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Hybrid coronary revascularization: position paper of the European Society of Cardiology Working Group on Cardiovascular Surgery and European Association of Percutaneous Cardiovascular Interventions

Matthias Thielmann [a,*,†], Nikolaos Bonaros [b,*,†], Emanuele Barbato [c,d], Fabio Barili [e], Thierry Folliguet [f], Guy Friedrich [g], Roman Gottardi [h], Jacek Legutko [i], Alessandro Parolari [j], Prakash Punjabi [k,l], Sigrid Sandner [m], Piotr Suwalski [n], Sharaf-Eldin Shehada [a], Daniel Wendt [o], Martin Czerny [h,p] and Claudio Muneretto [q]

[a]Department of Thoracic and Cardiovascular Surgery, West-German Heart and Vascular Center, University Hospital Essen, Essen, Germany
[b]Department of Cardiac Surgery, Medical University of Innsbruck, Austria
[c]Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy
[d]Cardiovascular Research Center Aalst OLV Hospital, Aalst, Belgium
[e]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[f]Chirurgie Cardiaque et Transplantation, Assistance Publique Hôpital Henri Mondor, Université Paris UPEC, Paris, France
[g]Department of Cardiology, Innsbruck Medical University, Innsbruck, Austria
[h]Department of Cardiovascular Surgery, University Heart Center Freiburg, Freiburg, Germany
[i]Department of Interventional Cardiology, Jagiellonian University Medical College, Institute of Cardiology, The John Paul II Hospital, Krakow, Poland
[j]Department of Biomedical Sciences for Health, University of Milan, Milan, Italy
[k]Department of Cardiothoracic Surgery, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, UK
[l]National Heart and Lung Institute, Imperial College London, London, UK
[m]Department of Cardiac Surgery, Medical University Vienna, Vienna, Austria
[n]Clinical Department of Cardiac Surgery, Central Clinical Hospital of the Ministry of Interior and Administration, Centre for Postgraduate Medical Education, Warsaw, Poland
[o]Faculty of Medicine, University Hospital Essen, Essen, Germany
[p]Faculty of Medicine, Albert-Ludwigs-University Freiburg, Freiburg, Germany
[q]Department and School of Cardiovascular Surgery, University of Brescia Medical School, Spedali Civili di Brescia, Brescia, Italy

* Corresponding authors. Department of Thoracic and Cardiovascular Surgery, West-German Heart and Vascular Center, University Hospital Essen, Hufelandstraße 55, 45122 Essen, Germany. Tel: +49-201-723-8-4908; fax. +49-201-723-6800; e-mail: matthias.thielmann@uni-due.de (M. Thielmann); University Clinic of Cardiac Surgery, Innsbruck Medical University, Innsbruck, Austria. Tel: +43 512 504 80764; e-mail: nikolaos.bonaros@i-med.ac.at (N. Bonaros).

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Abstract

Myocardial revascularization in coronary artery disease via percutaneous coronary intervention or coronary artery bypass graft (CABG) surgery effectively relieves symptoms, significantly improves prognosis and quality of life when combined with guideline-directed medical therapy. Hybrid coronary revascularization is a promising alternative to percutaneous coronary intervention or CABG in selected patients and is defined as a planned and/or intended combination of consecutive CABG surgery using at least 1 internal mammary artery to the left anterior descending (LAD), and catheter-based coronary intervention to the non-LAD vessels for the treatment of multivessel disease. The main indications for hybrid coronary revascularization are (i) to achieve complete revascularization in patients who cannot undergo conventional CABG, (ii) to treat patients with acute coronary syndromes and multivessel disease with a non-LAD vessel as the culprit lesion that needs revascularization and (iii) in highly select patients with multivessel disease with complex LAD lesions and simple percutaneous coronary intervention targets for all other vessels. Hybrid coronary revascularization patients receive a left internal mammary artery graft to the LAD artery through a minimal incision along with percutaneous coronary intervention to the remaining diseased coronary vessels using latest generation drug-eluting stents. A collaborative environment with a dedicated heart team is the optimal platform to perform such interventions, which aim to improve the quality and outcome of myocardial revascularization. This position paper analyses the rationale of hybrid coronary revascularization and the currently available evidence on the various techniques and delves into the sequence of the interventions and pharmacological management during and after the procedure.

†The first two authors share joint first authorship.

Keywords: Coronary artery disease • Revascularization • Coronary artery bypass grafting • Percutaneous coronary intervention • Hybrid coronary revascularization • Position paper

DEFINITION, RATIONALE AND CLINICAL CONCEPTS FOR HYBRID CORONARY REVASCULARIZATION

The role of coronary artery bypass grafting (CABG) as a revascularization strategy in patients with stable coronary artery disease (CAD) and acute coronary syndromes (ACS) has been well demonstrated in the past [1, 2]. A recent meta-analysis demonstrated that the combination of CABG and guideline-directed medical therapy led to a significant reduction in myocardial infarctions, compared with medical therapy alone [3]. Despite the anatomical indication, surgical revascularization may not be considered as the first choice due to (i) the unavailability of grafts, (ii) calcifications of the proximal aorta and (iii) peripheral coronary stenoses or diffuse CAD. Incomplete revascularization or observation strategies have been applied in such cases. The first is associated with increased major cardiovascular and cerebral events, and death after CABG [4, 5], especially if the affected major coronary vessels are not revascularized sufficiently.

A more convenient way to optimize revascularization outcomes in such conditions is with hybrid coronary revascularization (HCR), which is the combination of surgical and percutaneous techniques for the treatment of multivessel CAD (Fig. 1). The rationale of HCR is based on the following: (i) the left anterior descending artery (LAD) is responsible for the blood supply to >50% of the myocardium of the left ventricle, and revascularization of this vessel is associated with a clear clinical prognostic benefit over time [6], (ii) to date the placement of a left internal mammary artery (LIMA) to the LAD is the most effective strategy for revascularization of the anterior wall [7, 8] and (iii) the benefit of CABG over percutaneous cardiovascular interventions (PCI) for revascularization of non-LAD vessels based on the patients' clinical status and presentation remains ambiguous. Therefore, the advancement of stent manufacturing and implantation, the expansion of percutaneous treatment for CAD in patients with complex such as bifurcations and chronic total occlusions, and the development of minimally invasive techniques for surgical revascularization have led to an increased adoption of HCR over the past 2 decades [9]. It is important to emphasize that the principle of HCR does not necessarily stride with a multiarterial CABG approach [9], and that it facilitates but not necessarily dictates the use of minimally invasive techniques for performing surgical revascularization. Especially multiarterial grafting is associated with substantially lower mortality rates at 10 years after coronary artery bypass grafting as shown by the ART trial (The Arterial Revascularization Trial) [10].

Of note, the most recent ESC/EACTS Guidelines on myocardial revascularization provided a class IIb recommendation for HCR [11]. However, the use of minimally invasive techniques for the surgical part of HCR provides a number of advantages, including a sternum-sparing procedure and use of the best arterial conduit without manipulation of the aorta. A minimally invasive approach for the surgical stage of HCR provides several advantages, such as sternum-sparing procedures, utilization of multiple arterial conduits without aortic manipulation, shorter recovery time and prompt return to daily life activities.

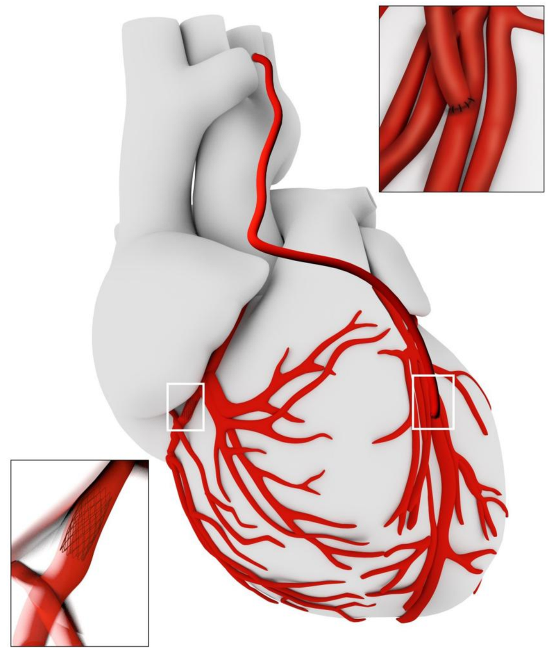

Figure 1: Hybrid coronary revascularization—a combination of coronary bypass surgery and PCI. (Source: J. Heger, West-German Heart and Vascular Center, University Hospital Essen, Germany). FFR: fractional flow reserve; PCI: percutaneous cardiovascular interventions.

