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FULL RESEARCH PAPER

Combined assessment of stress cardiovascular magnetic resonance and angiography to predict the effect of revascularization in chronic coronary syndrome patients

Jose Gavara [1†], Nerea Perez [2†], Victor Marcos-Garces[3], Jose V. Monmeneu [4], Maria P. Lopez-Lereu[4], Cesar Rios-Navarro [2], Elena De Dios[5], Clara Bonanad[2,3,6], Joaquim Cánoves[3], David Moratal[1]*, Patricia Palau [2,3,6], Gema Miñana[2,3,6], Julio Nunez[2,3,5,6], Francisco Javier Chorro [2,3,5,6], and Vicente Bodi [2,3,5,6]*

[1]Center for Biomaterials and Tissue Engineering, Universitat Politècnica de València, Camí de Vera s/n, 46022 Valencia, Spain; [2]Instituto de Investigacion Sanitaria INCLIVA, Calle de Menéndez y Pelayo 4, 46010 Valencia, Spain; [3]Department of Cardiology, Hospital Clinico Universitario de Valencia, Avenida Blasco Ibáñez 17, 46010 Valencia, Spain; [4]Cardiovascular Magnetic Resonance Unit, Exploraciones Radiologicas Especiales (ERESA), Calle del Marqués de San Juan 6, 46015 Valencia, Spain; [5]Centro de Investigación Biomédica en Red - Cardiovascular (CIBER-CV), Avenida Monforte de Lemos 3-5, 28029 Madrid, Spain; and [6]Department of Medicine, Faculty of Medicine and Odontology, University of Valencia, Avenida Blasco Ibáñez 17, 46010 Valencia, Spain

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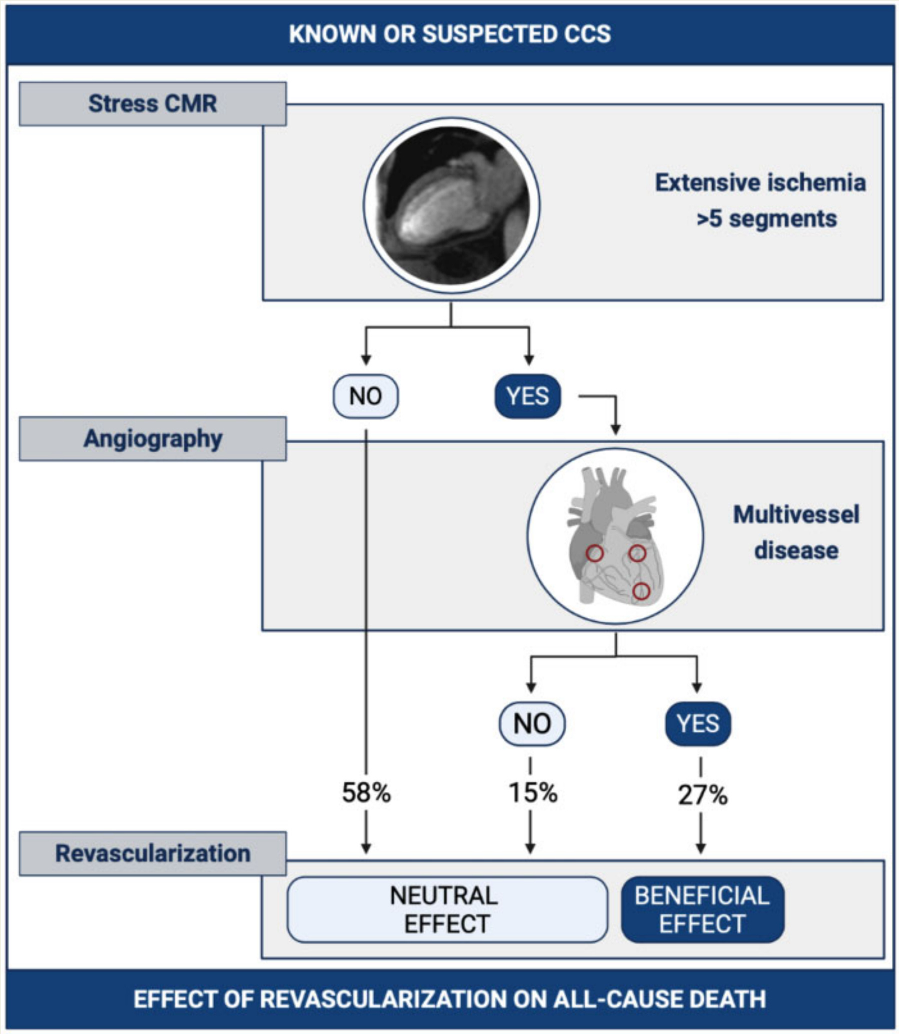
Aims The role of revascularization in chronic coronary syndrome (CCS) and the value of ischaemia vs. anatomy to guide decision-making are in constant debate. We explored the potential of a combined assessment of ischaemic burden by vasodilator stress cardiovascular magnetic resonance (CMR) and presence of multivessel disease by angiography to predict the effect of revascularization on all-cause mortality in CCS.

Methods and results The study group comprised 1066 CCS patients submitted to vasodilator stress CMR pre-cardiac catheterization (mean age 66 ± 11 years, 69% male). Stress CMR-derived ischaemic burden (extensive if >5 ischaemic segments) and presence of multivessel disease in angiography (two- or three-vessel or left main stem disease) were computed. The influence of revascularization on all-cause mortality was explored and adjusted hazard ratios (HRs) with the corresponding 95% confidence intervals were obtained. During a median 7.51-year follow-up, 557 (52%) CMR-related revascularizations and 308 (29%) deaths were documented. Revascularization exerted a neutral effect on all-cause mortality in the whole study group [HR 0.94 (0.74–1.19), $P = 0.6$], in patients without multivessel disease [$n = 598$, 56%, HR 1.12 (0.77–1.62), $P = 0.6$], and in those with multivessel disease without extensive ischaemic burden [$n = 181$, 17%, HR 1.66 (0.91–3.04), $P = 0.1$]. However, compared to non-revascularized patients, revascularization significantly reduced all-cause mortality in patients with simultaneous multivessel disease and extensive ischaemic burden ($n = 287$, 27%): 3.77 vs. 7.37 deaths per 100 person-years, HR 0.60 (0.40–0.90), $P = 0.01$.

