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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REVIEW TOPIC OF THE WEEK

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. (J Am Coll Cardiol 2015;65:85–97) © 2015 by the American College of Cardiology Foundation.

Hybrid coronary revascularization (HCR) was first introduced in the mid-1990s (1) as a pioneering treatment approach to multivessel coronary artery disease (CAD), hoping to bring together the "best of both worlds" (2). HCR aims to reduce surgical trauma while preserving long-term survival and minimizing adverse cardiovascular events.

The hybrid approach includes left internal mammary artery (LIMA) anastomosis to the left anterior descending coronary artery (LAD), typically via a minimally invasive approach, and percutaneous coronary intervention (PCI) for the remaining (non-LAD) lesions. Variations to this schema were discussed in a recent nomenclature paper (3), including the grafting of multiple coronary vessels (e.g., LIMA to LAD and saphenous graft to diagonal).

THE RATIONALE FOR HCR

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).

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft surgery

DES = drug-eluting stent(s)

HCR = hybrid coronary revascularization

LAD = left anterior descending artery

LIMA = left internal mammary artery

MIDCAB = minimally invasive direct coronary artery bypass grafting

PCI = percutaneous coronary intervention

SVG = saphenous vein graft

VEIN GRAFT PATENCY VERSUS STENT RESTENOSIS 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 (bioresorbable polymer-based or polymer-free stents) durable polymers 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 amphilimus-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 stenting provide strong competition for SVG revascularization 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 compared with stent thrombosis (10), the clinical consequences 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 characterized 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 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 cardiopulmonary 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 "primary purpose of performing HCR is to decrease the morbidity rate of traditional CABG in high-risk patients" (27). Even in the more recent European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization (28), HCR has a Class IIb recommendation for specific patient subsets and only at experienced centers. The lack of several large randomized controlled 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" procedure. 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 disadvantages (**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

CENTRAL ILLUSTRATION **Advantages and Disadvantages of Simultaneous and Staged HCR Procedures**

ONE STAGE (SIMULTANEOUS)	TWO-STAGE HCR	
MID-CAB followed by PCI within minutes	**MID-CAB 1st, then PCI**	**PCI 1st, then MID-CAB**
Advantages • LIMA-LAD graft can be studied by the interventional cardiologist before PCI stent implantation • PCI to high-risk non-LAD lesions can be performed with a protected LAD area • In cases of unsuccessful stent implantation, conventional CABG remains an option • Cost effective, as it reduces hospital length of stay (single-step complete revascularization) • Patient satisfaction: condenses revascularization therapy in one patient encounter	**Advantages** • Allows angiographic validation of the LIMA-LAD graft • Full antiplatelet inhibition following CABG with no perioperative bleeding risk • Protected anterior wall, lowering procedural risks during PCI of non-LAD vessels • On some occasions, after minimally invasive LIMA to LAD, patients become asymptomatic in the immediate post-operative period	**Advantages** • Allows angiographic evaluation of the size of LIMA • Lower risk of ischemia during the MID-CAB in a partially revascularized heart • Useful in the setting of acute myocardial infarction when culprit is a non-LAD lesion • In cases of unsuccessful stent implantation, suboptimal CABG can be performed
Disadvantages • Only feasible in hybrid suites, featuring state-of-the-art surgical and interventional equipment • Inflammatory response to surgery offers a risk for stent thrombosis • Dual antiplatelet therapy increases the risk of bleeding • Chronic kidney disease patients are exposed to the dual nephrotoxic insult of surgery and contrast media utilization	**Disadvantages** • Risk of ischemia of non-LAD territories during the LIMA-LAD grafting (although this is very unlikely in stable patients) • Risk of a high-risk surgical reintervention in case of an unsuccessful PCI	**Disadvantages** • No angiographic control of LIMA-LAD graft • Higher risk of stent thrombosis during surgery (due to inflammatory response to surgery/discontinuation of dual antiplatelet therapy/platelet transfusion) • Increased perioperative bleeding risk due to dual antiplatelet therapy during surgery • Risk of adverse events in the LAD territory during the between-stages interval

