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Hybrid Coronary Revascularization in Selected Patients With Multivessel Disease

5-Year Clinical Outcomes of the Prospective Randomized Pilot Study

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ABSTRACT

OBJECTIVES This study aimed to investigate the 5-year clinical follow-up of the Hybrid Revascularization for Multivessel Coronary Artery Disease (HYBRID) trial.

BACKGROUND HYBRID trial, the only randomized study involving thorough analysis of outcome after the 2 procedures, suggested that hybrid coronary revascularization (HCR) is feasible in selected patients with multivessel coronary disease referred for conventional coronary artery bypass grafting (CABG). There are currently no long-term outcome data from randomized trials in this setting.

METHODS A total of 200 patients with multivessel coronary disease referred for conventional surgical revascularization were randomly assigned to undergo HCR or CABG. The primary endpoint was the occurrence of all-cause mortality at 5 years.

RESULTS Nine patients (4 in HCR and 5 in CABG group) were lost to the 5-year follow-up. Finally, 191 patients (94 in HCR and 97 in CABG group) formed the basis of this study. The groups were well balanced in terms of pre-procedural characteristics. All-cause mortality at 5-year follow-up was similar in the 2 groups (6.4% for HCR vs. 9.2% for CABG; $p = 0.69$). The rates of myocardial infarction (4.3% vs. 7.2%; $p = 0.30$), repeat revascularization (37.2% vs. 45.4%; $p = 0.38$), stroke (2.1% vs. 4.1%; $p = 0.35$), and major adverse cardiac and cerebrovascular events (45.2% vs. 53.4%; $p = 0.39$) were also similar in the 2 groups.

CONCLUSIONS HCR has similar 5-year all-cause mortality when compared with conventional coronary bypass grafting (Safety and Efficacy Study of Hybrid Revascularization in Multivessel Coronary Artery Disease; NCT01035567). (J Am Coll Cardiol Intv 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

Conventional coronary artery bypass grafting (CABG) is still an evidence-based, gold standard in the treatment of patients with multivessel coronary artery disease (MVCAD) (1,2). Most important clinical benefit is related to left internal mammary artery (LIMA) to left anterior descending artery (LAD) conduit with 10-year patency rate greater than 90% (3,4). However, conventional open-chest CABG is a relatively invasive and high-risk procedure, and poor saphenous vein graft patency declines significantly with time: 10% to 25% of grafts occlude within 1 year; an additional 1% to 2%

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

EuroScore = European System for Cardiac Operative Risk Evaluation score

HCR = hybrid coronary revascularization

LAD = left anterior descending

LIMA = left internal mammary artery

MACCE = major adverse cardiac and cerebrovascular events

MI = myocardial infarction

MVCAD = multivessel coronary artery disease

PCI = percutaneous coronary intervention

SYNTAX = Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery

occlude each year during the 5-year period (5,6). Conventional CABG drawbacks may be avoided when minimally invasive techniques are implemented. These findings, combined with the advancement in percutaneous coronary intervention (PCI) with drug-eluting stents in non-LAD coronary arteries, formed the rationale for hybrid coronary revascularization (HCR). HCR is defined as a planned intervention combining cardiac surgery with bypass LIMA to LAD with a catheter-based intervention performed within a predefined time in non-LAD targets. It means that HCR connects the best parts derived from surgical and percutaneous coronary revascularization options and seems to be a very attractive coronary revascularization alternative. In the POLMIDES (HYBRID) (Safety and Efficacy Study of Hybrid Revascularization in Multivessel Coronary Artery Disease) we compared HCR with CABG in randomly assigned patients with MVCAD and demonstrated that HCR is feasible and safe with similar 12-month mortality and major adverse cardiac events (7). However, there is a lack of robust clinical data, and available data are mostly limited to observational studies with short-term follow-up. Accordingly, the aim of this study was to evaluate the 5-year clinical outcome for the patient population from the HYBRID study. Additionally, all patients in the 2 compared groups were stratified by the clinical score system, European System for Cardiac Operative Risk Evaluation (EuroScore), and the angiographic score system, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX), which sought to identify which subgroup of patients may have optimal outcomes (8,9).

