holzhey et al., 2008 (44)</td>
<td>1996–2007</td>
<td>117</td>
<td>64.6 ± 12.3</td>
<td>83.8</td>
<td>24.8</td>
<td>59.2 ± 13.1</td>
<td>4.3 (UA)</td>
<td>5 1-stop</td>
<td>59 CABG 1st</td>
<td>53 PCI 1st</td>
<td>4.3 (Log E)</td>
<td>MIDCAB (107)</td>
<td>OP TECAB (8) TECAB (2)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Kiaei et al., 2008 (38)</td>
<td>2004–2007</td>
<td>58–60</td>
<td>59.9 ± 11.7</td>
<td>78</td>
<td>23</td>
<td>N/A</td>
<td>17 (MI)</td>
<td>58 1-stop</td>
<td>N/A</td>
<td>N/A</td>
<td>Endo-ACAB OP</td>
<td>2</td>
<td>A/B1: 31 B2/C: 28</td>
<td>53/6 stents</td>
<td>49 PES 3 SES 6 BMS</td>
</tr>
</tbody>
</table>

Values are mean ± SD, median (interquartile range), n, or % as indicated. *If a single number, this indicates patients undergoing HCR.

ACS = acute coronary syndrome(s); ACAB = atraumatic coronary artery bypass; Add = additive; AH = arrested heart; BH = beating heart; BMS = bare-metal stent(s); CABG = coronary artery bypass graft surgery; DES = drug-eluting stent(s); E = EuroSCORE; EF = ejection fraction; Endo-ACAB = endoscopic atraumatic coronary artery bypass; HCR = hybrid coronary revascularization; Log = logistic; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MIDCAB = minimally invasive direct coronary artery bypass grafting; N/A = not available; OP = off pump; PES = paclitaxel eluting stent(s); PCI = percutaneous coronary intervention; POBA = plain old balloon angioplasty; S = Society of Thoracic Surgeons score; SES = sirolimus-eluting stent(s); SYNTAX = SYNergy Between PCI With TAXus and Cardiac Surgery; TECAB = totally endoscopic coronary artery bypass grafting; UA = unstable angina; ZES = zotarolimus-eluting stent(s).
<table>
<thead>
<tr>
<th>First Author, Year (Ref. #)</th>
<th>HCR*</th>
<th>Age, yrs</th>
<th>Male, %</th>
<th>Diabetes, %</th>
<th>LVEF, %</th>
<th>ACS, %</th>
<th>Timing</th>
<th>HCR</th>
<th>SYNTAX Score</th>
<th>Risk Score</th>
<th>Surgical Technique</th>
<th>Conversion to Open</th>
<th>Angiographic Lesions</th>
<th>DES/BMS</th>
<th>Type of DES</th>
<th>HCR Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shen et al., 2013 (36)</td>
<td>Retrospective, matched cohort study (propensity matched) Recruitment: 2007-2010</td>
<td>141 HCR</td>
<td>62 ± 9.9</td>
<td>88.7</td>
<td>26.2</td>
<td>62.7 ± 7.1</td>
<td>N/A</td>
<td>1-stop</td>
<td>27.6 ± 7.9</td>
<td>3.1 ± 2.3 (Add E)</td>
<td>MIDCAB</td>
<td>N/A</td>
<td>N/A</td>
<td>27/0 stents</td>
<td>210 SES 8 PES 12 E-ZES 41 R-ZES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>141 CAGB</td>
<td>62.4 ± 7.8</td>
<td>90.1</td>
<td>18.4</td>
<td>62.6 ± 8.0</td>
<td>N/A</td>
<td>28.2 ± 9.4</td>
<td>3.3 ± 2.3 (Add E)</td>
<td>OP 20.6%</td>
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<tr>
<td></td>
<td></td>
<td>141 PCI</td>
<td>61.7 ± 10.3</td>
<td>87.2</td>
<td>19.9</td>
<td>61.2 ± 9.3</td>
