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Hybrid coronary revascularization in multivessel disease: Long-term clinical outcomes of the prospective randomized study

Short title: Hybrid coronary revascularization

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INTRODUCTION

Conventional coronary artery bypass grafting (CABG) remains an evidence-based treatment option for patients with severe multivessel coronary artery disease (MVCAD) [1, 2].

The recently published guidelines highlight hybrid coronary revascularization (HCR) to be a promising management strategy [2].

In the POL-MIDES (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

and 5-year mortality and major adverse cardiac events rates [3, 4]. Similar findings were recently published, however with short-term follow-up [5]. Accordingly, the aim of this study was to evaluate the long-term clinical outcome for the patient population from the HYBRID study.

METHODS

The HYBRID study (ClinicalTrials.gov number, NCT01035567) was a prospective, single-center, randomized, open-label, parallel, pilot study. 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 stable coronary disease and angiographically confirmed MVD involving left anterior descendens artery and critical (>70%) lesion in at least one (apart left anterior descendens artery) major epicardial vessel referred to conventional surgical revascularization were randomly assigned to undergo CABG or HCR.

The primary endpoint of the study included the occurrence of all-cause long-term mortality. An occurrence of major adverse cardiac and cerebrovascular events such as all-cause death, myocardial infarction (MI), stroke, repeat revascularization (percutaneous coronary intervention and/or coronary artery bypass graft) throughout the 10-year period after randomization was also assessed. 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 was available for all of the patients enrolled in the HYBRID study. The follow-up status regarding the occurrence of MI, stroke, and repeat revascularization was available for 95.1% and 95.9 % (for CABG and HCR, respectively) of all included patients. The rationale, and design of the HYBRID trial has been published previously [6].

Statistical analysis

The continuous variables are presented as the means, standard deviations or as medians and interquartile ranges. The categorical variables are presented as percentages. To test for differences between CABG and HCR groups, Student's t-test and the chi-square test were used, respectively. All-cause mortality events and combined follow-up endpoint were analyzed with the use of the Kaplan–Meier method and the log-rank test. All analyses were based on the intention-to-treat principle. A 2-sided *P*-value of less than 0.05 was considered statistically significant. Statistical tests were performed with STATISTICA 10PL software (StatSoft, Inc.).

RESULTS AND DISCUSSION

From November 2009 to July 2012 two hundred patients with confirmed MVD and referred to conventional CABG were randomized to HCR (n = 98) or CABG (n = 102). The median follow-up was 12.21 years (range 10.72–13.42 years) (Figure 1A). Nine patients (4 in HCR and 5 in CABG group) were lost to the follow-up. Finally, 191 patients (94 in the HCR group and 97 in the CABG group) formed the basis of this study. No gender-based differences were present.

All-cause mortality available for the entire cohort at long-term follow-up was significantly lower in patients after hybrid revascularization as compared to patients after CABG (20.4% vs. 36.3%; $P = 0.02$, respectively) (Figure 1B). A significant difference in the rates of myocardial infarction (13.3% vs. 16.7%; $P = 0.63$), repeat revascularization (45.9% vs. 51.0%; $P = 0.57$), stroke (5.9% vs. 7.1%; $P = 0.72$), and major adverse cardiac and cerebrovascular events (56.1% vs. 68.6%; $P = 0.09$), respectively for the HCR and CABG group, was not observed (Figure 1C–F).

The presented study is the first and only RCT reporting long-term survival after HCR as compared to CABG. In this trial, we revealed significantly lower all-cause mortality in selected patients with MVCAD after HCR. Accordingly, the current study provides unique long-term insights into survival after HCR versus CABG by extending follow-up to median 12.2 years, which could provide an important argument in the decision-making process for determining the optimal revascularization strategy for patients with MVCAD. Moreover, the primary endpoint of all-cause death focuses on the most robust endpoint that is clinically relevant for both patients and physicians. Last but not least, follow-up was complete for all randomly assigned patients in the HYBRID study.

Correctly carried out RCT provides unique data in terms of evidence and remains the gold standard to prove the efficacy and feasibility of clinical intervention. However, the follow-up periods may be limited due to economic and logistical issues. The main reason for extending randomized trials is to estimate the potential long-term benefits of an intervention. Following a scoping review of RCTs performed by Fitzpatrick et al. [7], in nearly 20% of RCTs, statistically significant long-term benefits regarding hard-point events were seen only in the trial extension phase.