METHODS

STUDY DESIGN AND PATIENT POPULATION. The study design has been described in detail elsewhere (10). Briefly, the HYBRID study was a prospective, single-center, randomized, open-label, parallel, pilot study. The primary endpoint of the primary publication was the evaluation of feasibility of HCR. Feasibility endpoint was defined by means of percentage of patients with complete hybrid procedure according to study protocol and a percentage of conversion to standard CABG. Angiographic follow-up was performed 12 months after the indexed procedures. The authors designed the study in collaboration with the Ministry of Science and Higher Education of Poland. The study protocol was approved by the local ethics committee and complies with the Declaration of Helsinki. Written informed consent was obtained from all study participants.

In summary, 200 consecutive patients with angiographically confirmed MVD involving LAD and critical (>70%) lesion in at least 1 (apart LAD) major epicardial vessel amenable to both PCI and CABG and referred to conventional surgical revascularization were randomly assigned to undergo 1 of the 2 treatment options (CABG or HCR).

REVASCULARIZATION AND PHARMACOLOGIC TREATMENT. In both arms of the study patients were treated with the intention of achieving complete revascularization of all vessels at least 2.0 mm in diameter with stenosis of 50% or more, as identified by the local heart team. The surgical technique for CABG, the approaches used for HCR stages, and the post-procedure medication regimen were chosen according to local clinical practice and European Society of Cardiology Guidelines. In patients in HCR arm who underwent PCI, dual antiplatelet therapy with aspirin and clopidogrel was recommended for at least 12 months after stent implantation. For CABG surgery, arterial revascularization was encouraged. Aspirin was prescribed indefinitely for all patients who underwent randomization. Use of the standard of post-intervention care was recommended.

STUDY ENDPOINTS. The primary endpoint of the study was the occurrence of all-cause mortality at 5 years. An occurrence of major adverse cardiac and cerebrovascular events (MACCE), such as all-cause death, myocardial infarction (MI), stroke, and repeat revascularization (PCI and/or CABG) throughout the 5-year period after randomization was also assessed. Cutoffs for division into 3 groups based on the result of EuroScore were determined by the consensus (low, ≤2; medium, >2 and <6; high, ≥6). Subgroups of the SYNTAX score were identified by commonly used tertiles (low, ≤22; medium, >22 and <33; high, ≥33). The follow-up data for each deceased patient with accompanying exact dates of death, MI, stroke, or repeat revascularization were obtained from the official National Health Fund records. The vital status at 5 years was available for all of the patients enrolled in the HYBRID study. The follow-up status regarding occurrence of MI, stroke, and repeat revascularization at 5 years was available for 95.1% and 95.9% (for CABG and HCR, respectively) of all of the initially included patients and gathered during follow-up visit from discharge forms, general practitioners' and specialists' clinical records and consultations, laboratory tests, and a direct conversation with the patients.

TABLE 1 Baseline Characteristics of Patients, According to Study Groups*

	HCR (n = 94)	CABG (n = 97)	p Value
Age at randomization, yrs	62.1 ± 8.1	63.3 ± 8.3	0.41
Male	78.6	73.6	0.17
Body mass index, kg/m²*	28.3 ± 3.2	29.3 ± 4.1	0.09
Medically treated diabetes†	25.7	29.4	0.41
Current smoker	31.6	34.7	0.52
Previous myocardial infarction	54.2	56.8	0.55
Previous stroke	4.1	4.9	0.95
Previous transient ischemic attack	1.0	2.9	0.64
Hypertension	86.8	83.2	0.22
Carotid artery disease	9.2	11.8	0.55
Hyperlipidemia	56.3	58.8	0.63
Angina			
Stable	84.7	84.9	0.58
Unstable	14.3	16.7	0.64
Ejection fraction	49.2	50.6	0.39
EuroScore value	3.1	3.4	0.23
SYNTAX score	23.6 ± 6.1	22.9 ± 5.4	0.49
Lesions, n	3.9 ± 1.4	3.6 ± 1.2	0.18
Total occlusion			
Left anterior descending	22.5	29.7	0.41
Right coronary artery	6.3	6.7	0.82
Ramus circumflex	8.1	10.1	0.26
No. of grafts	1.1 ± 0.7	2.5 ± 0.7	NA
No. of arterial grafts	1.1 ± 0.1	1.6 ± 0.9	NA
Complete arterial revascularization	–	24.6	NA
Post-procedural LIMA patency	96.9	–	NA
Stents used, n	2.4 ± 1	–	NA
Total drainage, ml	1,016 ± 725	1,145 ± 496	0.1
Time MIDCAB to PCI, h	21 ± 5.7	–	NA
In-hospital stay, days	8.6 ± 4.1	8.5 ± 5.2	0.86
Complete revascularization	77.6	78.2	0.81