Issues of definition and categorization of hybrid coronary revascularization

Definition of hybrid coronary revascularization. HCR is defined as a planned and/or intended combination of consecutive CABG surgery using at least 1 internal mammary artery to the LAD, and catheter-based coronary intervention to the non-LAD vessels for the treatment of multivessel CAD [12].

Types of hybrid coronary revascularization. According to the extent of required revascularization and the number of diseased vessels, one can differentiate between conventional and advanced HCR [13]. The first is related to single-vessel PCI and single-vessel CABG and reflects the simplest form of HCR for the treatment of a double-vessel disease. The second can be performed in terms of single-vessel PCI + multiple CABG or multiple vessel PCI + single CABG.

Intention-to-treat concept

One of the major requirements for HCR is to perform the procedure on an intention-to-treat basis. This is mainly related to patients considered for HCR as the primary treatment concept and excludes patients undergoing HCR to treat complications of either a planned PCI, CABG or both. This exclusion of the HCR concept relates to patients with unsuccessful PCI (failed lesion crossing, insufficient stent expansion) or complications of the latter (coronary dissection, stent thrombosis or early in-stent-restenosis) requiring CABG of the primary PCI targets, before completion of the hybrid procedure. Similarly, the same is true for unsuccessful attempted CABG (incomplete revascularization due to poor grafts or targets) or complications of the latter (graft occlusion or dysfunction, inadequate flow) before addressing the PCI targets. Such cases are not considered as HCR because the hybrid concept was not initially planned, and it was used to treat complications of the PCI or CABG.

Heart team

If a patient is considered as a candidate for HCR, the final decision for a hybrid approach should be discussed using an institutional multidisciplinary heart-team guided approach. Especially in complex CAD, the heart-team approach is a class I recommendation in contemporary guidelines [11]. In this structured process, representatives from cardiac surgery, interventional cardiology and non-invasive cardiology and anesthesiology should be included. The heart team should also assess the sequence of HCR.

Considerations in regards to patient selection

The rationale for a hybrid approach as the primary option can be summarized with the following concepts:

- Patients with chronic coronary syndromes on the basis of anatomically complex lesions of the proximal LAD and concomitant severe stenoses of non-LAD territories.
- Patients with chronic coronary syndromes on the basis of an isolated distal left main disease including lesions of the left main bifurcation or trifurcation.

In addition to the above approach, there are several concepts that may fit to the principles of HCR but are not scope of this article. These include patients with combined coronary and valvular disease who undergo simultaneous PCI and transcatheter or minimally invasive valve surgery.

Procedure-specific considerations

Minimally invasive techniques for surgical revascularization: The HCR approach mostly involves PCI in combination with a minimally invasive CABG technique. This is not a prerequisite as per definition, as HCR implies some kind of surgical revascularization independent from access or the use of cardiopulmonary bypass (CPB) or not. However, due to the fact that HCR implies use of the LIMA for revascularization of the LAD, minimally invasive techniques are recommended. The procedure can be performed through Minimally Invasive Direct Coronary Artery Bypass (MIDCAB), and in some cases through a totally robotic endoscopic approach or via lower partial sternotomy. Minimally invasive operations are commonly performed without the use of CPB and cardioplegic arrest. Contemporary data shows several advantages of minimally invasive techniques in terms of perioperative major adverse cardiac events (MACE) at least in patients with a high operative risk, without compromising graft quality [14, 15]. On the other hand, younger patients with lower perioperative risks should not be excluded from multiple arterial revascularizations for the sake of the hybrid concept. Total arterial grafting has been associated with markedly lower all-cause death in the long-term and should be definitely be encouraged in selected patients with reasonable life expectancy. Multiple arterial revascularizations can be achieved nowadays in a minimally invasive way, based on the use of bilateral internal mammary arteries or combinations with the radial artery [13, 16].

In addition, there are intraprocedural factors, which may influence early- and long-term outcomes, such as:

1. The access or the technique used for the surgical or interventional part of the revascularization (e.g. mini-thoracotomy or sternotomy for CABG, femoral or radial access for PCI and on or off-pump for CABG).
2. The material used for the components of revascularization (e.g. types of stents or grafts).
3. The procedural sequence (PCI first, CABG first or one-stop procedure).
4. The initial clinical presentation of the patient (e.g. stable angina or acute coronary syndrome) since in the acute setting more complex minimally invasive strategies or HCR are rarely being performed.

All the factors mentioned above are important for decision-making and clinical treatment and should be thoroughly documented.

Procedural sequence. The concept of HCR is based on 2 revascularization strategies (CABG and PCI), which are performed concomitantly or at a specific interval. The main principle driving the procedural sequence should be to first treat the true ischaemic culprit [17]. For instance, revascularization of the LAD should be performed first in patients with a tight proximal lesion of the LAD and significant stenosis of any non-LAD targets. On the other hand, a patient with subtotal occlusion of the right coronary artery (RCA) should be addressed by PCI before surgical revascularization of a collateralized LAD with a chronic occlusion. The principle of HCR allows for all 3 possible combinations (CABG first, PCI first or a one-step intervention) as each may be used for a specific rationale. Table 1 addresses decision-making for sequencing the interventions. The procedural sequence of HCR indications is also illustrated in Fig. 2.

The advantage of a simultaneous revascularization approach (*simultaneous strategy*) is that the patient only needs 1 single intervention. The team of heart surgeons and interventional cardiologists can switch from surgery to PCI and vice versa at any time point of the operation. The drawback of this approach may be the dual antiplatelet therapy (DAPT) required by the PCI

Table 1: Anatomical factors influencing decision-making on the sequence of revascularization

	PCI first	CABG first	Simultaneous
Non-LM/LAD as most significant coronary lesion	+	−	−
LM/LAD culprit lesion	−	+	+
ACS with non-LM/LAD culprit lesion	+	−	−
Unprotected LM	−	+	+

ACS: acute coronary syndromes; CABG: coronary artery bypass graft; LAD: left anterior descending; LM: left main; PCI: percutaneous cardiovascular interventions.

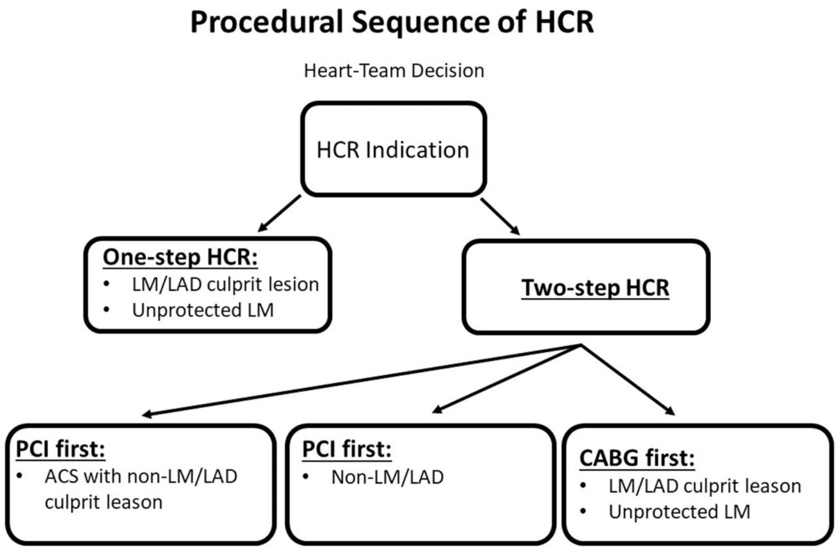

Figure 2: Procedural sequence of hybrid coronary revascularization. ACS: acute coronary syndromes; CABG: coronary artery bypass graft; HCR: hybrid coronary revascularization; LAD: left anterior descending; LM: left main; PCI: percutaneous cardiovascular interventions.

procedure, the logistics and planning behind the time sequencing, and, of course, the need for a hybrid room.