Conclusions In patients with CCS submitted to catheterization, evidence of simultaneous extensive CMR-related ischaemic burden and multivessel disease identifies the subset in whom revascularization can reduce all-cause mortality.

* Corresponding authors. Tel: +34 96 1973500, Fax: +34 96 1973979, Email: vicente.bodi@uv.es (V.B.); Tel: +34 96 3877007, Email: dmoratal@eln.upv.es (D.M.)
†The first two authors contributed equally to the study.



Graphical Abstract In ~75% of chronic coronary syndrome patients (cases without extensive ischaemic burden and those with extensive ischaemic burden but without multivessel disease), use of revascularization did not associate with a reduction in all-cause mortality. However, in around a quarter of cases (patients with simultaneous multivessel disease and extensive ischaemic burden) revascularization significantly associated with less all-cause mortality. CCS, chronic coronary syndrome; CMR, cardiovascular magnetic resonance.

Keywords Cardiovascular magnetic resonance • Ischaemic heart disease • Ischaemic burden • Prognosis • All-cause mortality • Revascularization

Introduction

Whether coronary revascularization can improve prognosis in chronic coronary syndrome (CCS) patients and the relative role of myocardial ischaemia and coronary anatomy in the decision-making process are matters of constant debate.[1] Whereas randomized trials have repeatedly failed to demonstrate a solid benefit of revascularization in terms of death or myocardial infarction across different levels of ischaemia,[2–4] certain concerns persist,[1] and an overly restrictive view could ultimately hamper the potential benefit of revascularization in very high-risk patients not systematically represented in clinical trials.[5]

Pre-revascularization stress test imaging as well as on-site use of pressure wires could potentially achieve a more personalized and judicious use of revascularization.[5–7] However, in a significant number of patients, angiography is the only imaging tool used in decision-making and this can potentially lead to overuse of invasive resources.[1,7]

Vasodilator stress cardiovascular magnetic resonance (CMR) reliably determines the magnitude of ischaemic burden. It enables comprehensive evaluation of CCS patients and is already considered a first-choice tool for diagnosis and risk stratification.[5] In CCS patients, however, so far there are no data indicating the role of combined use of stress CMR and coronary angiography to guide decision-making.

In a large registry of CCS patients who underwent stress CMR prior to cardiac catheterization we explored the potential of a combined assessment of ischaemic burden via vasodilator stress CMR and presence of multivessel disease as derived from coronary angiography to predict the effect of revascularization on all-cause mortality.

Methods

Registry

This project stems from a large registry including 6700 consecutive patients submitted to vasodilator stress CMR for known or suspected CCS in our health department from 2001 to 2016.[5] For the purpose of the present study, the final study group was retrospectively selected and comprised those 1066 patients who underwent CMR-related cardiac catheterization (within 3 months following index stress CMR, provided there had been no hospitalization admission for cardiovascular indications during that time period). The flow chart is displayed in Supplementary material online, *Figure S1*. The attending cardiologists had full and unrestricted access to all the variables shown in this study and decision-making was at their discretion.

Our registry was compiled in accordance with the Helsinki declaration. Patients gave written informed consent prior to CMR imaging. Baseline and CMR data were prospectively recorded and immediately entered into the pre-defined database. In September 2018, the local research ethics committee approved a revision of the registry. Angiographic data and the occurrence of all-cause death were retrospectively collected. Authorized personnel carried out this revision using the electronic regional health system registry. The data underlying this article will be shared on reasonable request to the corresponding author.

Cardiovascular magnetic resonance data analysis

Technical aspects related to CMR studies are depicted in Supplementary material online and elsewhere.[5,8,9] Images were examined by two experienced cardiologists using customized software (Syngo, Siemens, Erlangen, Germany). If necessary, both operators subsequently evaluated the studies and the final results were adjudicated by consensus.

Left ventricular (LV) ejection fraction (LVEF, %) and LV end-diastolic and end-systolic volumes indices (mL/m^2) were quantified in cine images. Using the 17-segment model,[10] two segmental post-contrast CMR indices were visually defined as detailed below.

(1) Ischaemic burden: Segmental perfusion defect was defined as a persistent delay (in at least three consecutive temporal images compared with other segments in the same slice) during myocardial first pass of contrast agent after vasodilator infusion. Ischaemic burden was defined by the number of ischaemic segments (showing perfusion defects in post-stress imaging). The presence of stress-induced perfusion defect was ruled out in segments exhibiting transmural late gadolinium enhancement (LGE) and those with simultaneous perfusion defect and non-transmural LGE in which perfusion defect extent was not clearly greater than extent of LGE. Extensive ischaemic burden was considered if more than five ischaemic segments were detected. This was the best cut-off value to predict all-cause mortality and effect of revascularization on this event (Supplementary material online, *Figure S2*).

(2) LGE extent was visually defined as the number of segments manifesting LGE.

Inter- and intra-observer variability for all CMR indices used in the present registry is <5% and has been previously published.[5]

Cardiovascular magnetic resonance-related cardiac catheterization and revascularization

Cardiovascular magnetic resonance-related cardiac catheterization and revascularization [either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)] were identified as procedures performed within 3 months following the index vasodilator stress CMR study, provided no hospital admission for cardiovascular indications had taken place during that time period (in which case patients were censored upon re-admission). This definition has previously been used by our group[5,9] and by other authors.[11]

As a general rule in our institution, stress CMR results are the predominant consideration to guide revascularization, but the final decision regarding its use and the areas to be revascularized is taken by consensus agreement among clinical and invasive cardiologists, and if necessary by cardiac surgeons.