Values are mean ± SD or %. Data are given for the intention-to-treat population. *The body mass index is the weight in kilograms divided by the square of the height in meters. †Medically treated diabetes was defined as diabetes for which the patient was receiving oral hypoglycemic agents or insulin at the time of enrollment.

CABG = coronary-artery bypass grafting; EuroSCORE = European System for Cardiac Operative Risk Evaluation score; HCR = hybrid coronary revascularization; LIMA = left internal mammary artery; MIDCAB = minimally invasive coronary artery bypass; PCI = percutaneous coronary intervention; NA = not applicable; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

TABLE 2 5-Year Clinical Outcomes*·†

	HCR (n = 94)	CABG (n = 97)	p Value
All-cause mortality‡	6.4	9.2	0.69
Myocardial infarction§	4.3	7.2	0.30
Coronary reintervention‖	37.2	45.4	0.38
Stroke	2.1	4.1	0.35
Any major adverse cardiac or cerebrovascular events¶	45.2	53.4	0.39

Values are %. *Data are given for the intention-to-treat population. †Median follow-up, 5.89 years; range, 4.99 to 6.69 years. ‡All-cause mortality available for entire cohort; HCR (n = 98) versus CABG (n = 102). §Without perioperative myocardial infarction. ‖Percutaneous and/or surgical coronary reintervention. ¶Including all-cause death, myocardial infarction, any coronary reintervention, stroke.

Abbreviations as in Table 1.

STATISTICAL ANALYSIS. The continuous variables are presented as the mean ± SD. The categorical variables are presented as percentages. To test for differences between CABG and HCR groups, the Student *t* test and chi-square test were used, respectively. All-cause mortality events were analyzed with the use of Kaplan-Meier method, log-rank test and an observed difference with 95% confidence interval was calculated. All analyses were based on the intention-to-treat principle. A 2-sided p value of <0.05 was considered statistically significant. Statistical tests were performed with STATISTICA 10PL software (StatSoft, Inc., Tulsa, Oklahoma).

RESULTS

From November 2009 to July 2012 a total of 200 patients with confirmed multivessel coronary artery disease and referred to conventional CABG were randomized to HCR (n = 98) or CABG (n = 102). The median follow-up was 5.89 years (range 4.99 to 6.69 years). Nine patients (4 in HCR and 5 in CABG group) were lost to the 5-year follow-up. Finally, 191 patients (94 in HCR and 97 in CABG group) formed the basis of this study. As in the main study, demographic, clinical, angiographic, and procedural characteristics were well balanced and similar in both treatment groups (Table 1) (7). No sex-based differences were present.

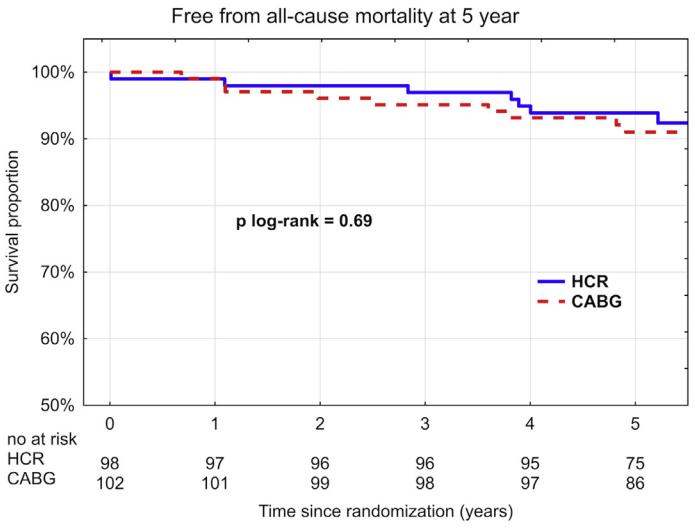
All-cause mortality available for entire cohort at 5-year follow-up was similar in the 2 groups (6.4% for HCR vs. 9.2% for CABG; p = 0.69) (Table 2, Figure 1). Significant difference in the rates of MI (4.3% vs. 7.2%; p = 0.30), repeat revascularization (37.2% vs. 45.4%; p = 0.38), stroke (2.1% vs. 4.1%; p = 0.35), and MACCE (45.2% vs. 53.4%; p = 0.39), respectively, for HCR and CABG group, was not observed (Table 2).