CURRENT RESULTS IN HYBRID CORONARY REVASCULARIZATION

The evaluation of safety, effectiveness and long-term outcomes of HCR has grown in recent years. Nonetheless, evidence is still limited, and any conclusions should be taken with caution as studies in this particular field face specific challenges. Although HCR has been have led to an increased interest over the past 2 decades, the current limitations are related to the still relatively low routine adoption of this treatment option. Although the first series was described in the late 1990s and one-third of the hospitals in the United States report the use of HCR, it still represents less than 1% of the total CABG volume with 5% performed in experienced centres, reflecting the inadequacy of sample size for trials and observational studies [18, 19].

Notwithstanding a potential benefit of HCR, there is currently insufficient evidence to support its widespread use. The 2018 ESC/EACTS Guidelines on myocardial revascularization [20] recommend hybrid procedures in specific patient subgroups at experienced centres and assign HCR a IIb recommendation.

Results of hybrid coronary revascularization versus percutaneous cardiovascular intervention

The 'Hybrid coronary revascularization trial' (*NCT03089398*), a project designed to evaluate potential superiority of HCR compared with PCI using the composite of major adverse cardiac and cerebrovascular events (MACCE) in a large cohort of 2354 multivessel patients was discontinued after enrolment of 200 patients because of delayed recruitment (Table 2) [21]. A recent multicentre prospective cohort study [22] that provided a defined set of anatomic and clinical eligibility criteria for HCR, enrolled 200 HCR-eligible patients who received HCR and 98 HCR-eligible patients who underwent multivessel PCI along with drug eluding stents (DES). Risk-adjusted MACCE rates were similar between the groups at 12 months, with a non-significant trend favouring HCR at 18 months. Of note, there was a high rate of agreement between cardiac surgeons and interventional cardiologists regarding patients' anatomic eligibility for HCR [22].

Defining perioperative end-points that compare PCI and HCR is more complex, as some are typically associated with the surgery, such as ventilation time, intensive care unit (ICU) length of stay (LOS), as well as blood transfusions. In a recent retrospective analysis of a large registry, Lowenstern and colleagues showed that risk-adjusted in-hospital mortality was comparable between HCR and PCI [23]. This outcome was also supported by a previous propensity score matched study [22]. The small amount of data available does not show differences in perioperative MACCEs, although significant reductions in hospital LOS and bleeding have been reported in the PCI group [24].

Results of hybrid coronary revascularization versus coronary artery bypass graft

Other possible issues related to HCR versus CABG are differences in expertise and practice patterns, including on-off-pump CABG, lack of equipoise, learning curve effects, challenges in blinding operators, as well as lack of specific indications for HCR that led to different use among centres [20]. Considering its hybrid nature, the various control groups employed to validate HCR have also not been standardized, with PCI, CABG or OPCAB all chosen, leading to difficulties in summarizing and interpreting results [25]. Similarly, the choice of end-points reflects the difficulties in planning and conducting adequate studies in HCR. Recently more studies have focused on perioperative outcomes [26], while follow-up studies are mostly limited to 3 years, leaving with insufficient long-term performance data of the HCR procedure, in terms of mortality and repeat revascularization [25, 27, 28].

Both prospective trials as well as observational studies have shown that HCR is a safe and effective treatment option for treating patients with multivessel disease [25]. In-hospital and/or

Table 2: Major recent studies comparing HCR with PCI and/or CABG

First author and year of publication	Type of study	Number of patients	Bleeding complication, (%)	Stroke, (%)	30-Day mortality, (%)	Hospital stay, (%)	Follow-up time, years	MACCE, (%)	Revascularization, (%)	Overall mortality, (%)
Studies comparing HCR with PCI										
Bagiella *et al.*, 2021	Randomized-controlled trial	$N = 200$	NA	NA	NA	NA	NA	NA	NA	NA
Puskas *et al.*, 2016	Prospective study	HCR = 200 PCI = 98	NA	2.5 ($P = 0.021$) 0	0.5 0	NA	2 years	11.5 ($P = 0.103$) 12.2 ($P = 0.103$)	7 ($P = 0.061$) 10.2 ($P = 0.084$)	1.5 ($P = 0.012$) 2 ($P = 0.016$)
Studies comparing HCR with CABG (ONCAB/OPCAB)										
Wang *et al.* 2021	Meta-analysis of 23 Studies	HCR = 2,403 CABG = 8,065	66 0 OR: 0.38 (0.17–0.82)	5 1 OR: 1.00 (0.45–2.23)	11 10 OR: 1.10 (0.60–2.00)	NA	≥1 year	1 0 OR: 0.83 (0.48–1.44)	50 19 OR: 0.87 (0.21–3.54)	NA
Esteves *et al.*, 2020	Prospective randomized study	HCR = 40 CABG = 20	NA	0 0	12.5 0	NA	2 years	19.3 5.9	14.5 5.9	12.5 0
Hage *et al.*, 2019	Retrospective (PMA)	HCR = 147 OPCAB = 216	15 ($P = 0.6$) 28	2.1 1	0 ($P = 0.15$) 1	4.5 ($P = 0.1$) 8.1	8 years	NA	9 ($P = 0.8$) 8	4 ($P = 0.054$) 15
Nolan *et al.* 2018	Meta-analysis of 9 Studies	HCR = 306, CABG/ OPCAB = 918	48 67 OR: 0.43 (0.27–0.68)	1.6 2.5 OR: 0.76 (0.34–1.73)	4.9 2.1 OR: 1.35 (0.72–2.52)	NA	≥1 year	8 12 OR: 0.71 (0.31–1.62)	6.3 1.8 OR: 3.1 (1.39–6.9)	2.4 3.9 OR: 0.64 (0.28–1.47)
Reynolds *et al.* 2018	Meta-analysis of 14 Studies	HCR = 1,350, CABG = 2,910	22.8 46.1 OR: 0.38 (0.31–0.46)	0.9 1.4 OR: 0.72 (0.31–1.69)	NA	Mean difference: −1.48	≥1 year	NA	NA	1.7 1.8 OR: 1.15 (0.69–1.92)
Tajstra *et al.*, 2018	Prospective randomized study	HCR = 94 CABG = 97	19 ($P = 0.23$) 26	2.1 ($P = 0.35$) 4.1	0 0	8.6 ± 4.1 ($P = 0.86$) 8.5 ± 5.2	5 years	45.4 ($P = 0.39$) 53.4	NA	6.4 ($P = 0.69$) 9.2
Sardar *et al.* 2018	Meta-analysis of 9 Studies	HCR = 735, CABG/ OPCAB = 1,510	19 44 OR: 0.29 (0.14–0.56)	1.2 0.9 OR: 1.72 (0.38–7.82)	4.9 2.1 OR: 1.35 (0.72–2.52)	NA	≥1 year	3.6 5.4 OR: 0.53 (0.24–1.16)	3.8 4.5 OR: 1.28 (0.50–2.83)	1.3 1.5 OR: 0.85 (0.38–1.88)
Song *et al.*, 2016	Prospective (PMA) study	HCR = 573 OPCAB = 700	29.2 ($P = 0.076$) 39.6	0 ($P = 0.046$) 3.6	NA	7 ($P = 0.627$) 7	3 years	7.4 ($P = 0.612$) 8	4.7 ($P = 0.488$) 2.3	2.7 ($P = 1.0$) 2.8
Harskamp *et al.*, 2014	Meta-analysis of 6 studies	HCR = 366, CABG/ OPCAB = 824	NA	0.3 0.6 OR: 0.93 (0.24–3.59)	0.6 0.8 OR: 0.85 (0.24–2.99)	NA	≥1 year	4.1 9.1 OR: 0.49 (0.20–1.24)	8.3 3.4 OR: 3.25 (1.80–5.87)	4.5 7.3 OR: 0.73 (0.29–1.85)
Bachinsky *et al.*, 2012	Prospective study	HCR = 25 CABG = 27	12 ($P < 0.001$) 67	0 0	0 ($P = 0.99$) 3.7	5.1 ± 2.8 ($P = 0.008$) 9.1 ± 5.4	30 days	0 0	NA	0 ($P = 0.99$) 3.7