The extent of coronary artery disease was retrospectively recorded. Affected vessels were defined as those with >2 mm diameter and at least one stenosis >50%. The presence of multivessel disease (regarded as two or more affected vessels and/or left main stem disease) was used throughout as a proxy of extensive angiographic coronary disease. Additionally, the Bypass Angioplasty Revascularization Investigation (BARI) score was also obtained and divided into terciles for categorical analyses.[12] Presence of chronic total occlusion, stenosis >90%, and proximal left anterior descending disease were also registered.

Rationale of the present study

We selected all-cause mortality as the endpoint and vasodilator stress CMR as the non-invasive imaging technique to determine ischaemic burden prior to catheterization. Multivessel disease was regarded as a proxy of extensive angiographic coronary disease.

Amid a paradigm shift in health systems, all-cause death has appeared as the indisputable endpoint when evaluating the consequences of potentially risky therapies. Moreover, considering the retrospective collection of events, all-cause mortality represents the most verifiable outcome.[5,13,14]

The value of stress CMR for diagnosis and risk stratification in patients with known or suspected CCS has largely been validated over recent decades.[8,11] Moreover, we recently reported the potential of stress CMR for decision-making in a large registry of CCS patients. Revascularization was associated with lower all-cause mortality in patients with extensive CMR-related ischaemia (>5 segments).[5] However, only 18% of the whole population underwent CMR-related angiography and only 9% CMR-related revascularization,[5] thus casting uncertainty over the validity of this finding across the spectrum of angiographic disease.

Several current recommendation-based indications for revascularization and modality selection (CABG or PCI) are grounded on extent of angiographic disease.[15] This is a widely accepted strategy and in general, a higher percentage of multivessel disease patients are treated with revascularization, while optimal medical treatment without revascularization is reserved for patients with less extensive angiographic disease.[15] However, multivessel disease in CCS represents a very challenging scenario for decision-making. Recent data suggest that in ∼80% of cases, revascularization is undertaken without prior (by non-invasive imaging tests) or on-site (by pressure wire) information regarding the ischaemic burden or its location.[7]

Endpoint

The endpoint was to explore in CCS patients the potential of a combined assessment of ischaemic burden via vasodilator stress CMR and presence of multivessel disease as derived from coronary angiography to predict the effect of revascularization on all-cause mortality.

Statistical analysis

Standards tests for assessing normal distribution of variables and for comparisons of normally distributed and non-parametric data were applied.

The association of variables with time to all-cause mortality was assessed for all purposes using Cox proportional hazard regression models. Hazard ratios with the corresponding 95% confidence intervals [HR (95% CIs)] were computed. The proportional hazards assumption based on Schoenfeld residuals was fulfilled at *P*-value >0.05.

Martingale residuals were used to detect non-linearity in continuous variables. Co-linearity of variables tested in the multivariate model was assessed using the tolerance statistic (excessive if <0.20) and the variance inflation factor (excessive if >5).

The cut-off point used for dichotomizing the extent of the ischaemic burden (extensive if >5 ischaemic segments) was derived from the Youden index applied to the receiver operating curve analysis for prediction of all-cause mortality (Youden index at this point = 0.07). This is also the point at which the survival curves of revascularized and non-revascularized patients diverged (Supplementary material online, *Figure S2*). To analyse the in-study accuracy of the ischaemic burden (number of segments) and angiographic disease (number of affected vessels) to predict all-cause mortality, the respective areas under the receiver operating curves as well as the diagnostic odds ratio (95% CI) of the presence of extensive ischaemic burden (>5 segments as derived from vasodilator stress CMR) and multivessel disease were computed.

We constructed a propensity score aimed at minimizing potential selection bias of patients submitted to revascularization. This score was obtained using a non-parsimonious model[16] that included cofactors independently related to CMR-related revascularization use. We used multivariable logistic regression models and the respective odds ratios (95% CI) were computed. The resulting propensity score (Supplementary material online) was used for adjustments in multivariable analyses.

Incidence rates of all-cause mortality (expressed as deaths per 100 person-years) were determined. Two-tailed *P*-values were obtained using mid-p adjustments. The adjusted effect of revascularization on all-cause mortality was determined in the whole study group as well as in patients stratified according to the presence of extensive ischaemic burden and multivessel disease. The association of variables with time to all-cause mortality was assessed using Cox proportional hazard regression multivariable models. Hazard ratio (95% CI) and interactions (likelihood ratio) were computed. Cofactors independently associated with all-cause mortality in multivariable analysis [age, diabetes mellitus (DM), and LVEF] and the propensity score to undergo CMR-related revascularization were used for adjustments of analyses addressed to assess the effect of CMR-related revascularization on survival.

A summary of statistical tests applied and their respective function is shown in Supplementary material online, *Table S1*. Statistical significance was achieved at a two-tailed *P*-value <0.05. The SPSS statistical package (version 15.0, SPSS Inc., Chicago, IL, USA) and STATA (version 9.0, StataCorp, College Station, TX, USA) were used throughout.

Results

During a median follow-up of 7.51 years (392 weeks; range 221–597 weeks), all-cause mortality occurred in 308 patients (29%). The baseline characteristics of the study group, as well as of survivors and deceased patients, are displayed in *Table 1*.

Association of all-cause mortality with stress cardiovascular magnetic resonance and angiographic indices

Regarding vasodilator stress CMR indices, the occurrence of all-cause mortality associated with more dilated LV end-systolic and end-diastolic volumes indices, more depressed LVEF, larger ischaemic burden, and LGE extent (*Table 1*). We used a cut-off point of five ischaemic segments to stratify patients into categories of extensive ($n = 448$, 42%) and non-extensive ($n = 618$, 58%) ischaemic burden. All-cause mortality was higher in patients with extensive ischaemia: 4.34 vs. 3.31 deaths per 100 person-years ($P = 0.02$); diagnostic odds ratio: 1.34 (1.02–1.74). The area under the receiver operating curve of the ischaemic burden (as derived from the number of ischaemic segments) to predict all-cause mortality was 0.56 (0.52–0.59).