STRATIFICATION BY EuroScore AND SYNTAX SCORE. In all EuroScore tertiles, the MACCE rate in the hybrid group did not differ significantly with those in the CABG. Similarly, in all based on SYNTAX score 3 value groups the MACCE rate was parallel (Table 3).

DISCUSSION

The HCR concept follows from well-documented survival benefit conferred by LIMA-to-LAD grafts and the use of new-generation stents featuring lower stent restenosis and thrombosis rates compared with

FIGURE 1 Kaplan-Meier Estimates for All-Cause Mortality



Free from all-cause mortality at 5 years. CABG = coronary artery bypass graft; HCR = hybrid coronary revascularization.

venous graft stenosis and occlusion rates, respectively (11-15).

The POLMIDES (HYBRID) was the first randomized study for an integrated, 2-stage HCR procedure in patients with MVD referred for standard, open-chest CABG. In HYBRID trial we have proved that HCR is safe and feasible in a selected population of patients with MVCAD and we have recorded that minimally invasive direct coronary artery bypass with LIMA to LAD preceding endovascular as a first-stage procedure in HCR patients was not associated with a significant increase in adverse events. Regrettably, to our best knowledge, the HYBRID trial is the only randomized trial worldwide and there is still paucity of clinical data including significant number of patients with long-term follow-up. Therefore, the 2012 American College of Cardiology Foundation/American Heart Association guidelines recommend HCR as "reasonable only if CABG or PCI of the LAD are contraindicated due to severe clinical and/or anatomical reasons or recommend as worth considering in place of CABG or multiple PCI to improve the overall risk-benefit ratio of these procedures" (2). Even in the more recent European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization, HCR has a class IIb recommendation for specific patient subsets and only at experienced centers (1). Consequently, physicians and surgeons do not implement HCR broadly in routine everyday clinical practice. In a recent study from the Society of Thoracic Surgeons Adult Cardiac Surgery Database, HCR was performed in only 0.48% of the total isolated CABG volume (n = 198,622) in one-third of participating centers between July 2011 and March 2013 (16). Bearing in mind all the aspects mentioned previously, we decided to carefully analyze in our study the fate of the patients included in the HYBRID trial during the 5-year follow-up.

In this trial we revealed no difference in all-cause mortality, MI, stroke, repeat coronary revascularization, and MACCEs during 5-year follow-up. Our findings are consistent with the recently published, albeit with only 1-year observation, meta-analysis (17). Similarly, a prior analysis and pooled results from the 2 propensity-matched cohort studies comparing HCR with CABG demonstrate similar long-term mortality, but increased revascularization rate in patients undergoing HCR (18-20). In contrast, in the current investigation the incidence of coronary reintervention events in the HCR and CABG groups showed no statistical difference (p = 0.38) (**Table 2**) but the observed trend and the numerical difference was quite remarkable (37.2% vs. 45.4%) in favor of HCR.

