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ORIGINAL RESEARCH

Impact of Complete Revascularization on Development of Heart Failure in Patients With Acute Coronary Syndrome and Multivessel Disease: A Subanalysis of the CORALYS Registry

Francesco Bruno, MD; Giorgio Marengo, MD; Ovidio De Filippo, MD; Wojciech Wanha, MD, PhD; Sergio Leonardi, MD; Sergio Raposeiras Roubin, MD; Enrico Fabris, MD; Maja Popovic, MD, PhD; Giuseppe Giannino, MD; Alessandra Truffa, MD; Zenon Huczek, MD; Nicola Gaibazzi, MD; Alfonso Ielasi, MD; Bernardo Cortese, MD; Andrea Borin, MD; Iván J. Núñez-Gil, MD; Daniele Melis, MD; Fabrizio Ugo, MD; Matteo Bianco, MD; Lucia Barbieri, MD; Federico Marchini, MD; Piotr Desperak, MD; Claudio Montalto, MD; Maria Melendo-Viu, MD; Edoardo Elia, MD; Massimo Mancone, MD; Andrea Buono, MD; Marcos Ferrandez-Escarabajal, MD; Nuccia Morici, MD; Marco Scaglione, MD; Domenico Tuttolomondo, MD; Gennaro Sardella, MD; Mariusz Gasior, MD; Maciej Mazurek, MD; Guglielmo Gallone, MD; Gianluca Campo, MD; Wojciech Wojakowski, MD; Emad Abu-Assi, MD; Gianfranco Sinagra, MD; Gaetano Maria De Ferrari, MD; Fabrizio D'Ascenzo, MD, PhD; Collaborators*

BACKGROUND: The impact of complete revascularization (CR) on the development of heart failure (HF) in patients with acute coronary syndrome and multivessel coronary artery disease undergoing percutaneous coronary intervention remains to be elucidated.

METHODS AND RESULTS: Consecutive patients with acute coronary syndrome with multivessel coronary artery disease from the CORALYS (Incidence and Predictors of Heart Failure After Acute Coronary Syndrome) registry were included. Incidence of first hospitalization for HF or cardiovascular death was the primary end point. Patients were stratified according to completeness of coronary revascularization. Of 14 699 patients in the CORALYS registry, 5054 presented with multivessel disease. One thousand four hundred seventy-three (29.2%) underwent CR, while 3581 (70.8%) did not. Over 5 years follow-up, CR was associated with a reduced incidence of the primary end point (adjusted hazard ratio [HR], 0.66 [95% CI, 0.51–0.85]), first HF hospitalization (adjusted HR, 0.67 [95% CI, 0.49–0.90]) along with all-cause death and cardiovascular death alone (adjusted HR, 0.74 [95% CI, 0.56–0.97] and HR, 0.56 [95% CI, 0.38–0.84], respectively). The results were consistent in the propensity-score matching population and in inverse probability treatment weighting analysis. The benefit of CR was consistent across acute coronary syndrome presentations (HR, 0.59 [95% CI, 0.39–0.89] for ST-segment elevation myocardial infarction and HR, 0.71 [95% CI, 0.50–0.99] for non-ST-elevation acute coronary syndrome) and in patients with left ventricular ejection fraction >40% (HR, 0.52 [95% CI, 0.37–0.72]), while no benefit was observed in patients with left ventricular ejection fraction ≤40% (HR, 0.77 [95% CI, 0.37–1.10], *P* for interaction 0.04).

Correspondence to: Francesco Bruno, MD, Division of Cardiology, "Città della Salute e della Scienza di Torino" Hospital. Department of Medical Sciences, University of Turin, Turin 10126, Italy. Email: cescobruno@hotmail.it

*A complete list of the collaborators can be found in the Supplemental Material.

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CONCLUSIONS: CR after acute coronary syndrome reduced the risk of first hospitalization for HF and cardiovascular death, as well as first HF hospitalization, and cardiovascular and overall death both in patients with ST-segment elevation myocardial infarction and non-ST-elevation acute coronary syndrome.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT 04895176.

Key Words: acute coronary syndrome ■ complete revascularization ■ heart failure ■ multivessel disease ■ myocardial infarction ■ percutaneous coronary intervention

CLINICAL PERSPECTIVE

What Is New?