All-cause mortality was associated with more extensive angiographic disease (*Table 1*). Patients with multivessel disease (two- or three-vessel or left main stem disease; $n = 468$, 44%) exhibited a higher all-cause mortality rate than those with zero- or one-vessel disease ($n = 598$, 56%): 4.79 vs. 2.95 deaths per 100 person-years ($P < 0.001$); diagnostic odds ratio: 1.74 (1.33–2.27). The area under the receiver operating curve of the extent of angiographic disease (as derived from the number of affected vessels) to predict all-cause mortality was 0.57 (0.53–0.61).

In multivariable analysis, older age, DM, and LVEF emerged as the independent predictors of all-cause mortality in the whole study group (*Table 2*).

Effect of cardiovascular magnetic resonance-related revascularization on all-cause mortality

All patients included in the study group underwent angiography and 557 (52%) of them were treated with CMR-related revascularization ($n = 383$, 69%, PCI; $n = 174$, 31%, CABG). Reasons for ruling out CMR-related revascularization are shown in Supplementary material online, *Figure S1*. Supplementary material online, *Table S2* displays the baseline, CMR, and angiographic characteristics of patients treated or not with CMR-related revascularization. Supplementary material online, *Table S3* shows the derived propensity score aimed to predict use of CMR-related revascularization.

Across the whole study group, CMR-related revascularization was not associated with a significant reduction of all-cause mortality [3.62 vs. 3.82 deaths per 100 person-years, adjusted HR (95% CI) 0.94 (0.74–1.19), $P = 0.6$] (Supplementary material online, *Figure S3A*).

Cardiovascular magnetic resonance-related revascularization exerted a neutral effect in patients without extensive ischaemic burden [3.82 vs. 2.97 deaths per 100 person-years, adjusted HR (95% CI) 1.32 (0.94–1.87), $P = 0.1$] (Supplementary material online, *Figure S3B*). This neutral effect of CMR-related revascularization in patients without extensive ischaemic burden persisted both in patients without (*Figure 1*) and with (*Figure 2*) multivessel disease.

Nevertheless, CMR-related revascularization associated with a protective effect in patients with extensive ischaemic burden [3.44 vs. 5.76

Table 1 Baseline, cardiovascular magnetic resonance, and angiographic characteristics of the whole registry and patients with and without all-cause mortality

	All patients (n = 1066)	All-cause mortality		*P*-value
		Yes (n = 308)	No (n = 758)	
Age (years)	66 ± 11	70 ± 10	64 ± 11	<0.001
Male sex (%)	731 (69)	211 (69)	520 (69)	0.9
DM (%)	376 (35)	144 (47)	232 (31)	<0.001
Hypertension (%)	830 (78)	257 (83)	573 (76)	0.006
Hypercholesterolemia (%)	691 (65)	206 (67)	485 (64)	0.4
Current smoker (%)	233 (22)	52 (17)	181 (24)	0.01
Previous revascularization (%)	336 (32)	84 (27)	252 (33)	0.06
Previous infarction (%)	264 (25)	91 (30)	173 (23)	0.4
ST-segment depression (%)	62 (6)	28 (9)	34 (4)	0.03
T-wave inversion (%)	111 (10)	41 (13)	70 (9)	0.3
Left bundle branch block (%)	53 (5)	17 (6)	36 (5)	0.6
CMR indices				
LVEF (%)	60 ± 14	56 ± 16	62 ± 13	<0.001
LV end-diastolic volume index (mL/m^2)	75 ± 27	80 ± 32	73 ± 24	<0.001
LV end-systolic volume index (mL/m^2)	33 ± 24	40 ± 31	30 ± 20	<0.001
Ischaemic burden (number of segments with PD post-stress)	5 (2–8)	5 (3–9)	5 (2–7)	0.004
LGE (number of segments)	1 (0–3)	1 (0–4)	0 (0–3)	0.001
Angiographic indices				
Proximal LAD	184 (17)	52 (17)	132 (17)	0.8
Stenosis > 90%	399 (37)	116 (38)	283 (37)	0.9
Total occlusion	94 (9)	33 (11)	61 (8)	0.3
BARI	21 (0–46)	21 (0–46)	17 (0–46)	0.3
Vessels (number of affected vessels)				<0.001
0	233 (22)	58 (19)	175 (23)	
1	365 (34)	84 (27)	281 (37)	
2	239 (23)	78 (25)	161 (21)	
3	229 (21)	88 (29)	141 (19)	
Multivessel disease (%)	468 (44)	165 (54)	303 (40)	<0.001

BARI, Bypass Angioplasty Revascularization Investigation; CMR, cardiovascular magnetic resonance; DM, diabetes mellitus; LAD, left anterior descending artery; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; PD, perfusion defect.

deaths per 100 person-years, adjusted HR (95% CI) 0.64 (0.46–0.90), P = 0.01] (Supplementary material online, *Figure S3C*). However, this protective effect of CMR-related revascularization in patients with extensive ischaemic burden occurred in patients with multivessel disease [3.77 vs. 7.37 deaths per 100 person-years, adjusted HR (95% CI) 0.60 (0.40–0.90), P = 0.01] (*Figure 2*) but not in those without multivessel disease [2.60 vs. 3.69 deaths per 100 person-years, adjusted HR (95% CI) 0.78 (0.39–1.54), P = 0.5] (*Figure 1*) (*Graphical abstract*).

Out of 598 patients without multivessel disease, 161 (15% of the whole study group) displayed extensive ischaemic burden and 437 (41% of the whole study group) did not. Cardiovascular magnetic resonance-related revascularization was not correlated with lower all-cause mortality in patients without multivessel disease [2.90 vs. 2.98 deaths per 100 person-years, adjusted HR (95% CI) 1.12 (0.77–1.62), P = 0.6] (*Figure 1*).