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CABG = coronary artery bypass grafting; HCR = hybrid coronary revascularization; LAD = left anterior descending artery; LIMA = left internal mammary artery; MI = myocardial infarction; MID-CAB = minimally invasive direct coronary artery bypass grafting; PCI = percutaneous coronary intervention.

interventional equipment. Often, CABG is performed first, allowing the interventional cardiologist to study the LIMA-LAD graft before stent implantation. Thus, PCI to high-risk, non-LAD lesions is performed with a protected LAD territory. In case of unsuccessful stent implantation, surgical bailout graft implantation 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 1 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 LIMA 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, thoracoscopic and robotic techniques have been developed. These include the endoscopic atraumatic coronary artery bypass (Endo-ACAB), which allows thoracoscopic/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 1 HCR Registries Published Since 2008

First Author, Year (Ref. #)	Registry Recruitment	HCR/Total Assessed (N = 998)*	Age, yrs	Male, %	Diabetes, %	LVEF, %	ACS, %	Timing	SYNTAX Score	Risk Score	Surgical Technique	Conversion to Open	Angiographic Type/Location of PCI Lesions	DES/BMS	Type of DES
Adams et al., 2013 (37)	2004–2012	94-96	64 ± 12	72.9	N/A	N/A	38 (UA)	1-stop	N/A	N/A	MIDCAB Da Vinci-OP	2	N/A	95/10 stents	91 PES 3 SES 1 ZES
Halkos et al., 2013 (33)	2003–2012	269-300	64.12 ± 12.1	68.3	36.7	54.7 ± 69.2	34 (MI)	21 1-stop 192 CABG 1st 56 PCI 1st		1.6 ± 2.1 (S)	<2,009 Endo-ACAB >2,009 MIDCAB Da Vinci-OP	6	N/A	232/28 patients 28 DES + BMS 4 POBA 3 Unknown	N/A
Repossini et al., 2013 (43)	2004–2011	166	65.8 ± 10.3	90.4	24.1	9.6 (EF <30%)	58.4	60 CABG 1st 106 PCI 1st	29.3 ± 7.37	3.49 ± 4.77 (EII) 4.69 ± 3.77 (S)	MIDCAB-OP	4	N/A	57/109 patients	N/A
Bonatti et al., 2012 (35)	N/A	140-162	61 (31-85)	79.3	28.6	60 (20-79)	43.6 (MI)	28 1-stop 74 CABG 1st 38 PCI 1st	N/A	2 (0-13) (Add E) 0.5 (0.2-9.9) (S)	Robotic TECAB On & off pump	22	N/A	98/34 patients 5 patients POBA 3 patients aspiration	N/A
Rab et al., 2012 (57)	N/A	22	61.0 ± 13.7	59.1	27.3	54.8 ± 8.8	N/A	22 CABG 1st	22.3 ± 10.0	1.6 ± 1.9 (S)	MIDCAB Da Vinci-OP	NA	N/A	21/1 patients	N/A
Bonaros et al., 2011 (61)	2001–2009	130	58 (41-75)	77	N/A	N/A	N/A	21 1-stop 97 CABG 1st 12 PCI 1st	N/A	NA	OP MIDCAB (3) AH-TECAB (96) BH-TECAB (31)	13	N/A	N/A	N/A
Holzhey et al., 2008 (44)	1996–2007	117	64.6 ± 12.3	83.8	24.8	59.2 ± 13.1	4.3 (UA)	5 1-stop 59 CABG 1st 53 PCI 1st	N/A	4.3 (Log E)	MIDCAB (107) OP TECAB (8) TECAB (2)	N/A	N/A	N/A	N/A
Kiaii et al., 2008 (38)	2004–2007	58-60	59.9 ± 11.7	78	23	N/A	17 (MI)	58 1-stop	N/A	N/A	Endo-ACAB OP	2	A/B1: 31 B2/C: 28	53/6 stents	49 PES 3 SES 6 BMS