- In patients with acute coronary syndrome (both ST-segment elevation myocardial infarction and non-ST-elevation acute coronary syndrome) and multivessel disease, complete revascularization reduced the risk of first hospitalization for heart failure and cardiovascular death, as well as first heart failure hospitalization, and cardiovascular and overall death.

What Are the Clinical Implications?

- Complete revascularization should be performed in all patients with acute coronary syndrome to reduce the incidence of heart failure and death at follow-up.
- However, further evidence is needed among patients with reduced left ventricular ejection fraction and impaired kidney function.

Nonstandard Abbreviations and Acronyms

CR	complete revascularization
ICR	incomplete revascularization

Primary percutaneous coronary intervention (PCI) has greatly improved short- and long-term outcomes after acute coronary syndrome (ACS); however, its impact on the development of heart failure (HF) remains unclear.[1–3] Currently, HF represents one of the major drivers of morbidity and mortality after ACS and due to the increased long-term survival after myocardial Infarction (MI), the incidence of HF may continue to increase over time.[2–6]

Although complete revascularization (CR) has been largely demonstrated to be associated with improved outcomes at follow-up in patients with ST-elevation myocardial infarction (STEMI), including a lower all-cause and cardiac death and a lower incidence of MI, less evidence is available for its impact in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with multivessel disease.[7–10] The physiopathological benefit of CR for STEMI and potentially NSTE-ACS on improved survival relies on the prevention of recurrent events due to nonculprit lesions, although potentially the improvement of left ventricular ejection fraction (LVEF) after CR may lead to a reduced development of incident HF.[11]

However, the impact of CR on the incidence of HF during the follow-up after ACS and its impact on survival has not been investigated so far.[3]

The main aim of this subanalysis of the CORALYS (Incidence and Predictors of Heart Failure After Acute Coronary Syndrome) registry is to evaluate the impact of CR on adverse outcome at follow-up, including HF hospitalization in patients with ACS and multivessel coronary artery disease undergoing PCI.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

The CORALYS registry (NCT 04895176) is an international, multicenter, retrospective, observational study including consecutive patients admitted for ACS in 16 European Centers from 2015 to 2020, enrolling 14 699 patients Figure S1, Data S1).[12] All the included centers are reported in Figure S2. Consecutive patients with ACS (STEMI and NSTE-ACS) treated with PCI in the participating centers were included. Patients with a known history of congestive HF, previous hospitalizations for HF, medical therapy with loop diuretics for HF, clinical sign of HF detected before ACS or reduced LVEF (LVEF <40%) before the index hospitalization for ACS were excluded. The study complied with the provisions of the Declaration of Helsinki and was approved by the institutional review board of each center. The requirement for written informed consent was waived due to the retrospective nature of the study.

Definitions

Demographics and clinical and main angiographic characteristics were retrospectively retrieved and abstracted on prespecified electronic forms. The presence of cardiovascular risk factors, atrial fibrillation, chronic obstructive pulmonary disease, malignancies, peripheral artery disease, and the history of previous MI or myocardial revascularizations and stroke was deduced from medical history records. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m^2, according to the Modification of Diet in Renal Disease equation. The diagnoses of STEMI, NSTE-ACS, and cardiogenic shock at admission were defined according to the current European Society of Cardiology guidelines definitions and they were retrospectively assessed and retrieved from patients' medical history records and hospital discharge letters.[13,14] Major bleedings were defined as Bleeding Academic Research Consortium 3, 5 bleedings.[15] Multivessel disease was defined as >1 coronary vessel with critical stenosis (≥70% diameter stenosis at angiographic evaluation or vessels with flow-limiting lesions as assessed by intracoronary physiology, either resting or hyperemic indexes). LVEF was assessed by 2D transthoracic echocardiography and computed according to bidimensional Simpson formula [(left ventricular end diastolic volume—left ventricular end systolic volume]/left ventricular end diastolic volume).

After PCI, all patients received dual antiplatelet therapy and were discharged on optimal medical therapy, including β blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and mineralocorticoid receptor antagonist at the discretion of the treating clinicians. Follow-up data were obtained from electronic medical records of each participating center, clinical visit, telephonic contact, or formal query to the primary care physicians, if necessary.