Out of 468 patients with multivessel disease, 287 (27% of the whole study group) displayed extensive ischaemic burden and 181 (17% of the whole study group) did not. A non-significant trend towards lower all-cause mortality occurred in patients with multivessel disease submitted to CMR-related revascularization [4.21 vs. 5.73 deaths per 100 person-years, adjusted HR (95% CI) 0.82 (0.60–1.13), P = 0.2] (*Figure 2*). As pointed out above, stress CMR pinpointed the subset of patients who most benefitted from CMR-related revascularization, namely multivessel disease patients with extensive ischaemic burden (*Figure 2*) (*Graphical abstract*).

The respective all-cause mortality rates, adjusted HR (95% CI), and interactions when comparing revascularized vs. non-revascularized patients stratified by CMR-derived ischaemic burden and angiographic variables are displayed as a forest plot in *Figure 3A*. Overall, the only significant interaction detected was between the presence of extensive ischaemic burden and the role of revascularization in all-cause mortality (*Figure 3* and Supplementary material online, *Figure S2*). This occurred in patients with but not in those without multivessel disease (*Figure 3B*).

Data on cardiovascular death can be consulted in Supplementary material online.

Table 2 Predictors of all-cause mortality: multivariable analysis

	HR (95% CI)	*P*-value
Age (years)	1.06 (1.04–1.07)	<0.001
DM (%)	1.47 (1.17–1.84)	0.001
Hypertension (%)	1.005 (0.72–1.40)	0.9
Current smoker (%)	1.12 (0.80–1.56)	0.5
ST-segment depression (%)	0.93 (0.62–1.38)	0.7
LVEF (%)	0.98 (0.98–0.99)	<0.001
Ischaemic burden (number of segments with PD post-stress)	0.98 (0.94–1.01)	0.2
LGE (number of segments)	1.03 (0.99–1.09)	0.2
Multivessel disease (%)	1.29 (0.99–1.63)	0.06
CMR-related revascularization (%)	0.97 (0.75–1.25)	0.8

All variables significantly associated with all-cause mortality in univariate analysis ($P < 0.05$ in *Table 1*) were included as cofactors. LV end-systolic volume index and LV end-diastolic volume index were removed of multivariable analysis due to excessive collinearity (variance inflation factor > 5 and tolerance statistic < 0.2) with LVEF. The variable 'number of affected vessels' was removed from multivariable analysis due to excessive collinearity (variance inflation factor > 5 and tolerance statistic < 0.2) with multivessel disease.
CMR, cardiovascular magnetic resonance; DM, diabetes mellitus; HR (95% CI), hazard ratio (95% confidence interval); LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; PD, perfusion defect.

Discussion

The main finding of the present study is that in CCS patients submitted to cardiac catheterization, prior stress CMR can help identify the subset of patients in whom revascularization can reduce all-cause mortality, namely those with simultaneous extensive ischaemic burden and multivessel disease.

Approximately half of the study group (52%) underwent CMR-related revascularization and 308 (29%) deaths were documented during a 7.5-year median follow-up. Therefore, considering the limitations derived from the observational and retrospective nature of our study, the number of patients treated and the percentage of events documented had sufficient statistical power to gain insight into the issue addressed.

Both in the whole study group and in patients with non-extensive ischaemic burden, CMR-related revascularization exerted a neutral effect on all-cause mortality. In patients with non-extensive ischaemic burden, this neutral effect of CMR-related revascularization persisted in patients both with and without multivessel disease and across the BARI score terciles. This observation is in line with results obtained in seven major trials carried out over previous decades.[2,3] Beyond a certain superiority of CABG over PCI in patients with extensive coronary disease (especially those with diabetes) and of PCI over optimal medical treatment alone in terms of soft events (unplanned