<td>N/A</td>
<td>26.0 ± 8.2</td>
<td>3.5 ± 2.6 (Add E)</td>
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<tr>
<td>Leach et al., 2013 (56)</td>
<td>Retroactive cohort study (group stratification) Recruitment 2005-2009</td>
<td>80 HCR</td>
<td>62 (32-85)</td>
<td>79</td>
<td>42</td>
<td>50 (20-70)</td>
<td>58</td>
<td>1-stop</td>
<td>4 (0-12) (Add E)</td>
<td>OP 22%</td>
<td>NA</td>
<td>NA</td>
<td>62/7 patients</td>
<td>NA</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>301 CAGB</td>
<td>74 (32-84)</td>
<td>62</td>
<td>31</td>
<td>50 (20-65)</td>
<td>61</td>
<td>6 (1-14) (Add E)</td>
<td>OP 31%</td>
<td>10/3 patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>236 CAGB</td>
<td>63 (32-89)</td>
<td>75</td>
<td>38</td>
<td>55 (10-80)</td>
<td>71</td>
<td>4 (0-14) (Add E)</td>
<td>OP 15%</td>
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<tr>
<td></td>
<td></td>
<td>248 CAGB</td>
<td>62 (32-83)</td>
<td>83</td>
<td>32</td>
<td>50 (10-70)</td>
<td>57</td>
<td>4 (0-15) (Add E)</td>
<td>OP 16%</td>
<td></td>
<td></td>
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<tr>
<td>Bachinsky et al., 2012 (31)</td>
<td>Prospective cohort study, no matching Recruitment: 2009-2011</td>
<td>25 HCR</td>
<td>63.2 ± 10.5</td>
<td>10</td>
<td>36</td>
<td>55.3 ± 10.4</td>
<td>32</td>
<td>1-stop</td>
<td>33.52 ± 8</td>
<td>0.46 ± 0.24 (S)</td>
<td>MIDCAB (OP-Da Vinci) 100%</td>
<td>N/A</td>
<td>A: 14% (n = 6) B1: 26% (n = 11) B2: 50% (n = 21) C: 10% (n = 4)</td>
<td>42/18 patients</td>
<td>42 EES 18 BMS</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>27 OPCAB</td>
<td>66.78 ± 10.7</td>
<td>59†</td>
<td>48</td>
<td>51.48 ± 12.0</td>
<td>37</td>
<td>34.89 ± 8.2</td>
<td>0.96 ± 0.93 (S)†</td>
<td></td>
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<tr>
<td>Halkos et al., 2011 (34)</td>
<td>Retrospective matched cohort study (propensity matching) Recruitment: 2003-2010</td>
<td>147 HCR</td>
<td>64.3 ± 12.8</td>
<td>38.1†</td>
<td>39.5</td>
<td>54.7 ± 8.7</td>
<td>13.6 MI</td>
<td>N/A</td>
<td>N/A</td>
<td>0.02 ± 0.023 (S)</td>
<td>EndoACAB MIDCAB (OP-Da Vinci)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>588 CAGB</td>
<td>64.3 ± 12.5</td>
<td>35.5</td>
<td>54.6 ± 8.7</td>
<td>12.4 MI</td>
<td>N/A</td>
<td>N/A</td>
<td>0.018 ± 0.021 (S)</td>
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<tr>
<td>Vassiliadis et al., 2009 (46)</td>
<td>Retrospective cohort study (no matching, propensity score adjustment) Recruitment: 2003-2007</td>
<td>91 HCR</td>
<td>64.7 ± 13.7</td>
<td>76.3</td>
<td>40.7</td>
<td>51.5 ± 9.4</td>
<td>18.7†</td>
<td>85 CABG 1st 6 PCI 1st</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>2</td>
<td>N/A</td>
<td>109/18 stents 1 POBA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4,175 OPCAB</td>
<td>62.8 ± 11.7</td>
<td>69.1</td>
<td>37.3</td>
<td>50.9 ± 12.7</td>