Patients with multivessel disease were divided in 2 groups according to revascularization strategy: complete revascularization (CR group) and incomplete revascularization (ICR group). Complete revascularization was defined as treatment for all significant coronary lesions in major proximal coronary vessels (or side branches >2.5 mm in diameter) during the index hospitalization or in the first 30 days after the discharge. Lesion significance was defined as >70% diameter stenosis on angiography or lesions between 50% and 70% diameter stenosis with demonstrable reversible ischemia on invasive or noninvasive testing.[16]

End Points

The composite of first hospitalization for HF or cardiovascular death was the primary end point. The occurrence of a first hospitalization for HF after the index ACS, confirmed through review of hospital records, consultation notes, discharge letters, and pertinent laboratory data, along with cardiovascular and all-cause death, were the secondary end points. Hospitalization for HF was defined according to the American College of Cardiology/American Heart Association taskforce definition: hospital admission (lasting at least 24 hours or extends over a calendar date) with a primary diagnosis of HF with new or worsening symptoms of HF on presentation, objective evidence of new or worsening HF and initiation or intensification of treatment specifically for HF.[17]

Subgroup analysis on the impact of CR in all the baseline characteristics was performed. Subanalysis of the primary end point according to ACS type (STEMI versus NSTE-ACS) and according to LVEF at discharge (LVEF ≤40% versus LVEF >40%) was also performed. A LVEF cut-off of 40% was used according to the definition of HF with reduced ejection fraction reported in the latest guidelines.[18]

Statistical Analysis

Continuous and categorical variables are reported as mean and SD or median and interquartile range and as frequencies and percentages, respectively. Differences in clinical and procedural features between patients with CR and without CR were investigated by performing χ^2 test for categorical data. For continuous data, normality with Kolmogorov–Smirnov was checked and in case of non-normal distribution, a Kruskal–Wallis test was used, while in case of normal distribution a *t* test was used. The Kaplan–Meier method was used to evaluate survival curves. Three types of multivariate analyses were performed: a Cox multivariate analysis, a Propensity Score with Matching, and an IPTW. For the Cox multivariate analysis, all the baseline variables with $P<0.10$ between patients with CR and patients without CR at univariate were included in the model. The proportionality of the hazard functions over the time was tested using Schoenfeld residuals and the linearity of continuous covariates using martingale residuals, with no evidence of violation of the Cox proportional hazard models assumptions. We checked for influential observations by plotting the deviance residuals against individual predictors and against time. The propensity score (PS) was generated for each patient from a multivariable logistic regression model based on pretreatment covariates as independent variables with complete revascularization as dependent outcome. Pairs of patients were derived using greedy 1:1 matching with a caliper of width of 0.2 SD of the logit of the PS. A Cox regression model, stratified by the propensity to have complete or incomplete revascularization, was used to analyze outcomes. All the variables used for PS analysis as well as the *P* values of their differences in the PS population are reported in Table S1.

At visual examination, a good overlap between groups was noted (Figure S3); moreover, balance was tested with pstest command as reported in Table S1.

For the IPTW analysis, we assigned to each patient a stabilized weight equal to [1-p]/[1-PS] if a control, or equal to p/PS if a treated patient, where *P* is the probability of treatment without any covariate and PS is the value of the PS for that patient using the "stteffects" package of Stata. Balance of the model was tested with tebalance. A sensitivity analysis including also medication at discharge in the IPTW and PS matching model was also performed. All *P* values <0.05 were considered statistically significant. Analyses were performed with SPSS Statistics v24 and STATA v17 (StataCorp, College Station, TX).