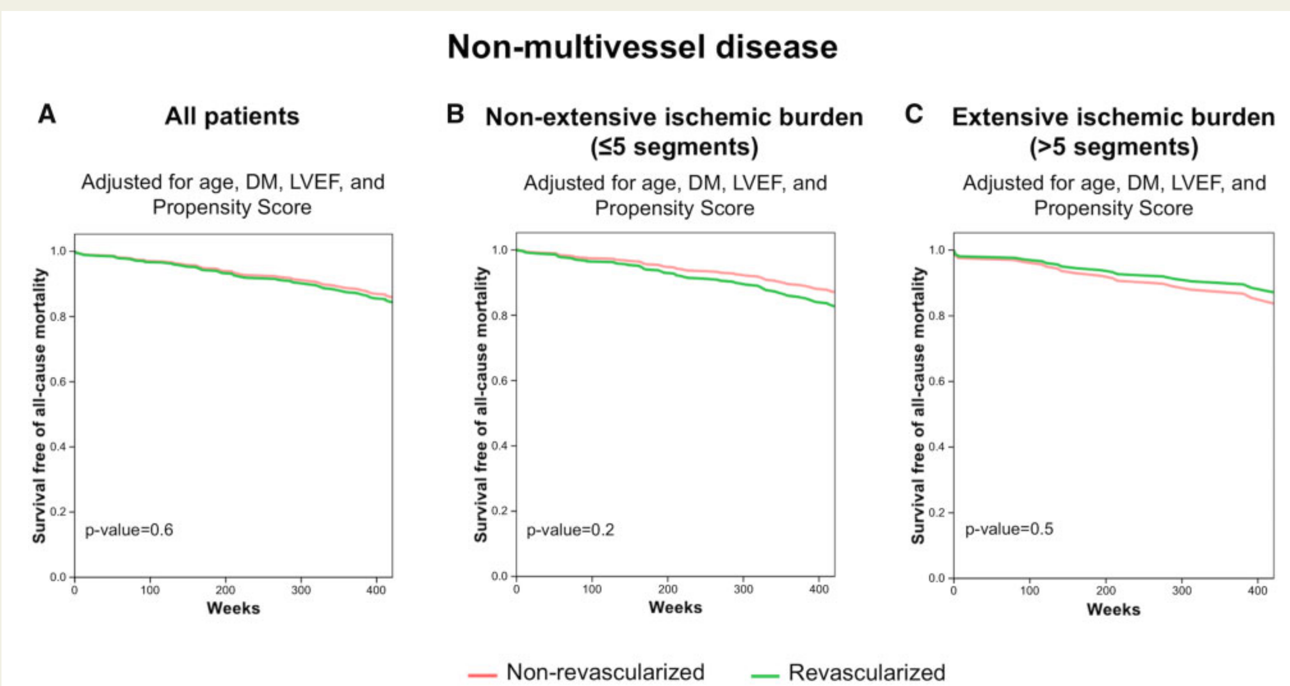


Figure 1 Effect of cardiovascular magnetic resonance-related revascularization on all-cause mortality in patients without multivessel disease. Survival curves. In all non-multivessel disease patients, and in patients with and without extensive ischaemia, cardiovascular magnetic resonance-related revascularization shows a neutral effect in terms of all-cause mortality risk (*A*, *B*, and *C*, respectively). Cofactors independently associated with all-cause mortality in multivariable analysis (age, diabetes mellitus, and left ventricular ejection fraction) and the propensity score to undergo cardiovascular magnetic resonance-related revascularization were used for adjustment of survival curves. DM, diabetes mellitus; LVEF, left ventricular ejection fraction.

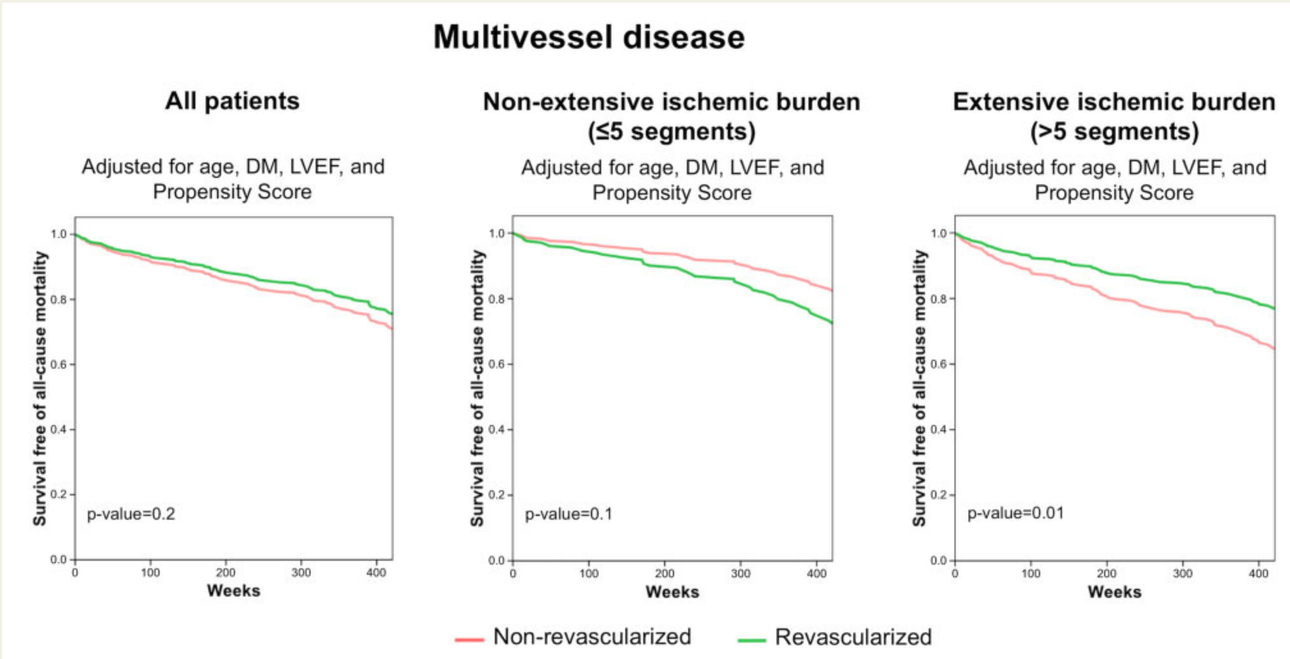


Figure 2 Effect of cardiovascular magnetic resonance-related revascularization on all-cause mortality in patients with multivessel disease. Survival curves. In multivessel disease patients, and those without extensive ischaemia, cardiovascular magnetic resonance-related revascularization shows a neutral effect in terms of all-cause mortality risk (*A and B*, respectively). However, in patients with multivessel disease and extensive ischaemia (>5 ischaemic segments), patients with cardiovascular magnetic resonance-related revascularization displayed a significantly lower risk of all-cause mortality than those without cardiovascular magnetic resonance-related revascularization (*C*). Cofactors independently associated with all-cause mortality in multivariable analysis (age, diabetes mellitus, and left ventricular ejection fraction) and the propensity score to undergo cardiovascular magnetic resonance-related revascularization were used for adjustment of survival curves. DM, diabetes mellitus; LVEF, left ventricular ejection fraction.

procedures and symptoms improvement), no significant reduction of mortality by revascularization was reported in CCS patients.[2,3]

However, taken out of context, this initial 'medical management for all' message can lead to over-scepticism among decision-makers and underuse in high-risk subsets. Due to inclusion criteria, or in many cases 'self-censorship' bias by which local researchers are reluctant to randomize high-risk patients, the effect of revascularization in this scenario has probably gone unaddressed in trials.[4,5] Indeed, the two largest real-life registries focused on the effect of revascularization on all-cause death in consecutive CCS patients submitted to stress imaging indicated that revascularization was associated with lower mortality in patients with extensive ischaemia.[5,17,18] These observations seem to suggest that patients with 'really severe' ischaemia could have been underrepresented in trials. Unsurprisingly, the effect on 'low or moderate risk' randomized patients has been repeatedly found to be neutral in terms of hard events.