Continued

Table 2: Continued

First author and year of publication	Type of study	Number of patients	Bleeding complication, (%)	Stroke, (%)	30-Day mortality, (%)	Hospital stay, (%)	Follow-up time, years	MACCE, (%)	Revascularization, (%)	Overall mortality, (%)
Halkos *et al.*, 2011	Retrospective (PMA)	HCR = 147	35.4 ($P < 0.001$)	0.7 ($P = 0.8$)	0.7 ($P = 0.84$)	6.6 ± 6.7 ($P = 0.48$)	5 years	2 ($P = 1.0$)	12.2 ($P < 0.001$)	13.2 ($P = 0.61$)
		OPCAB = 588	56	0.7	0.9	6.1 ± 4.7		2	3.7	15.7
Vassiliades *et al.*, 2009	Prospective (PMA)	HCR = 91	NA	0 ($P = 0.31$)	0 ($P = 0.20$)	NA	3 years	10	NA	6 ($P = 0.14$)
		OPCAB = 4,175		1.1	1.7			NA		11
Studies comparing HCR with CABG with PCI										
Van den Eynde *et al.* 2021	Meta-analysis of 119 Studies	HCR = 3,119	NA	Prob. (SUCRA 35.3%)	Prob. (SUCRA 16.3%)	NA	≥1 year	Prob. (SUCRA 69.8%)	Prob. (SUCRA 51.8%)	Prob. (SUCRA 53.8%)
		PCI = 213,536		Prob. (SUCRA 92.5%)	Prob. (SUCRA 94.8%)			Prob. (SUCRA 0.7%)	Prob. (SUCRA 0.7%)	Prob. (SUCRA 25.8%)
		CABG = 438,743		Prob. (SUCRA 17.1%)	Prob. (SUCRA 27.4%)			Prob. (SUCRA 71.0%)	Prob. (SUCRA 88.5%)	Prob. (SUCRA 74.1%)
		OPCAB = 44,980		Prob. (SUCRA 55.1%)	Prob. (SUCRA 61.4%)			Prob. (SUCRA 58.6%)	Prob. (SUCRA 59.1%)	Prob. (SUCRA 47.4%)
Ganyukov *et al.*, 2020	Prospective randomized study	HCR = 49	9.6	3.2	1.9	13.5	1 years	13.4 ($P = 0.83$)	13.5 ($P = 0.095$)	5.8 ($P = 0.78$)
		PCI = 49	0	0	0	13.8		13.2	17	3.8
		CABG = 51	20	0	0	4.5		12	4	2
Qui *et al.*, 2019	Retrospective (PMA)	HCR = 47	NA	4.5	0	15.3 ± 4.5 ($P = 0.027$)	5 years	11 ($P = 0.007$)	4.5 ($P = 0.002$)	1 ($P = 0.811$)
		PCI = 47		6.8	0	NA		35	2.2	2
		OPCAB = 47		6.8	2	17.6 ± 5.4		13	22	2
Shen *et al.*, 2013	Retrospective (PMA)	HCR = 141	21.3	2 (0.083)	NA	8.19 ± 2.54	3 years	9 ($P = 0.003$)	6 ($P < 0.001$)	0.7 ($P = 0.034$)
		PCI = 141	NA	3		NA		19	18	3.5
		CABG = 141	31.9	9		8.49 ± 2.54		32	3	2.8

CABG: coronary artery bypass graft; HCR: hybrid coronary revascularization; MACCE: major adverse cardiac and cerebrovascular events; PCI: percutaneous cardiovascular interventions.

30-day mortality are comparable between HCR and CABG, irrespective of the surgical technique employed (CABG, OPCAB or minimally invasive coronary revascularization [MICR]) [26–36]. LOS is one of the main outcomes used to compare HCR and surgical myocardial revascularization in the short term. Shorter LOS in HCR has been demonstrated in some comparative studies [33, 37–39], supported by the pooled results of a recent meta-analysis by Reynolds and colleagues [26] and also corroborated in some subsets of surgery patients, such as those undergone MICR [30]. Risk of perioperative blood transfusions was significantly lower in HCR compared with CABG, as shown in a meta-analyses and single centre studies [26, 29, 30, 33, 35, 40]. HCR appears to be superior to surgery in regards to ventilation time [26, 30], and non-inferior to surgery for rates of postoperative atrial fibrillation, renal complications, myocardial infarction and stroke [26, 28–30], and it also compares favourably to MICR in terms of reduced risk for reoperation and incidence of postoperative infection [30]. Harskamp and colleagues also showed a significant reduction in perioperative troponin I release after HCR compared with OPCAB [41]. Of note, the non-inferiority in terms of stroke should be carefully considered, also in meta-analyses, as the low incidence of this specific complication requires a high sample size to detect any statistically significant differences.

Evaluation of mid- and long-term outcome is more complex, as evidence is limited and inhomogeneous. Long-term efficacy of HCR should be confirmed by adequately powered trials. Mortality at follow-up is comparable between HCR and CABG, as shown by 4 meta-analyses [28–30, 42] and prospective studies [31, 33], although follow-up was mostly limited to up to 3 years so that longer term evaluation was not possible. With the same limitations, MACCE incidence was not different between surgery and HCR [27–31, 33]. Repeat revascularization, however, was probably the key issue in the mid-term comparison between surgery and HCR. In an early meta-analysis by Harskamp and colleagues, HCR was shown to be a risk factor for repeat revascularization compared with CABG, with an hazard ratio increasing from 2.65 (95% CI: 1.16–6.06, $P = 0.021$) to 3.25 (95% CI: 1.8–5.87, $P < 0.001$) at 3 years [43]. This negative effect was repeated in a recent meta-analysis which reported a superimposable hazard ratio of 3.1 (95% CI: 0.139–6.9) [29], confirmed by another meta-analysis showing a similar incidence of repeat revascularization [28]. Nevertheless, these results are biased as they mix different follow-up periods, with the hazard ratio of 1.28 (95% CI: 0.58–2.83, $P > 0.05$) as shown by Sardar and colleagues summarizing 1-month follow-up in 2 studies, 12-month follow-up in 3 studies and 36-month follow-up in 1 study [28]. Also, recent prospective trials have shown contrasting results. The 5-year outcomes of the POLMIDES study [31], a randomized-controlled trial (RCT) comparing 2-stage HCR to standard CABG, found a comparable incidence of repeat revascularization between the 2 groups, which contradicts the results of another small and under-powered trial, which found an association between HCR and repeat revascularization at 2 years [32]. In the same way, retrospective evaluations have found opposing outcomes, although the same methodology for balancing groups were employed [35, 37, 40]. Mortality, MACCE and repeat revascularization up to 18 months were found to be comparable between HCR and PCI [22, 24], although the small number of published evidence has to be taken into account. As stated, all these studies included different follow-up time points, which were predominantly shorter term; so it comes as no surprise that outcomes don't differ significantly during this early follow-up period, as the benefit of CABG becomes more evident in the long term. This may not be an issue, though, as patients considered candidates for HCR are higher risk, with an expected lower estimated survival.

Results of hybrid coronary revascularization versus coronary artery bypass graft versus percutaneous cardiovascular intervention

RCT's comparing HCR versus CABG have been small in size [31, 32], with the only RCT to date comparing HCR with multivessel PCI terminated prematurely due to slow recruitment [21]. Prospective trials that directly compared HCR with CABG and PCI are currently limited to only 1 randomized study, which was also small in sample size, and reported no difference between the 3 treatment arms [24]. Moreover, a recent meta-analysis of 119 studies with a maximum follow-up of 1 year reported no significant difference between the 3 treatment modalities [44]. In summary, the evidence for the best treatment option is currently uncertain and future prospective randomized trials comparing HCR with CABG and PCI are still warranted.

Invasive functional evaluation of coronary stenosis before pci or surgical revascularization. Invasive functional evaluation is recommended to assess the haemodynamic relevance of intermediate-grade coronary stenosis when other evidence of ischaemia is not available [20]. This is often the case in patients being considered for possible HCR who present with multivessel disease (MVD) or left main involvement. In these cases, non-invasive functional evaluation has shown lower diagnostic accuracy, especially in terms of spatial resolution (e.g. ability to identify the ischaemic vessel/myocardial territory) [45, 46]. In addition, systematic implementation of invasive functional assessment might enable the LAD artery to be specifically targeted with the LIMA, treating the remaining coronary segments with stenting or medical therapy depending upon their relative functional significance (Fig. 3) [47]. Invasive functional assessment is currently recommended with fractional flow reserve (FFR) and with instantaneous wave-free ratio (iwFR) [20].