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 2 Cohorts Comparing HCR With Conventional On- or Off-Pump CABG Published Since 2008

First Author, Year (Ref. #)	HCR*	Age, yrs	Male, %	Diabetes, %	LVEF, %	ACS, %	Timing HCR	SYNTAX Score	Risk Score	Surgical Technique	Conversion to Open	Angiographic Type/Location of PCI Lesions	DES/BMS	Type of DES HCR Group
Shen et al., 2013 (36) Retrospective, matched cohort study (propensity matched) Recruitment: 2007–2010	141 HCR	62 ± 9.9	88.7	26.2	62.7 ± 7.1	N/A	1-stop	27.6 ± 7.9	3.1 ± 2.3 (Add E)	MIDCAB	N/A	N/A	271/0 stents	210 SES 8 PES 12 E-ZES 41 R-ZES
	141 CABG	62.4 ± 7.8	90.1	18.4	62.6 ± 8.0	N/A		28.2 ± 9.4	3.3 ± 2.3 (Add E)	OP 20.6%				
	141 PCI	61.7 ± 10.3	87.2	19.9	61.2 ± 9.3	N/A		26.0 ± 8.2	3.5 ± 2.6 (Add E)					
Leacche et al., 2013 (56) Retrospective cohort study (group stratification) Recruitment 2005–2009	80 HCR													
	SYNTAX ≤32 (67)	62 (32–85)	79	42	50 (20–70)	58	1-stop		4 (0–12) (Add E)	OP 22%	NA	NA	62/7 patients	NA
	SYNTAX >32 (13)	74 (32–84)	62	31	50 (20–65)	61			6 (1–14) (Add E)	OP 31%			10/3 patients	
	301 CABG													
	SYNTAX ≤32 (226)	63 (32–89)	75	38	55 (10–80)	71			4 (0–14) (Add E)	OP 15%				
	SYNTAX >32 (75)	62 (32–83)	83	32	50 (10–70)	57			4 (0–15) (Add E)	OP 16%				
Bachinsky et al., 2012 (31) Prospective cohort study, no matching Recruitment: 2009–2011	25 HCR	63.2 ± 10.5	80†	36	55.3 ± 10.4	32	1-stop	33.52 ± 8	0.46 ± 0.24 (S)†	MIDCAB (OP-Da Vinci) 100%	N/A	A: 14% (n = 6) B1: 26% (n = 11) B2: 50% (n = 21) C: 10% (n = 4)	42/18 stents	42 EES 18 BMS
	27 OPCAB	66.78 ± 10.7	59†	48	51.48 ± 12.0	37		34.89 ± 8.2	0.96 ± 0.93 (S)†					
Halkos et al., 2011 (34) Retrospective matched cohort study (propensity matching) Recruitment: 2003–2010	147 HCR	64.3 ± 12.8	38.1†	39.5	54.7 ± 8.7	13.6 MI	N/A	N/A	0.02 ± 0.023 (S)	EndoACAB	N/A	N/A	N/A	N/A
	588 CABG	64.3 ± 12.5	28.6†	35.5	54.6 ± 8.7	12.4 MI		N/A	0.018 ± 0.021 (S)	MIDCAB (OP-Da Vinci)				
Vassiliades et al., 2009 (46) Retrospective cohort study (no matching, propensity score adjustment) Recruitment: 2003–2007	91 HCR	64.7 ± 13.7	76.3	40.7	51.5 ± 9.4	18.7†	85 CABG 1st 6 PCI 1st	N/A	N/A	Endo-ACAB MIDCAB	2	N/A	109/18 stents 1 POBA	NA
	4,175 OPCAB	62.8 ± 11.7	69.1	37.3	50.9 ± 12.7	36.2†		N/A	NA	OP 100%				
Zhao et al., 2009 (40) Retrospective cohort study (no matching) Recruitment: 2005–2007	112 HCR	63 (32–85)	71	39	50 (15–70)	74	1-stop	N/A	N/A	OP open† 20%	N/A	N/A	95/9 patients 8 both	N/A
	254 CABG	63 (32–89)	76	39	54 (10–72)	68				OP open 6.7%				
Kon et al., 2008 (30) Matched prospective cohort study (unclear matching method) Recruitment: 2005–2006	15 HCR	61 ± 10	73	27	47 ± 14	N/A	1-stop	N/A	N/A	MIDCAB OP	N/A	N/A	22/0 stents	11 PES 11 SES
	30 OPCAB	65 ± 10	63	40	45 ± 14	N/A		N/A	N/A	OP -open				
Reicher et al., 2008 (39) Prospective, matched cohort study (propensity matching) 2005–2006	13 HCR	62 ± 10	80	29	31 (EF <40%)	0	CABG 1st	N/A	N/A	OP MIDCAB	0	C: 77%	22/0 stents	11 SES 11 PES
	26 CABG	64 ± 10	83	41	27 (EF <40%)	N/A		N/A	N/A	OP open				