Nevertheless, when examined in detail, revascularization has also exerted a certain beneficial tendency in patients with severe ischaemic burden in randomized trials. This was first suggested four decades ago in trials comparing CABG with medical treatment. More recently in a small subset of 314 patients enrolled in the nuclear substudy of the 'Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation' (COURAGE), fewer events occurred in patients with large areas of ischaemic myocardium (≥10%) in whom the amount of ischaemic myocardium was reduced at follow-up.[3] Similarly, a non-significant tendency towards fewer events in patients with most extensive ischaemic burden was also observed in the 'International Study Of Comparative Health Effectiveness With Medical And Invasive Approaches' (ISCHEMIA).[4]

In summary, the results of our registry indicate that in ∼60% of CCS patients submitted to CMR-related angiography (those without extensive ischaemic burden), use of revascularization does not associate with a reduction in all-cause mortality. However, in around a quarter of cases (those 27% of patients with simultaneous multivessel disease and extensive ischaemic burden) if anatomically feasible, revascularization can be effective in prolonging survivorship (*Figure 4*). In the small proportion of patients (15%) with extensive ischaemic burden but without multivessel disease, we must individualize decision-making and accept ambiguity: revascularization could be justified for symptomatic improvement but benefits in terms of mortality area unclear. Risks and benefits should be frankly exposed and, in this setting, decisions should always be made after thorough consideration of patient's characteristics, symptoms, and preferences.

It should be emphasized that the study sample (made up of CCS patients evaluated with stress CMR and subsequently submitted to intracoronary angiography) was made up of a high-risk CCS population. In fact, the mortality of the studied population (29% vs. 11%) and the ischaemic burden [5 (2–8) segments vs. 0 (0–4) segments] was much higher than that of our stem registry[5] that included all

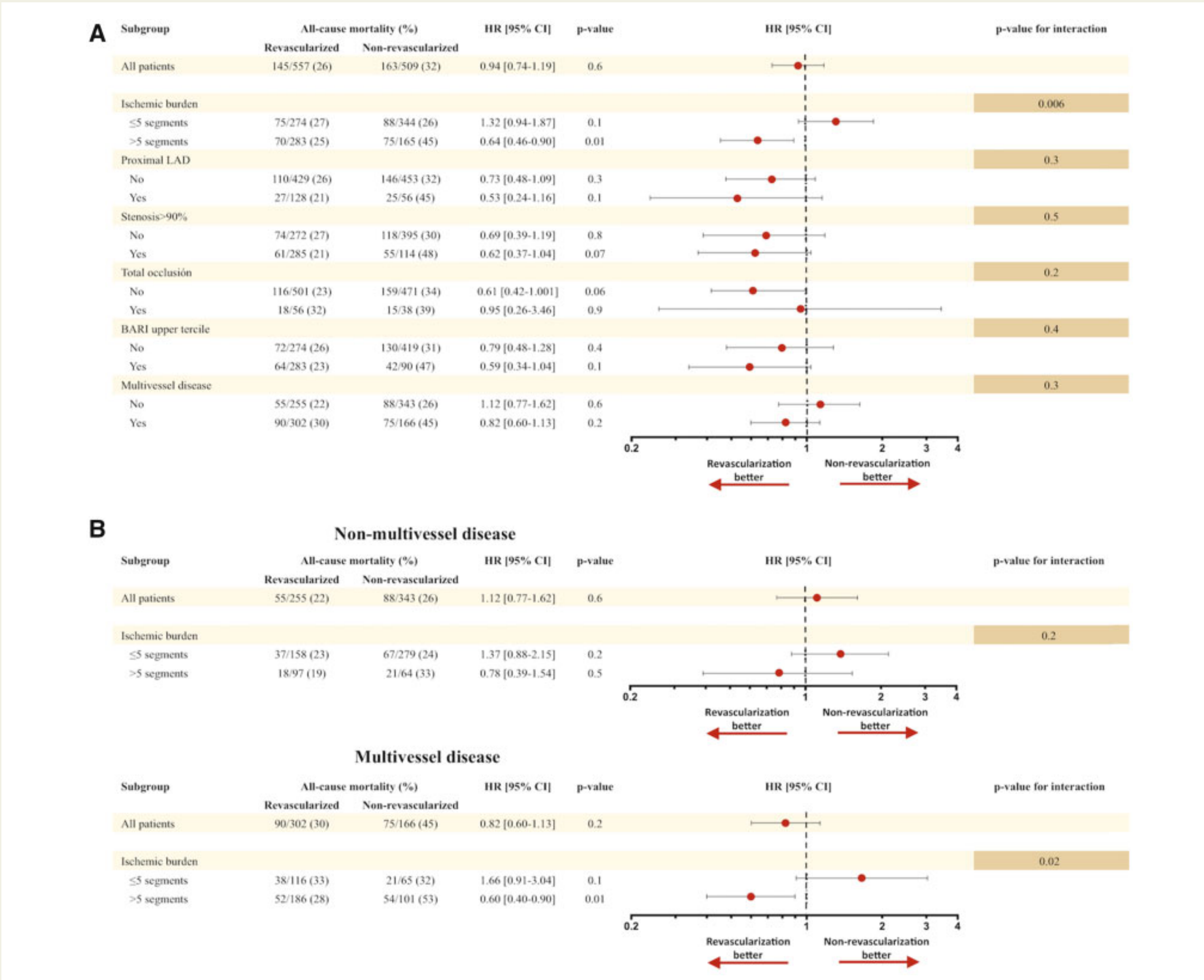


Figure 3 Forest plot of the effect of cardiovascular magnetic resonance-related revascularization on all-cause mortality. (*A*) Cardiovascular magnetic resonance-related revascularization had a neutral effect on all-cause mortality in the whole study group and in subgroups dichotomized by proximal left anterior descending, stenosis >90%, total occlusion, Bypass Angioplasty Revascularization Investigation upper tercile, and multivessel disease. However, it exerted a protective effect in patients with extensive ischaemia (>5 segments) but not in those with non-extensive ischaemia (≤5 segments) (*P*-value for interaction<0.01). (*B*) This occurred in patients with but not in those without multivessel disease. Cofactors independently associated with all-cause mortality in multivariable analysis (age, diabetes mellitus, and left ventricular ejection fraction) and the propensity score to undergo cardiovascular magnetic resonance-related revascularization were used for adjustments of analyses. BARI, Bypass Angioplasty Revascularization Investigation; HR (95% CI), hazard ratio (95% confidence intervals); LAD, left anterior descending artery.

consecutive CCS patients studied with stress CMR. Future studies will be needed to confirm the results of the present study in a wider population of CCS patients.