Functional strategy ahead of percutaneous cardiovascular intervention

FFR has been extensively validated in PCI guidance, especially in patients with stable CAD or stabilized ACS. In stable patients, deferring revascularization with an intermediate stenosis in 1 coronary artery based upon a preserved FFR value was associated with a favourable clinical outcome [48]. Importantly, after 15 years of follow-up, the lesions with negative FFR treated with medical therapy remained stable, while lesions with negative FFR treated with bare metal stenting had an excess incidence of myocardial infarction [49]. These results have been recently confirmed with contemporary drug-eluting stents in 2 large registries and a pooled analysis of 2 large randomized clinical trials (Fig. 4) [50–52]. In patients with MVD with stable CAD or stabilized ACS, FFR-guided PCI has shown improved clinical outcomes compared with PCI guided by the angiographic appearance of the coronary stenoses up to 5 years [53–55]. In patients with stable angina with at least 1 lesion with positive FFR ($\leq$0.80) in a large coronary artery territory, FFR-guided PCI was superior to a conservative strategy with the best available

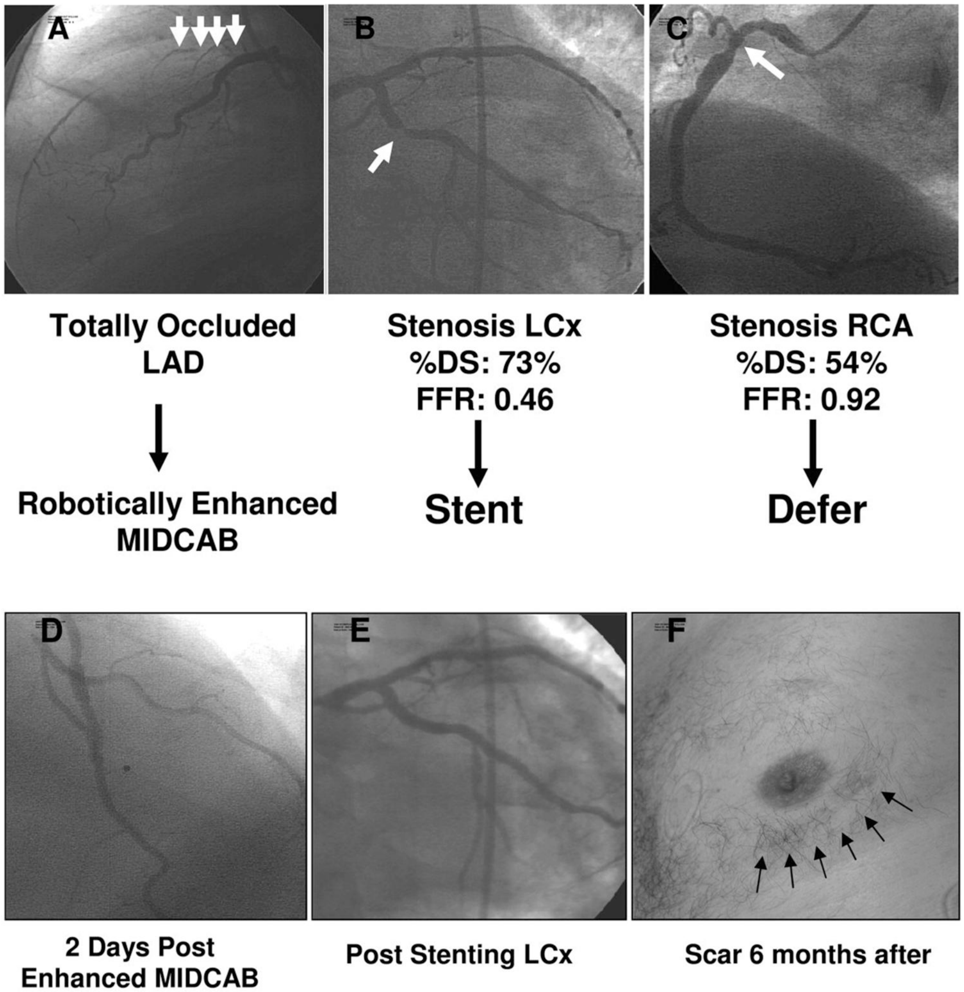

Figure 3: Example of a patient with a chronic total occlusion of the LAD that could not be recanalized percutaneously (**A**) and a stenosis in the left circumflex (**B**) and RCA (**C**). FFR in the LCx was 0.45 and in the RCA was 0.92. Accordingly, stenting of the LCx was performed, PCI of the RCA was deferred, and a robotically enhanced MIDCAB graft with a LIMA to the LAD was done. (**D**), Angiographic control of the LIMA graft to the LAD. (**E**), Poststent angiographic result in the LCx. (**F**), Minimal scars of the surgical incisions. (Source: Davidavicius et al. Circulation 2005; 112: I-317-I-322). FFR: fractional flow reserve; LAD: left anterior descending; LIMA: left internal mammary artery; MIDCAB: Minimally Invasive Direct Coronary Artery Bypass; PCI: percutaneous cardiovascular interventions; RCA: right coronary artery.

medical therapy [56, 57]. When analyzed as a continuous variable, the absolute value of FFR has been shown to have a prognostic value for predicting major adverse cardiovascular events (Figs 4 and 5) [58, 59]. At 5 years, a lower rate of myocardial infarction was observed in the FFR-guided PCI group of patients compared with patients managed conservatively [5]. In a recent meta-analysis, FFR-guided PCI resulted in a reduction of the composite of cardiac death or MI compared with medical therapy, which was driven by a decreased risk of MI [6]. FFR is also reliable in PCI guidance of patients presenting with ACS, as it pertains to the evaluation of the non-culprit stenotic vessel [60]. In 2 randomized trials [61, 62], the primary composite end-point was significantly reduced in patients treated with FFR-guided PCI of the non-infarct related artery, irrespective of whether PCI of the non-culprit lesion was performed during the same procedure as the primary PCI, or staged during the same index hospitalization.

IwFR has shown a good predictive value for FFR [63]. In patients with stable CAD and stabilized ACS, iwFR-guided PCI was reported to be non-inferior for a combined primary end-point of death from any cause, nonfatal myocardial infarction or unplanned revascularization compared with FFR-guided PCI up to 1-year follow-up (Fig. 6) [64, 65]. In addition, deferral of revascularization in intermediate coronary stenoses based on iwFR values is equally safe compared with FFR up to 1-year follow-up [60, 66].

Functional strategy ahead of coronary artery bypass graft

In up to 25% of cases, bypass grafts are anastomosed onto coronary arteries with no regional myocardial perfusion impairment [67]. Grafting a non-functionally significant stenotic vessel might accelerate atherosclerosis progression in the native coronary artery [68], leading to reduced graft patency rate [69]. On the other hand, recent evidence showed that the use of the mammary artery could present a positive effect on the endothelial metabolism of the coronary artery, and slow – or even return – atherosclerotic disease [70].