According to the rationale for HCR mentioned previously, because duration of long-term observation is longer, superiority of HCR regarding MACCEs may be observed. Several findings support this thesis. First, avoiding aortic clamping and manipulation is 1 of the unique advantages of the hybrid procedure in terms of post-operative cerebrovascular events (21). Avoiding aortic manipulation can provide superior neurologic outcomes irrespective of on- or off-pump strategy or severity of atherosclerotic disease (22,23). In the present study, the rate of neurologic events in the HCR and CABG group revealed no

TABLE 3 The Cumulative MACCE Rate in Entire, Hybrid, CABG Groups From Low to High EuroScore and SYNTAX Score Tertile

		Overall (n = 191)	HCR (n = 94)	CABG (n = 97)	Log-Rank p Value
EuroScore ≤2	n	77	42	35	
	% MACCE	38.9 (n = 30)	35.7 (n = 15)	42.8 (n = 15)	0.46
EuroScore 2-6	n	81	38	43	
	% MACCE	54.3.0 (n = 44)	52.6 (n = 20)	55.8 (n = 24)	0.74
EuroScore ≥6	N	33	14	19	
	% MACCE	45.5 (n = 20)	50.0 (n = 7)	68.4 (n = 13)	0.21
SYNTAX ≤22	N	75	36	39	
	% MACCE	44.0 (n = 33)	38.9 (n = 14)	48.7 (n = 19)	0.39
SYNTAX 22-33	N	98	48	50	
	% MACCE	60.2 (n = 59)	56.2 (n = 27)	64.0 (n = 32)	0.43
SYNTAX ≥33	N	8	6	2	
	% MACCE	25.0 (n = 2)	50.0 (n = 1)	50.0 (n = 1)	1.0

MACCE = major adverse cardiac or cerebrovascular event(s); other abbreviations as in Table 1.

significant difference (2.1% vs. 4.1%; p = 0.35) (**Table 2**), but the recorded numerical difference was quite notable. Second, combining LIMA to LAD with PCI using drug-eluting stents in non-LAD targets may be a significant factor determining the decrease in the frequency of repeat revascularization. Our 5-year results showed that HCR also had a similar revascularization rate to that in the CABG group (37.2% vs. 45.4%; p = 0.38). Longer follow-up time and larger sample sizes are necessary to validate this finding. Finally, lower invasiveness of HCR could be a key point of superior perioperative outcomes, including reduced lengths of intubation and intensive care unit stay, and less blood transfusion than CABG (24).

Few retrospective, small population, studies confirmed that HCR was safe and reliable in selected high-risk patients, with low mortality and morbidity rates (25-27). The propensity-matched cohort from Shen et al. (19) showed no difference in MACE rates between HCR and CABG in patients with high SYNTAX. Furthermore, the same study showed that among patients with high additive EuroScore, those who underwent 1-stop HCR demonstrated a significantly lower MACE rate versus CABG. In our study we have shown that there is no difference in MACCE frequency between the studied groups divided into tertiles accordingly with EuroScore and SYNTAX score.

STUDY LIMITATIONS. This study is a follow-up of a previously published feasibility study. The HYBRID study was not powered to detect differences in all-cause mortality between compared CABG and HCR treatment options. Therefore, all the discussion about the statistically insignificant difference that favors a hybrid approach may be speculative, misleading, and should be interpreted with caution. However, one of the strengths of the present study is that all-cause mortality assessment was performed via a central, national database, which allowed robust and complete capture of all deaths.

Our study showed a high proportion of patients with repeated coronary interventions. This can be explained by the fact that we have only general data on the occurrence of any recurrent coronary intervention (any PCI and/or any CABG), without details related to it, such as target lesion, target vessel, or de novo lesion reintervention. However, the definition of endpoints, such as coronary reintervention, in different studies varied to some degree, which may have weakened the evidence in our analysis.

CONCLUSIONS

Our study shows that HCR is a promising coronary revascularization strategy in selected patients with MVCAD. Compared with conventional CABG, HCR was associated with similar risk of death, MI, stroke, coronary reintervention, and MACCE. This warrants further validation in multicenter, adequately powered randomized studies to definitively assess the absolute benefits and risks of HCR.

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PERSPECTIVES

WHAT IS KNOWN? The HCR concept follows from well-documented survival benefit conferred by LIMA-to-LAD grafts and the use of new-generation stents featuring lower stent restenosis and thrombosis rates compared with venous graft stenosis and occlusion rates, respectively. There are currently no long-term outcome data from randomized trials in this setting.

WHAT IS NEW? Compared with conventional CABG, HCR was associated with similar risk of death, MI, stroke, coronary reintervention, and MACCE during 5-year follow-up.

WHAT IS NEXT? Broader implementation of HCR in daily practice after validation in multicenter, adequately powered randomized study.

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