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 Harskamp 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 score, in the few studies reporting it, varied from 22.3 (57) to 33.5 (31), suggesting that most patients recruited in HCR registries and cohorts belong to the intermediate SYNTAX group.

Perioperative HCR mortality ranged from 0% (30,37–39) to 2.6% (40) with the exception of the high 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).

TABLE 3 Angiographic and Clinical Follow-up Data in Patients in HCR Registries Published Since 2008

			Angiographic Follow-Up				In-Hospital Outcomes				Clinical Follow-Up		
First Author, Year (Ref. #)	Registry Recruitment	N	Follow- Up	Patients in Follow-Up, n	% LIMA Patency Fitzgibbon A or B	ISR >50%, %	IST (Occlusion), %	Perioperative Mortality, %	Blood Transfusion, %	ICU LOS	Hospital LOS, Days	Survival, % (Follow-Up Time)	Event-free Survival, % (Follow-Up Time)	% Revascularization (Follow-Up Time)
Adams et al., 2013 (37)	2004–2012	94	6.8 months	89	94	9	2.2 (2/89)	0	7.5	N/A	4 (3-7)	100 (1 yr) 91 (5 yrs)	88.8 (6.8 months)	13 (5 yrs)
Halkos et al., 2013 (33)	2003–2012	269	On day of MIDCAB	248	97.6	N/A	N/A	N/A	31.7	1 day (0–11 days)	5 (2–76)	–	–	–
Repossini et al., 2013 (43)	2004–2011	166	On day of MIDCAB	60	100	N/A	N/A	1.25	27.5	22.3 ± 15.8 h	6.5 ± 1.8	95.8 (1 yr) 93 (5 yrs)	93.1 (1 yr) 83 (5 yrs)	7.2 (4.5 yrs)
Bonatti et al., 2012 (35)	N/A	140	N/A	N/A	N/A	N/A	N/A	1.3	N/A	22 h (13–250 h)	6 (3–49)	95.2 (1 yr) 92.9 (5 yrs)	83.9 (1 yr) 75.2 (5 yrs)	16.9 (5 yrs)
Rab et al., 2012 (57)	N/A	22	3.8 days	22	100	N/A	N/A	N/A	9	1.1 ± 0.4 day	6.1 ± 2.4	95.5 (3.2 yrs)	95.5 (3.2 yrs)	0 (3.2 yrs)
Bonaros et al., 2011 (61)	2001–2009	130	N/A	N/A	N/A	N/A	N/A	0.7	N/A	20 h (12-1,048 h)	6 (3–50)	99 (2 yrs)	75 (2 yrs)	8 (2 yrs)
Holzhey et al., 2008 (44)	1996–2007	117	N/A	N/A	N/A	N/A	N/A	1.9	N/A	7.9 h ICU 26.5 h intermediate care	N/A	92.5 (1 yr) 84.8 (5 yrs)	85.5 (1 yr) 75.5 (5 yrs)	4.3 (1.8 yrs)
Kiaii et al., 2008 (38)	2004–2007	60	20.2 months	54	91	13	3.7	0	15	1.1 ± 0.43 day	4.3 ± 1.42	100 (20.2 months)	88.9 (20.2 months)	7.4 (20.2 months)