This study is a follow-up to a previously published feasibility study. The HYBRID study was not powered to detect differences in all-cause mortality between compared CABG and hybrid coronary revascularization treatment options. Because of the limited number of patients at risk at maximum follow-up, these results should be interpreted as hypothesis-generating and

could be used for sample size calculation in randomized controlled trials comparing HCR with CABG. Therefore, the discussion about the statistically insignificant difference that favours a hybrid approach may be speculative and 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 a 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.

Our study shows that HCR, as compared to conventional CABG, was associated with higher long-term survival. This warrants further validation in multi-center, adequately powered randomized studies to definitively assess the absolute benefits and risks of HCR. But even so, before the outcomes of such trial are widley available, our results might already be an important support when Heart-Team evaluates each patient with MVDCAD and recommends HCR as the potentially preferred course of treatment.

Article information

Conflict of interest: None declared.

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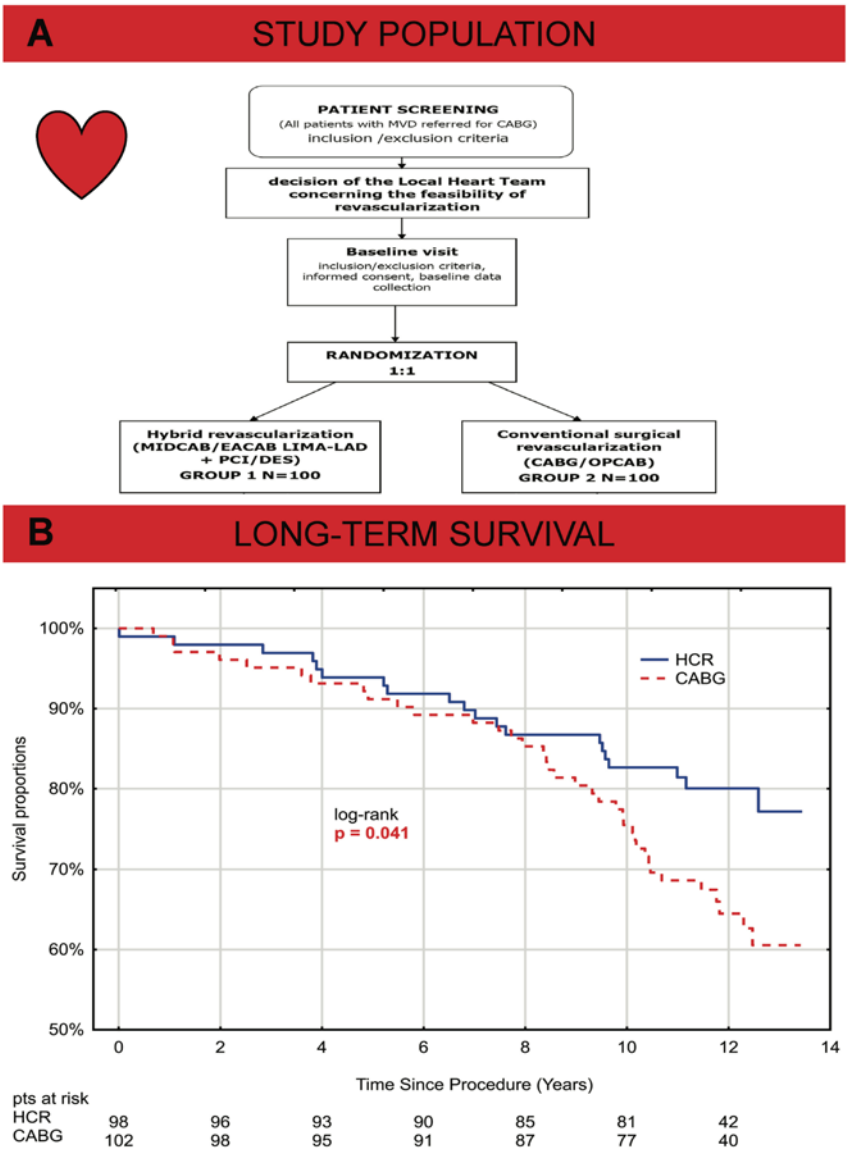

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Variable	HCR (n=94)	CABG (n=97)	p
All-cause mortality**, %	20.4	36.3	0.02
Myocardial infarction†, %	13.3	16.8	0.59
Coronary reintervention¶, %	47.1	51.0	0.27
Stroke, %	6.5	4.9	0.75
Any major adverse cardiac or cerebrovascular events‡, %	56.1	68.6	0.09

Figure 1. A. Study flowchart. **B.** Kaplan–Meier estimates for all-cause mortality. **C.** Long-term major adverse cardiac and cerebrovascular events in studied groups. Graphical presentation of the major findings coming from presented study