<td>36.2†</td>
<td>N/A</td>
<td>N/A</td>
<td>Endo-ACAB MIDCAB OP 100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Zhao et al., 2009 (40)</td>
<td>Retrospective cohort study (no matching) Recruitment: 2005–2007</td>
<td>112 HCR</td>
<td>63 (32-85)</td>
<td>71</td>
<td>39</td>
<td>50 (15-70)</td>
<td>74</td>
<td>1-stop</td>
<td>N/A</td>
<td>N/A</td>
<td>OP open 19%</td>
<td>N/A</td>
<td>N/A</td>
<td>95/9 patients 8 both</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>254 CAGB</td>
<td>63 (32-89)</td>
<td>76</td>
<td>39</td>
<td>54 (10-72)</td>
<td>68</td>
<td>N/A</td>
<td>OP open 6.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Kon et al., 2008 (30)</td>
<td>Matched prospective cohort study (unclear matching method) Recruitment: 2005-2006</td>
<td>15 HCR</td>
<td>61 ± 10</td>
<td>73</td>
<td>27</td>
<td>47 ± 14</td>
<td>N/A</td>
<td>1-stop</td>
<td>N/A</td>
<td>N/A</td>
<td>MIDCAB OP</td>
<td>N/A</td>
<td>N/A</td>
<td>22/0 stents</td>
<td>11 PES 11 SES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 OPCAB</td>
<td>65 ± 10</td>
<td>63</td>
<td>40</td>
<td>45 ± 14</td>
<td>N/A</td>
<td>N/A</td>
<td>OP -open</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Reicher et al., 2008 (39)</td>
<td>Prospective, matched cohort study (propensity matching) 2005-2006</td>
<td>13 HCR</td>
<td>62 ± 10</td>
<td>80</td>
<td>29</td>
<td>31 (EF &lt; 40%)</td>
<td>0</td>
<td>CABG 1st</td>
<td>N/A</td>
<td>N/A</td>
<td>OP MIDCAB</td>
<td>0</td>
<td>C: 77%</td>
<td>22/0 stents</td>
<td>11 SES 11 PES</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>26 CAGB</td>
<td>64 ± 10</td>
<td>83</td>
<td>41</td>
<td>27 (EF &lt; 40%)</td>
<td>N/A</td>
<td>N/A</td>
<td>OP open</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Values are mean ± SD, median (interquartile range), n, or % as indicated. *if single number, this indicates patients undergoing HCR. †Statistically significant difference between the 2 groups (p < 0.05). EES = everolimus-eluting stent(s); E-ZES = Endeavor zotarolimus-eluting stent(s); OP = off-pump coronary artery bypass; R-ZES = Resolute zotarolimus-eluting stent(s); other abbreviations as in Table 1.
using HCR, with a cumulative population of >3,000 patients (54), one-third of whom were included in registries published in the last 5 years (Table 1). In this time period (2008 to 2013), 624 patients who underwent HCR have been incorporated in purposefully designed cohorts comparing their outcomes with those from matched patients undergoing conventional CABG (Table 2). In a recent meta-analysis by Harsskamp et al. (55) comprising 1,190 patients (1 case control and 5 propensity-matched studies), no significant differences were found for the composite of death, myocardial infarction, stroke, or repeat revascularization at 1 year (hazard ratio: 0.49; 95% confidence interval: 0.2 to 1.24; p = 0.13).