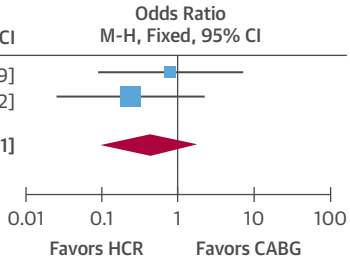
Values are mean ± SD, median (interquartile range), n, or % as indicated.
ICU = intensive care unit; ISR = in-stent restenosis; IST = in-stent thrombosis; LOS = length of stay; other abbreviations as in **Tables 1 and 2**.

FIGURE 1 Long-Term Mortality and Revascularization Rates in HCR Patients

A All-cause mortality (3-5 years)

Study or Subgroup	HCR Events	HCR Total	CABG Events	CABG Total	weight	Odds Ratio M-H, Fixed, 95% CI
Halkos M et al. 2011	1	147	5	588	33.3%	0.80 [0.09, 6.89]
Shen L et al. 2013	1	141	4	141	66.7%	0.24 [0.03, 2.22]
Total (95% CI)		**288**		**729**	**100.0%**	**0.43 [0.09, 2.01]**
Total events	2		9			

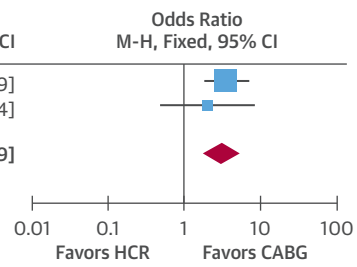
Heterogeneity: Chi^2= 0.57, df= 1 (P = 0.45); I^2= 0%
Test for overall effect: Z= 1.07 (P = 0.28)



B Any revascularization (3 years)

Study or Subgroup	HCR Events	HCR Total	CABG Events	CABG Total	weight	Odds Ratio M-H, Fixed, 95% CI
Halkos M et al. 2011	18	147	22	588	72.9%	3.59 [1.87, 6.89]
Shen L et al. 2013	6	141	3	141	27.1%	2.04 [0.50, 8.34]
Total (95% CI)		**288**		**729**	**100.0%**	**3.17 [1.74, 5.79]**
Total events	24		25			

Heterogeneity: Chi^2= 0.51, df= 1 (P = 0.47); I^2= 0%
Test for overall effect: Z= 3.76 (P = 0.0002)



Pooled results from the only 2 propensity-matched cohort studies comparing hybrid coronary revascularization (HCR) versus coronary artery bypass grafting (CABG) surgery available in the literature (search in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled trials from 2008 through December 2013) demonstrate similar long-term mortality **(A)** but increased revascularization rate **(B)** in patients undergoing HCR. In the absence of significant statistical heterogeneity (I^2), a fixed effects model was used. CI = confidence interval; M-H = Mantel-Haenszel.

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 O [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. In a study of 60 patients, Kiaii et al. (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. Leacche 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 = 0.003) and MACE (5% vs. 30%; p = 0.015) favored standard