The most important impact of invasive functional evaluation in patients who are potentially candidate for CABG is in the functional staging of the severity of CAD. In 497 patients with angiographic multivessel disease, the anatomic severity of CAD by the Syntax Score was reassessed by incorporating only the

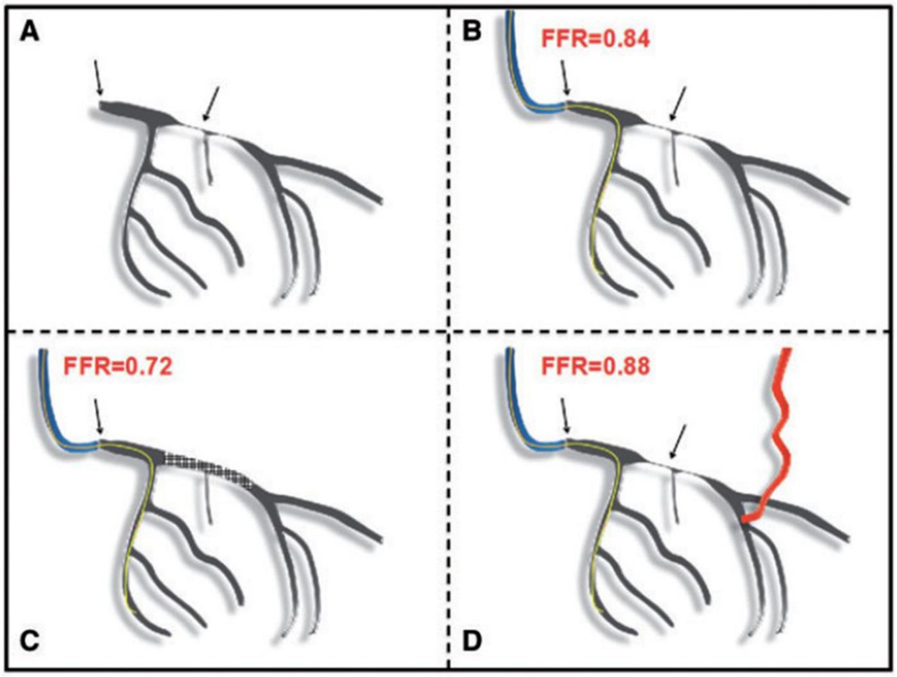

Figure 4: Schematic representation of a left coronary artery with sequential stenosis of the ostial LM and proximal LAD coronary artery (**A**, arrows). FFR of the LM measured with the pressure wire positioned in the left circumflex artery is 0.84 (**B**). If the proximal LAD was stented, FFR of the LM would lower to 0.72 as a consequence of the significant increase in the subtended myocardial mass (**C**). If a bypass graft would be implanted distal to the LAD stenosis, FFR of the LM would either remain the same or slightly increase, as a consequence of the fact that a large part of the left coronary artery territory is now being perfused by another vascular conduit (**D**). LAD: left anterior descending; LM: left main; FFR: fractional flow reserve. (Source: Pellicano et al. European Heart Journal 2017; 38:1959–1968).

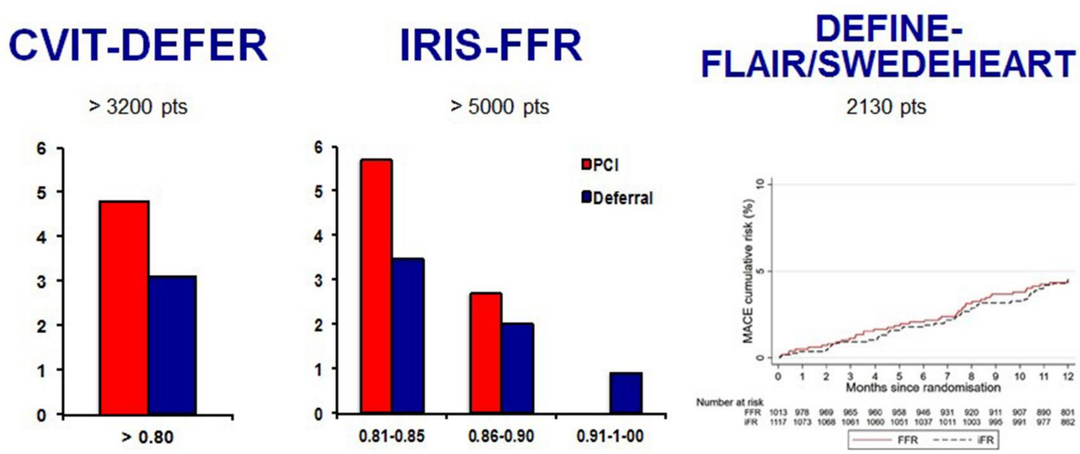

Figure 5: Safety of deferral of percutaneous revascularization in 2 large contermporary registries and a pooled analysis from 2 large randomized clinical trials. (Source: Tanaka et al. Circ J 2017; 81:1301–1306; Ahn et al. Circulation 2017; 135:2241–51; Escaned et al. JACC Intv 2018; 11:1437–1449). FFR: fractional flow reserve; PCI: percutaneous cardiovascular interventions.

coronary stenosis with abnormal FFR values into the calculation. By using the functional Syntax Score, CAD severity was downgraded in 32% of patients, with improved discrimination of the clinical end-points [71]. The application of the functional Syntax Score to the stratification of patients with MVD might significantly impact management strategies by moving patients from CABG to PCI, for example, in patients in whom the functional syntax score significantly downgrades the CAD severity. At this regard, the FAME 3 trial tests whether FFR-guided PCI in patients with multiple vessel disease is non-inferior to angiographically guided surgical revascularization [72]. Alternatively, patients might initially be considered for less invasive approaches such as hybrid therapy or minimally invasive CABG. Invasive functional evaluation might also reveal haemodynamically significant stenosis of the left main or proximal LAD artery, that had been classified as mild on the angiogram, therefore upgrading the functional severity of CAD.

The clinical impact of functionally guided surgical revascularization has been investigated thus far with only FFR. The occlusion rate at 1 year of the bypass grafts implanted on functionally non-significant stenoses (i.e. with preserved FFR) was twice as high compared with the bypass grafts implanted on functionally

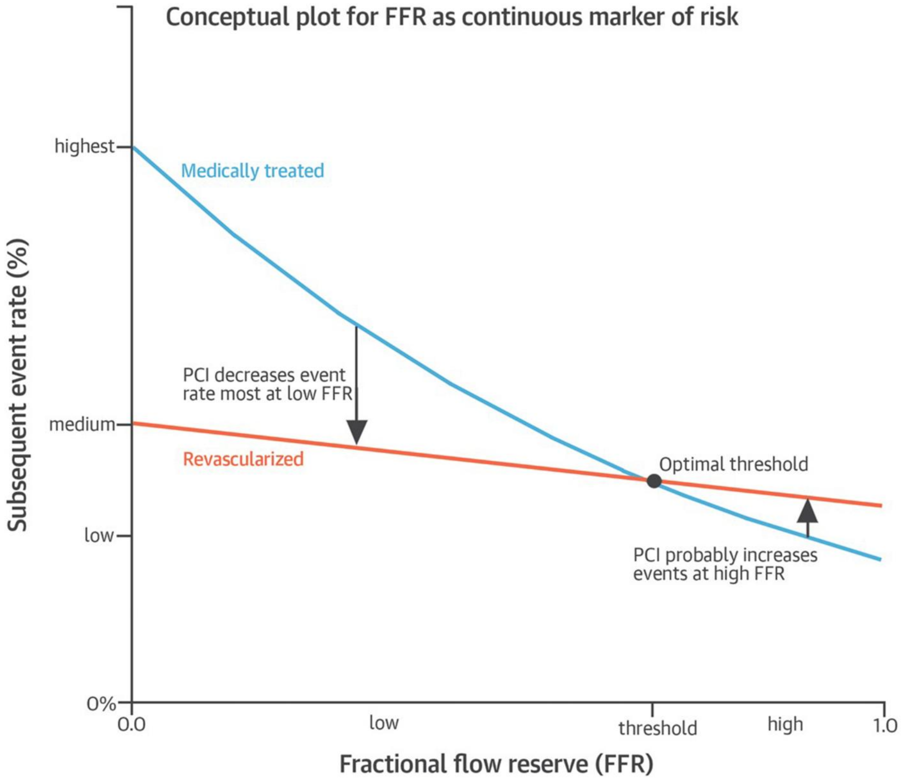

Figure 6: Conceptual plot for FFR as continuous marker of risk in patients treated with medical therapy (blue line) or revascularization (red line). (Source: Johnson et al. J Am Coll Cardiol 2014; 64:1641–54). FFR: fractional flow reserve; PCI: percutaneous cardiovascular interventions.

significant stenosis [69]. In 627 patients, FFR-guidance was associated with a significant downgrade in the rate of MVD [73]. This reclassification of patients led to a simplification of the surgical protocol as suggested by the lower number of anastomosis and lower rate of on-pump surgery observed in the FFR-guided CABG group of patients. Despite incomplete anatomical revascularization of these latter patients, at 3 years, there was no difference in terms of adverse cardiac events and an even lower rate of angina Canadian Class Society Class II–IV as compared with patients treated with a traditional strategy, suggesting the safety of performing functionally complete revascularization in these patients. In addition, exploratory analysis showed that the graft patency rate was higher when surgical revascularization was guided by FFR compared with angiography, confirming and extending up to 3 years the previous findings [69].