In the most recent registries (Table 1), CABG was performed before PCI in about one-half of the HCR procedures (50.6%; 504 of 996), whereas PCI was performed first in 26.6% (265 of 996). One-stop HCR proved the least popular (22.8%; 227 of 996), highlighting the practical difficulties of setting up and running a hybrid operating room. However, among cohort studies (Table 2) comparing HCR with conventional CABG, 1-stop HCR appears to be the most popular strategy, highlighting that the simultaneous approach is considered the gold standard for comparisons with other revascularization strategies. The majority of HCR patients are just over 60 years of age, are predominantly male (~70% to 80%), and have a diabetes prevalence varying from 23% to 40.7% (Tables 1 and 2). The presentation mode varied across the studies, with ACS prevalence as low as 0% (39) or 13.6% (34) to as high as 74% (40). In the majority of HCR cases, left ventricular ejection fraction was preserved or, at most, mildly impaired.

Most studies reported an average risk, using additive EuroSCORE, of 3.1 (36) to 6 (56), whereas STS score was as low as 0.018% (34) to 4.69% (43). SYNTAX-HCR group (n = 13; median additive EuroSCORE of 6) in the study by Leacche et al. (56) with a perioperative mortality of 23% (3 of 13). Most reports focus on the lower morbidity related to the minimally invasive nature of the procedure’s surgical component as compared with conventional CABG. Low morbidity is mirrored by reduced blood transfusion requirements (31,34,36), shorter intensive care and hospital length of stay, and faster recovery (30,31,39,58).
Among HCR cohorts, excellent LIMA patency rates have been reported at various intervals from grafting. Fitzgibbon A or B LIMA patency rates (A [excellent], B [fair], or 0 [occluded]) (59) have been reported in a high percentage of patients: ranging from 93% to 100% (31, 33, 40, 43, 46, 57) of patients in the perioperative period (on the day of surgery or pre-discharge); 90% (39) and 94% (37) of patients at 6 months; 100% (30) at 1 year; and 91% (38) of HCR patients at 2 years post-grafting. Only 2 studies in the last 5 years reported angiographic follow-up of patients who underwent HCR. I nas t u d yo f6 0p a t i e n t s, K i a i ie ta l. (38) reported 2-year angiographic follow up in 54 (90%) patients. Binary in-stent restenosis rates were 13%, whereas in-stent thrombosis was observed in 3.7% of patients. In another study of 94 HCR patients with 6-month angiographic follow-up (37), binary in-stent restenosis was reported in 9% of patients, whereas in-stent thrombosis was seen in 2.2%. These figures concur with those reported from studies using first-generation DES (7).