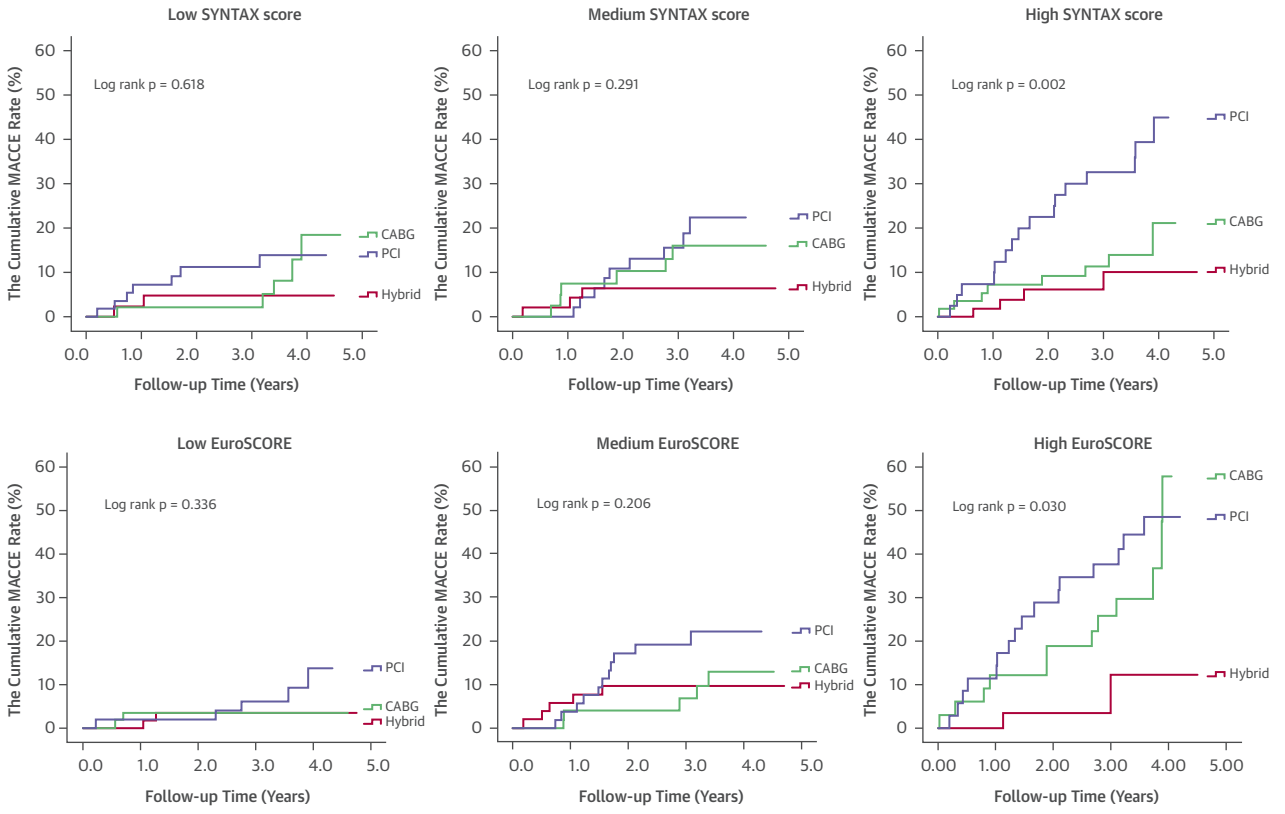
TABLE 4 Cohort Studies Comparing Angiographic and Clinical Follow-Up in Patients Undergoing HCR Versus CABG