The value used to define extensive ischaemia (five segments) was the best cut-off to predict all-cause mortality and also marks the point in the ischaemic burden where the risk of revascularized and non-revascularized patients diverged. This cut-off value is much higher than those used in randomized trials to consider 'severe' ischaemia (10% of ischaemic myocardium by nuclear medicine or >2 segments by stress echo and CMR).[4] This point is fundamental to understand the potential of revascularization in CCS. Overall, it seems reasonable that revascularization can exert a protective effect, even in terms of prolonging survival, in the small subset of CCS patients with multivessel disease and robust evidence of really severe ischaemia.

Study limitations

The effect of revascularization was adjusted using a dedicated propensity score aimed at compensating for potential bias between revascularized and non-revascularized patients. This statistical exercise is unable to consider all the myriad of factors relevant to the issue.

The registry database was planned with a limited number of variables to include a large number of patients over a long period, avoiding missing values and maximizing the robustness of data collection.

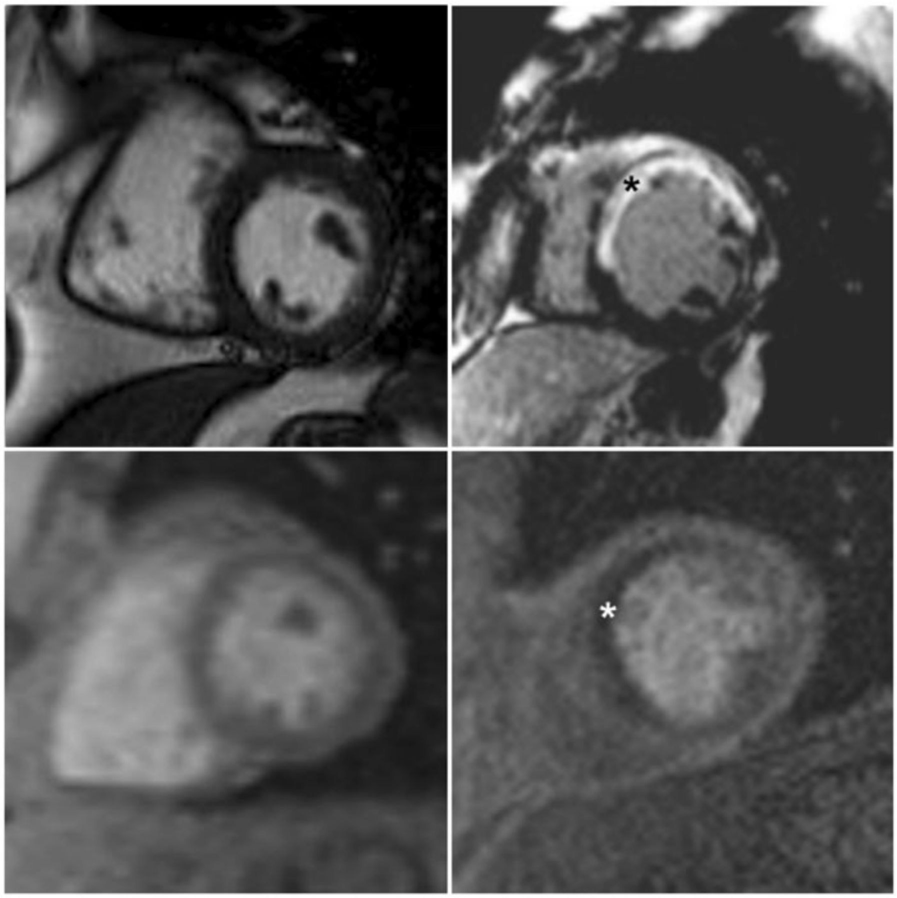


Figure 4 Sequences used in vasodilator stress cardiovascular magnetic resonance studies. Cine, late gadolinium enhancement, and stress perfusion images. Upper panels. Left: Cine images, used for quantification of left ventricular ejection fraction and left ventricular volumes indexes. Right: The asterisk indicates the core of a hyper-enhanced area in a patient with a previous myocardial infarction in the left anterior descending artery territory. Lower panels: Stress perfusion images. Left: Example of a patient without inducible ischaemia. Right: Example of a patient with extensive ischaemic burden. The asterisk indicates the hypo-perfused ischaemic area in the left anterior descending artery territory.

Availability of additional data, such as angina class, would have permitted relevant collateral analyses now unfeasible.

Other events, such as cardiovascular death, could have contributed a more holistic vision of outcomes. However, the retrospective collection of this information made it difficult a reliable assignment of the ultimate cause of death in a significant number of patients and, in our view, the derived results would be uncertain.[14] All-cause mortality is a verifiable and worrisome event, and the strategy of retrospective data review using a unified electronic regional health system guaranteed the quality of information obtained. This is the reason why we adhered to all-cause death as the only endpoint evaluated.

Conclusions

Our results strongly suggest that in order to expect a robust benefit from revascularization in terms of life expectancy in CCS patients, a combined approach to ischaemia and anatomy seems appropriate. Indeed, detection of simultaneous large ischaemic burden by stress CMR and multivessel disease by coronary angiography enables us to identify the small patient subset that can benefit most from revascularization, even in terms of all-cause mortality reduction.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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