Follow-up data from HCR registries (Table 3) demonstrate survival rates of 92.5% (44) to 100% (37) at 1 year and 84.8% (44) to 93% (43) at 5 years. MACE-free survival varied from 83.9% (35) to 93.1% (43) at 1 year down to 75.2% (35) to 83% (43) at 5 years. When pooling the results from 2 retrospective cohort studies comparing long-term survival and MACE between propensity-matched patients undergoing conventional CABG or HCR (34, 36), similar mortality rates (at 3 to 5 years) were observed (Figure 1A). However, at 3 years, HCR patients experienced an increased rate of repeat revascularization (hazard ratio: 3.17; 95% confidence interval: 1.74 to 5.79) (Figure 1B). Of note, patients recruited in both studies had relatively low surgical risk calculated with additive EuroSCORE and STS. Leac-h et al. (56) attempted to assess 30-day outcomes in HCR versus standard CABG after stratification for risk score (EuroSCORE) and disease complexity (SYNTAX score). They concluded that even though HCR may be a safe alternative in patients with less complex disease (SYNTAX score <32), CABG should be the preferred strategy in those with SYNTAX score >32 as survival (100% vs. 77%; p = 0.002) and MACE (5% vs. 30%; p = 0.015) favored standard
<table>
<thead>
<tr>
<th>First Author, Year (Ref. #)</th>
<th>N</th>
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<th>In-Hospital Outcomes</th>
<th>Clinical Follow-Up</th>
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<tr>
<td></td>
<td></td>
<td>Number of Patients in Follow-Up</td>
<td>% LIMA Patency</td>
<td>ISMR &gt;50% (Occlusion), %</td>
</tr>
<tr>
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<td>HCR</td>
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<td>N/A</td>
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<tr>
<td></td>
<td>141</td>
<td>CABG</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>141</td>
<td>PCI</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Leacche et al., 2013 (56)</td>
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<td>HCR</td>
<td>SYNTAX ≤32 (67)</td>
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<tr>
<td></td>
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<td>PCI</td>
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<td>SYNTAX &gt;32 (75)</td>
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<tr>
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<td>OPCAB</td>
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<td>HCR</td>
<td>SYNTAX ≤32 (206)</td>
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<td>SYNTAX &gt;32 (206)</td>
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<td>91</td>
<td>HCR</td>
<td>Prior to discharge</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>4,175</td>
<td>OPCAB</td>
<td>N/A</td>
<td>N/A</td>
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<td>Zhao et al., 2009 (40)</td>
<td>112</td>
<td>HCR</td>
<td>On the table</td>
<td>366</td>
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<tr>
<td></td>
<td>254</td>
<td>OPCAB</td>
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<td>N/A</td>
</tr>
<tr>
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<td>15</td>
<td>HCR</td>
<td>1 yr</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>OPCAB</td>
<td>0</td>
<td>N/A</td>
</tr>
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<td>HCR</td>
<td>6 months</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>OPCAB</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Values are mean ± SD, median (interquartile range), n, or % as indicated. *Statistically significant difference between the 2 groups (p < 0.05). Abbreviations as in Tables 1, 2, and 3.
surgery. However, these results may simply reflect the effect of unadjusted confounders (increased age by ~8 years in the HCR group). In contrast, the propensity-matched cohort from Shen et al. (36) showed no difference in MACE rates between HCR and CABG (p = 0.362) in patients with high SYNTAX scores (>30) (Table 4). Furthermore, the same study showed that among patients with high additive EuroSCORE (>6), those who underwent 1-stop HCR demonstrated a significantly lower MACE rate versus CABG (p = 0.030) (Figure 2). These data underscore the importance of meticulous patient selection for HCR procedures and support the hypothesis that high-risk candidates may benefit the most from hybrid procedures.

The results of the first RCT comparing HCR (CABG first) and standard CABG, POL-MIDES (Prospective Randomized PilOt Study Evaluating the Safety and Efficacy of Hybrid Revascularization in Multivessel Coronary Artery DiseaSe), were only recently published (60). A total of 200 consecutive patients with angiographically confirmed multi-vessel CAD involving the proximal LAD and a significant (>70%) lesion in at least 1 major non-LAD epicardial vessel amenable to both PCI and CABG were randomized in a 1:1 fashion to HCR (n = 98) (using MIDCAB and cobalt chromium EES) or conventional CABG (n = 102). Both groups had similar baseline demographic characteristics, risk factor profiles, and SYNTAX scores. HCR was feasible for 93.9% of patients whereas conversion to standard CABG was required for 6.1%. At 1 year, both groups had similar all-cause mortality (CABG 2.9% vs. HCR 2%; p = NS) and MACE-free survival rates (CABG 92.2% vs. HCR 89.8%; p log-rank = 0.54).

Even though larger RCTs with long-term follow up are needed before firm conclusions are drawn, available data suggest that HCR is feasible and safe, with short-term outcomes similar to conventional