		Angiographic Follow-Up					In-Hospital Outcomes				Clinical Follow-Up		
First Author, Year (Ref. #)	N	Follow-Up	Number of Patients in Follow-Up	% LIMA Patency Fitzgibbon A/B	ISR >50%, %	IST (Occlusion), %	Perioperative Mortality, %	Blood Transfusion, %	ICU LOS	Hospital LOS, Days	Survival, % (Follow-Up Time)	Event-Free Survival, % (Follow-Up Time)	Revascularization, % (Follow-Up Time)
Shen et al., 2013 (36) Retrospective, matched cohort study (propensity matched) Recruitment: 2007–2010	141 HCR	N/A	N/A	N/A	N/A	N/A	N/A	21.3*	N/A	8.19 ± 2.54	99.3 (3 yrs)	93.6 (3 yrs)*	6 (3 yrs)*
	141 CABG		N/A	N/A	N/A	N/A	N/A	31.9*	N/A	8.49 ± 3.53	97.2 (3 yrs)	86.5 (3 yrs)*	3 (3 yrs)*
	141 PCI	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	96.5 (3 yrs)	77.3 (3 yrs)*	18 (3 yrs)*
Leacche et al., 2013 (56) Retrospective cohort study (group stratification) Recruitment: 2005–2009	80 HCR												
	SYNTAX ≤32 (67)	N/A	N/A	N/A	N/A	N/A	1	18	N/A	N/A	99 (30 days)	96 (30 days)	N/A
	SYNTAX >32 (13)						23*	31			77 (30 days)*	70 (30 days)*	
	301 CABG												
	SYNTAX ≤32 (226)	N/A	N/A	N/A	N/A	N/A	2	17	N/A	N/A	98 (30 days)	93 (30 days)	N/A
	SYNTAX >32 (75)						0*	3			100 (30 days)*	95 (30 days)*	
Bachinsky et al., 2012 (31) Prospective cohort study, no matching Recruitment: 2009–2011	25 HCR	On the table	24	96 (A)	N/A	N/A	N/A	12*	28.5 ± 13.9 h	5.1 ± 2.8*	100 (30 days)	100 (30 days)	0 (30 days)
	27 OPCAB	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	96 (30 days)	0 (30 days)
Halkos et al., 2011 (34) Retrospective matched cohort study (propensity matching) Recruitment: 2003–2010	147 HCR	N/A	N/A	N/A	N/A	N/A	0.7	35.4*	52.7 ± 87.8 h	6.1 ± 4.7	86.8 (5 yrs)	98 (on discharge)	12.2 (3.2 yrs)*
	588 OPCAB	N/A	N/A	N/A	N/A	N/A	0.9	56*	57.4 ± 145.0 h	6.6 ± 6.7	84.3 (5 yrs)	98 (on discharge)	3.7 (3.2 yrs)*
Vassiliades et al., 2009 (46) Retrospective cohort study (no matching, propensity score adjustment) Recruitment: 2003–2007	91 HCR	Prior to discharge	91	100	N/A	N/A	N/A	20.9	NA	4.2 ± 2.5	98.9 (1 yr) 96.9 (2 yrs) 94 (3 yrs)	96.7 (30 days) 90 (1 yr)	0 (30 days) 5.5 (1 yr)
	4,175 OPCAB	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	94.5 (1 yr) 91.8 (2 yrs) 89.2 (3 yr)	97 (30 days) N/A (1 yr)	0.3 (30 days) N/A (1 yr)
Zhao et al., 2009 (40) Retrospective cohort study (no matching) Recruitment: 2005–2007	112 HCR	On the table	366	93	N/A	0.3	2.6	N/A	N/A	6 (1–97)	N/A	N/A	N/A
	254 CABG						1.5	N/A	N/A	5 (1–33)	N/A	N/A	N/A
Kon et al., 2008 (30) Matched prospective cohort study (unclear matching method) Recruitment: 2005–2006	15 HCR	1 yr	15	100 (HCR only)	N/A	N/A	0	N/A	0.98 ± 0.42 days*	3.7 ± 1.4*	100 (1 yr)	93 (1 yr)	3 (1 yr)
	30 OPCAB		30				0	N/A	2.42 ± 1.57 days*	6.4 ± 2.2*	100 (1 yr)	77 (1 yr)	15 (1 yr)
Reicher et al., 2008 (39) Prospective, matched cohort study (propensity matching) Recruitment: 2005–2006	13 HCR	6 months	10	90	N/A	10	0	N/A	20 ± 2.4 h	3.6 ± 1.5 *	0 (6 months)	84.6 (14 months)	15.4 (14 months)
	26 CABG						0	N/A	44.5 ± 36.4 h	6.3 ± 2.3*	0 (6 months)	77.8 (14 months)	22.2 (14 months)

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.

FIGURE 2 Improved MACCE in HCR Group



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.

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 multivessel 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

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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