More recently, the 'Fractional Flow Reserve versus Angiography Randomization for Graft Optimization' (FARGO) and the 'GRAft patency after FFR-guided versus angiography-gulded CABG' (GRAFFITI) trials confirmed a significant procedural impact in terms of simplification of the surgical operation [74–76]. Despite this, both failed to show lower graft failure rates in patients undergoing FFR-guided CABG compared with angiography-guided CABG at 6 and 12 months, respectively. This discrepancy with the previous findings might be explained by a time-sensitive impact of the invasive functional guidance on surgical revascularization. In fact, an extended clinical follow-up of a previous registry demonstrated that FFR-guided CABG is associated with a significant reduction in the rate of overall death or myocardial infarction at 6-year follow-up (Fig. 7) [77]. This clinical benefit with FFR-directed bypass graft compares to higher patency rate of arterial but not venous grafts up to 6 years follow-up (Fig. 8) [78].

ANTIPLATELET THERAPY IN HYBRID CORONARY REVASCULARIZATION

The type and extent of antiplatelet therapy in coronary revascularization is clearly defined by the most thrombogenic procedure which is PCI. However, no randomized-controlled data exist regarding HCR and the protocols followed, which were based on expert opinion or current practice for PCI and CABG. According to recent guidelines and newest drug-eluting stent technologies, a shorter period on DAPT may be suitable for many patients, depending on individual anatomical and clinical features. This allows for better selection of HCR candidates and for planning the strategy staging of the interventional steps.

Patients presenting with an ACS undergo primary PCI ('PCI first strategy') of the culprit lesion, if non-LAD vessels are involved. In this scenario, DAPT may be given for at least 4 weeks and the CABG procedure can be safely performed thereafter under single antiplatelet therapy [79–81]. DAPT starts on the day of the PCI procedure using clopidogrel (600 mg) as a loading dose. In patients with ACS and a low bleeding risk, a more aggressive medical approach is indicated, with ticagrelor or prasugrel administered as soon as possible after PCI, which is then discontinued before the CABG procedure or removed intraoperatively [82–84] and then readministered as soon as possible postoperatively and continued for the following 12 months [85].

In patients presenting with chronic coronary disease, the antiplatelet regimen in this setting may be reserved to aspirin mono therapy after surgery. DAPT is recommended in specific situations for those patients with severely diffused CAD or those undergoing coronary artery endarterectomy. Moreover, the 2017 EACTS guidelines on perioperative medication in cardiac

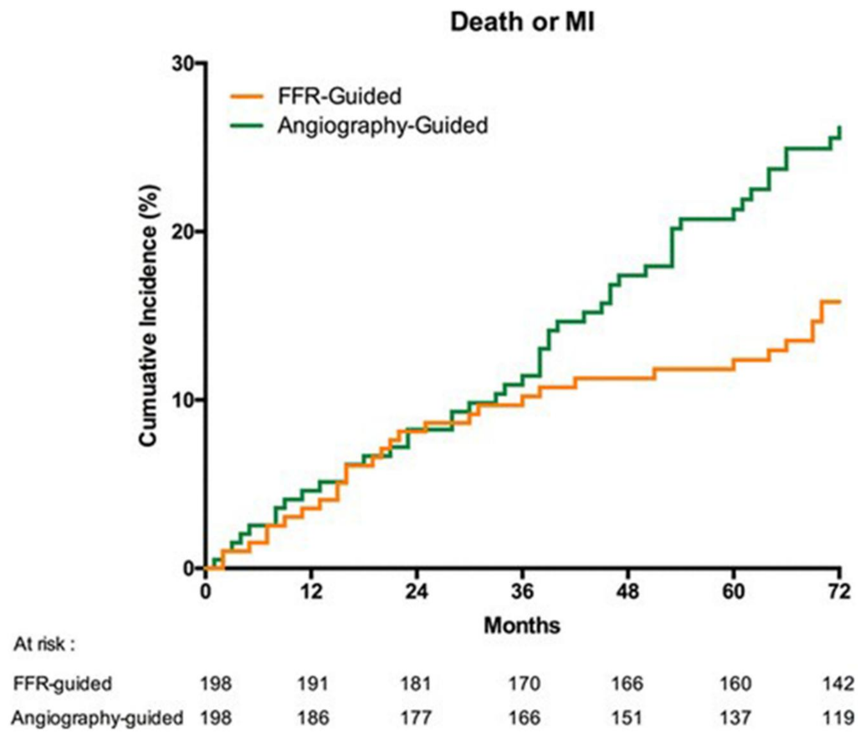

Figure 7: Cumulative incidence of death and myocardial infarction up to 6 years. (Source: Fournier et al. Circulation Cardiovasc Intv 2018; 11: e006368). FFR: fractional flow reserve.

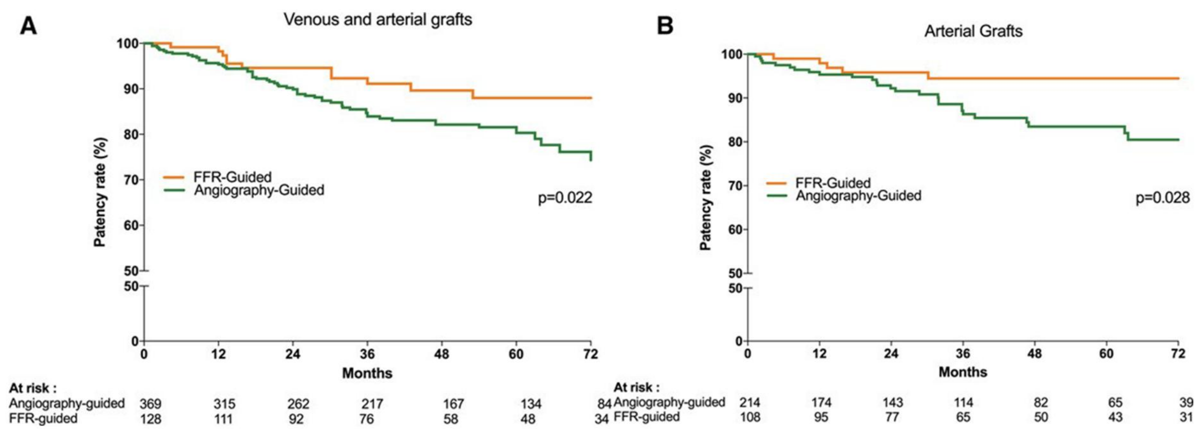

Figure 8: Kaplan–Meier graph reporting 6-years patency rate in all grafts and in arterial grafts. (Source: From Fournier S et al. Circulation Cardiovasc Interv 2019; 12: e007712).

surgery recommended DAPT as class IIb recommendation in CABG patients in CABG patients with a higher ischaemic risk (e.g. coronary endarterectomy or off-pump surgery) [86].

In patients with a high-risk coronary anatomy, bridging therapy is recommended in patients after PCI who require CABG within the next 4–6 weeks. In those patients less aggressive DAPT starts on the day of the PCI procedure adding clopidogrel (600 mg) as a loading dose to the aspirin therapy and continued with a normal dose up to the day of surgery, or clopidogrel therapy can be switched to intravenous heparinization within 48 hours from surgery to avoid any DAPT bleeding risks. DAPT should be resumed postoperatively as soon as possible and continued until the prescribed duration of therapy is completed taking into account the bleeding risk of a patient. Even in patients presenting with high bleeding risks and need for anticoagulation due to atrial fibrillation or recurrent thrombotic embolism, a very short period of DAPT after coronary stenting is advised by international guidelines [84].

CURRENT INDICATION AND PATIENT SELECTION FOR HYBRID CORONARY REVASCULARIZATION

Candidates for HCR may include patients who also have atheromatous aortic disease leading to high risk of stroke, patients with depressed left ventricular function, chronic kidney disease or patients undergoing repeat sternotomy, all conditions leading to a higher surgical risk. Also lack of availability of adequate bypass conduits might be an indication for HCR. In obese and/or poorly controlled diabetic patients, HCR offers the survival advantage of LIMA to LAD, reducing the (higher) risk for deep sternal wound infection associated with sternotomy [27].