---

**FIGURE 2 Improved MACCE in HCR Group**

<table>
<thead>
<tr>
<th>Low SYNTAX score</th>
<th>Medium SYNTAX score</th>
<th>High SYNTAX score</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Cumulative MACCE Rate (%)</td>
<td>The Cumulative MACCE Rate (%)</td>
<td>The Cumulative MACCE Rate (%)</td>
</tr>
<tr>
<td>Follow-up Time (Years)</td>
<td>Follow-up Time (Years)</td>
<td>Follow-up Time (Years)</td>
</tr>
<tr>
<td>Log rank p = 0.618</td>
<td>Log rank p = 0.291</td>
<td>Log rank p = 0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low EuroSCORE</th>
<th>Medium EuroSCORE</th>
<th>High EuroSCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Cumulative MACCE Rate (%)</td>
<td>The Cumulative MACCE Rate (%)</td>
<td>The Cumulative MACCE Rate (%)</td>
</tr>
<tr>
<td>Follow-up Time (Years)</td>
<td>Follow-up Time (Years)</td>
<td>Follow-up Time (Years)</td>
</tr>
<tr>
<td>Log rank p = 0.336</td>
<td>Log rank p = 0.206</td>
<td>Log rank p = 0.030</td>
</tr>
</tbody>
</table>

Improved major adverse cardiac and cerebrovascular events (MACCE) among patients in the HCR group versus conventional CABG and percutaneous coronary intervention (PCI) in the high EuroSCORE tertile. Adapted with permission from Shen et al. (36). SYNTAX = SYNergy Between PCI With TAXUS and Cardiac Surgery; other abbreviations as in Figure 1.
CABG in carefully selected, low- to intermediate-risk patients with intermediate CAD complexity.

UNRESOLVED ISSUES

The burning question that prevents HCR from taking off remains unanswered: why should institutes adopt a complex, costly procedure requiring state-of-the-art equipment, unique expertise, and close collaboration of interventional cardiologists and cardiac surgeons, when similar survival and morbidity outcomes can be obtained with a well-established, safe procedure available in most hospitals? First, a recent well-designed (albeit retrospective) study (36), shows signals of improved MACE outcomes in the HCR versus conventional CABG group for patients in the highest EuroSCORE tertile (>6), suggesting a potential target population that would benefit the most from this complex procedure (Figure 1).

Second, the use of HCR in lower- to intermediate-risk groups could be justified by improved patient satisfaction (30,31), shorter intensive care and hospital stays, faster return to work (HCR 1.75 ± 1 month vs. CABG 4.4 ± 3.1 months; p = 0.01) (30), and quicker return to normal daily activities. Conventional CABG advocates would claim that HCR is a more costly procedure, as demonstrated by in-hospital cost-specific data (30,31,39) and hidden costs involving construction and maintenance of hybrid operating rooms. Health commissioners and governments, however, may hold a different view when taking into account the working days lost due to delayed healing/recovery following conventional CABG.

Another unresolved issue: the appropriateness of HCR versus CABG comparisons without introducing a third group of patients treated with PCI, including new-generation DES implantation under fractional flow reserve guidance. Last, but not least, for patients who undergo LIMA to LAD first as part of an intended staged HCR, and who become asymptomatic post-procedure, the benefits of PCI to residual intermediate non-LAD lesions should be questioned. Optimal medical therapy—watchful waiting alongside ischemia testing when symptomatology is unclear—provides a reasonable alternative, albeit not evidence based.

CONCLUSIONS

Current evidence suggests that HCR is feasible and safe for a particular target group (just over 60 years of age; mainly stable, CAD favorable anatomy; intermediate risk and SYNTAX scores; and preserved or mildly impaired left ventricular ejection fraction) with acceptable midterm outcomes that are non-inferior to conventional CABG. However, data for higher-risk groups, who would theoretically benefit the most from HCR, are weak or lacking; hence, no inferences or generalizations can be made regarding the role of HCR in these patients. It is now in the hands of the scientific community and health managers to identify patients who would benefit the most and find ways to make HCR a cost-effective procedure for both hospitals and societies. If these goals are not achieved, HCR will remain a very reasonable, yet rarely implemented, revascularization option.

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JANUARY 6/13, 2015


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**KEY WORDS** coronary artery bypass graft surgery, hybrid coronary artery revascularization, minimally invasive direct coronary artery bypass grafting, percutaneous coronary intervention