It must be iterated that the heart-team approach is key to deciding which type of revascularization, including HCR, be advised for the individual patient, as mentioned above [25]. So that, in selected patients, HCR provides a further tool to treat coronary heart disease in the most appropriate way, according to each patients' findings, anatomical and clinical status.

Guidance when considering HCR

Table 3 summarizes all considerations and indications for HCR as follows:

Patients with double-vessel disease and a LAD lesion not amenable to PCI
Patients with multivessel disease and an indication for CABG requiring complete revascularization in whom a full sternotomy is contraindicated
Patients with multivessel disease and an indication for CABG requiring complete revascularization and lack of supplemental venous and/or arterial conduits
Patients with multivessel disease and a complex proximal LAD lesion and poor surgical targets in the circumflex artery (CX) or RCA territory amenable to PCI
Patients with multivessel disease undergoing emergent culprit lesion PCI of a CX or RCA lesion and staged surgical revascularization of a residual LAD lesion
Patients with multivessel disease and extensive atheromatous aortic disease at high risk of stroke in whom compete revascularization cannot be achieved without manipulation of the aorta
Clinical issues: elderly or high-risk patients with complex LAD lesions who may benefit from avoiding sternotomy and CPB. **HCR could be considered as bailout in patients** • with otherwise incomplete revascularization (patients' lack of graft conduits or severe atherosclerosis of the ascending aorta) • with relative contraindications to sternotomy for primary or repeat revascularization (multi- or comorbid patients, patients with severe mobility limitations, patients with impaired healing, relevant anatomical conditions e.g. pectus excavatus or carinatus, complex sternal reconstruction after previous surgery, previous procedures on the great vessels)

Based on these considerations, the indication for hybrid approaches can be summarized into 2 issues:

1. Anatomical issues: when the LAD has complex or diffuse disease and non-LAD lesions are suitable for PCI with short and relatively large stents which provide a lower risk for restenosis.
2. Clinical issues: young patients with complex LAD lesions (to avoid 'full metal jacket') and stenosis on the other vessels, particularly if kidney disease is present, in order to offer a long-term advantage over repeat revascularizations and probably on survival.

In addition, there are some other relevant factors where HCR could be considered or preferred. Regard this, Table 4 summarizes demographic, clinical and angiographic factors and provides an overview of the possibilities for favouring each revascularization method.

Table 3: Current indications for HCR

Patients with double-vessel disease and a LAD lesion not amenable to PCI
Patients with multivessel disease and an indication for CABG requiring complete revascularization in whom a full sternotomy is contraindicated
Patients with multivessel disease and an indication for CABG requiring complete revascularization and lack of supplemental venous and/or arterial conduits
Patients with multivessel disease and complex proximal LAD lesion and poor surgical targets in the circumflex (CX) or right coronary artery (RCA) territory amenable to PCI
Patients with multivessel disease undergoing emergent culprit lesion PCI of a CX or RCA lesion and staged surgical revascularization of a residual LAD lesion
Patients with multivessel disease and extensive atheromatous aortic disease at high risk of stroke in whom compete revascularization cannot be achieved without manipulation of the aorta

Source: adapted from Head et al. Eur Heart J 2013; 34:2873–86 [89].

CABG: coronary artery bypass graft; CX: circumflex artery; HCR: hybrid coronary revascularization; LAD: left anterior descending; PCI: percutaneous cardiovascular interventions; RCA: right coronary artery.

Table 4: Clinical and angiographic factors predisposing to a particular revascularization method

	PCI	HCR	CABG
Clinical characteristics			
Advanced age	+	+	−
Frailty	+	+	−
Low left ventricular ejection fraction (LV-EF) (≤30%)	−	+	+
Diabetes mellitus	−	+	+
Renal failure	−	+	+
Pulmonary dysfunction	+	−	−
Prior left thoracotomy	+	−	+
Prior sternotomy	+	+	−
Limited vascular access	−	−	+
Lack of available bypass conduits	+	+	−
Atheromatous asc. aortic disease	+	+	−
Contraindication for DAPT	−	−	+
Angiographic characteristics			
Unprotected left main (unsuitable for PCI)	−	+	+
Intramyocardial LAD	+	−	+
Complex LAD lesions	−	+	+
Complex non-LAD lesions	−	−	+

Source: adapted from Harskamp *et al*. Ann Thorac Surg 2013; 34:2873–86 [90].).

CABG: coronary artery bypass graft; DAPT: dual antiplatelet therapy; HCR: hybrid coronary revascularization; LAD: left anterior descending; PCI: percutaneous cardiovascular interventions.

CONCLUSION

With this consensus expert opinion position paper, the ESC Working Group on Cardiovascular Surgery in collaboration with EAPCI (European Association of Percutaneous Cardiovascular Interventions) is committed to providing guidance on hybrid coronary artery revascularization strategies and techniques according to the current state-of-the-art and available evidence.

Of note, it is essential to include also technical considerations such as off-pump CABG (aorta no-touch technique) or epiaortic scanning (porcelain aorta) into the revascularization strategy, which can be also applied in the minimally invasive setting. Also, the presence and amount of calcification in the coronary arteries should be considered as this would add technical complexity to the surgical approach [87].

Due to the increasing ageing population with a higher prevalence of comorbidities, a growing number of patients at higher risk are facing appropriate treatment of multivessel CAD either by PCI or CABG. HCR may play an important and complementary role in the treatment of multivessel coronary disease in the future. Emerging technological advances in both interventional and surgical revascularization strategies and techniques enhance the possibility of an integrated hybrid approach, in which the patient receives a minimally invasive LIMA revascularization to the LAD and PCI to the remaining diseased coronary vessels. However, the concept of multiarterial grafting especially in younger patients with reasonable life expectancy should not be influenced by HCR techniques.

Additionally, patients who present with an acute coronary syndrome could be assigned to HCR. In cases where the culprit lesion is localized to a non-LAD vessel, urgent PCI is performed, with concomitant complex LAD stenosis not amenable for PCI subsequently referred for surgical revascularization, according to the hybrid principle. The intention to perform HCR in these patients should be documented during the primary hospitalization and should be discussed using the heart-team approach. Any deviation from this concept due to relevant ischaemia or haemodynamic instability due to the remaining lesions should be considered as contraindication to perform HCR. However, planned PCI of a second non-LAD territory is still compatible with the hybrid concept. Treatment of ACS is based on immediate revascularization of the culprit lesion by PCI (within hours). In previous studies, almost 17% of HCR candidates presented with an ACS [88]. Of these, the RCA is involved in 63% of patients and the left circumflex artery in 50% [22]. In 47% and 70% of patients, a proximal and a mid-LAD lesion was noted. In these cases, the concept of HCR can be applied under the condition of successful revascularization of the culprit lesion by primary PCI and the presence of a tight lesion of the LAD.

Specialized surgical skills, advanced training and expertise are crucial for a broad acceptance of HCR. This is perhaps the main reason why as of now MIDCAB in combination with HCR has not presented a wider adoption. The same holds true for total endoscopic robotic CABG surgery, which is associated with a substantial learning curve. Such minimally invasive techniques should be implemented into clinical routine as a first step to ensure satisfactory results of HCR as the next step.

Therefore, the HCR approach performed by a dedicated heart team with close interaction between cardiologists and surgeons may represent an optimal and safe method with favourable long-term outcomes, performed in selected patients and at sites with broad experience of minimally invasive CABG surgery and consecutive PCI procedures.

LIMITATIONS

HCR is limited with the following points:

The lack of immediate complete myocardial revascularization may result in MACE. The different procedural risks of PCI and CABG might result in undesired outcomes. For instance, the need for antiplatelet therapy may increase the risk of bleeding after CABG. On the other hand, the pro-coagulant effects of the operative trauma and/or the need for reduced or shortened antiplatelet therapy may increase the risk of stent thrombosis. This may offset the long-term benefits of complete revascularization only achieved by the hybrid approach.

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Position Statement