RESULTS

Baseline Characteristics

Out of 14 699 patients in the CORALYS registry, 5054 presented with multivessel disease and were included in this analysis (Figure S1). Among them, 1473 (29.2%) underwent CR, while 3581 (70.8%) underwent ICR. Baseline characteristics of patients according to completeness of revascularization are reported in Table 1. Patients undergoing CR were younger (66.4±11.3 versus 67.3±12.4 years old, *P*=0.004), less frequently women (22.5% versus 28.8%, *P*<0.001), had a lower prevalence of hypertension (67.0% versus 77.5%, *P*<0.001), diabetes (27.0% versus 35.5%, *P*<0.001), dyslipidemia (49.4 versus 65.1%, *P*<0.001), previous MI (19.6% versus 31.4%, *P*<0.001), and previous percutaneous or surgical revascularization (respectively, 19.8% versus 32.2% and 5.6% versus 18.6%, all *P*<0.001). By contrast, prevalence of smoking (53.2% versus 37.1%, *P*<0.001), peripheral artery disease (8.4% versus 4.2%, *P*<0.001), and CKD (28.1% versus 22.4%, *P*<0.001) was higher in the CR group. STEMI presentation was more frequent in the CR group (52.3% versus 30.6%, *P*<0.001), as well as cardiogenic shock at presentation (3.3% versus 1.5%, *P*<0.001). Beta blockers (88.8% versus 82.6%, *P*<0.001), angiotensin-converting enzyme inhibitor and angiotensin receptor blocker (82.8% versus 79.1%, *P*=0.004), and mineralocorticoid receptor antagonist (24.1% versus 19.6%, *P*=0.001) were prescribed more often in the ICR group, while statins were prescribed more often in the CR group (95.6% versus 93.3%, *P*=0.002) (Table 1).

Primary End Point

Four thousand nine hundred twenty-eight (98%) patients had long-term follow-up data available (1389 CR and 3539 ICR). Median follow-up time was 2.60 years (interquartile range, 1.01–4.8 years). During follow-up, 128 (9.2%) patients in the CR group

Table 1. Baseline Characteristics of the Population

	Incomplete revascularization (n=3581)	Complete revascularization (n=1473)	*P* value
Age, y	66.4 (±11.3)	67.3 (±12.4)	0.004
Female sex	1032 (28.8%)	332 (22.5%)	<0.001
Hypertension	2776 (77.5%)	987 (67%)	<0.001
Diabetes	1270 (35.5%)	398 (27%)	<0.001
Dyslipidemia	2333 (65.1%)	727 (49.4%)	<0.001
PAD	145 (4.1%)	123 (8.4%)	<0.001
Current smoking	643 (18%)	463 (31.5%)	<0.001
eGFR <60 mL/min	794 (22.4%)	408 (28.1%)	<0.001
Previous MI	1123 (31.4%)	288 (19.6%)	<0.001
Previous CABG	664 (18.6%)	82 (5.6%)	<0.001
Previous PCI	1151 (32.2%)	289 (19.8%)	<0.001
AF	254 (7.1%)	140 (9.5%)	0.004
Prior stroke	71 (2%)	51 (3.5%)	0.002
Prior major bleeding (BARC 3–5)	37 (1%)	14 (1%)	0.79
Cancer	560 (16.5%)	191 (13%)	0.02
COPD	219 (6.1%)	113 (7.7%)	0.04
ACS type			<0.001
STEMI	1088 (30.7%)	765 (52.3%)	
NSTE-ACS	2466 (69.3%)	698 (47.7%)	
Cardiogenic shock at admission	54 (1.5%)	48 (3.3%)	<0.001
Killip class >2	140 (3.9%)	94 (6.4%)	<0.001
GRACE score >140	663 (18.5%)	378 (25.7%)	<0.001
Time symptoms-admission	12.97 (±32)	12.92 (±27.9)	0.30
ULM disease	267 (7.5%)	206 (14%)	<0.001
Bifurcation involvement	364 (10.2%)	388 (26.34)	<0.001
Number of stents	1.37 (±0.9)	2.13 (±1.4)	0.001
LVEF at discharge	50 (±7)	50 (±10)	<0.001
LVEF <50% at discharge	1571 (44%)	562 (40.7%)	<0.001
LVEF ≤40% at discharge	288 (8%)	259 (17.6%)	<0.001
ACE-I/ARB at discharge	2442 (82.8%)	1022 (79.1%)	0.004
Beta-blockers at discharge	3089 (88.8%)	1190 (82.6%)	<0.001
Statin at discharge	3141 (93.3%)	1397 (95.6%)	0.002
Diuretics at discharge	528 (27.2%)	343 (28.5%)	0.20
MRA at discharge	561 (24.1%)	267 (19.5%)	0.001

ACE-I indicates angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NSTE, non-ST-elevation; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; and ULM, unprotected left main.

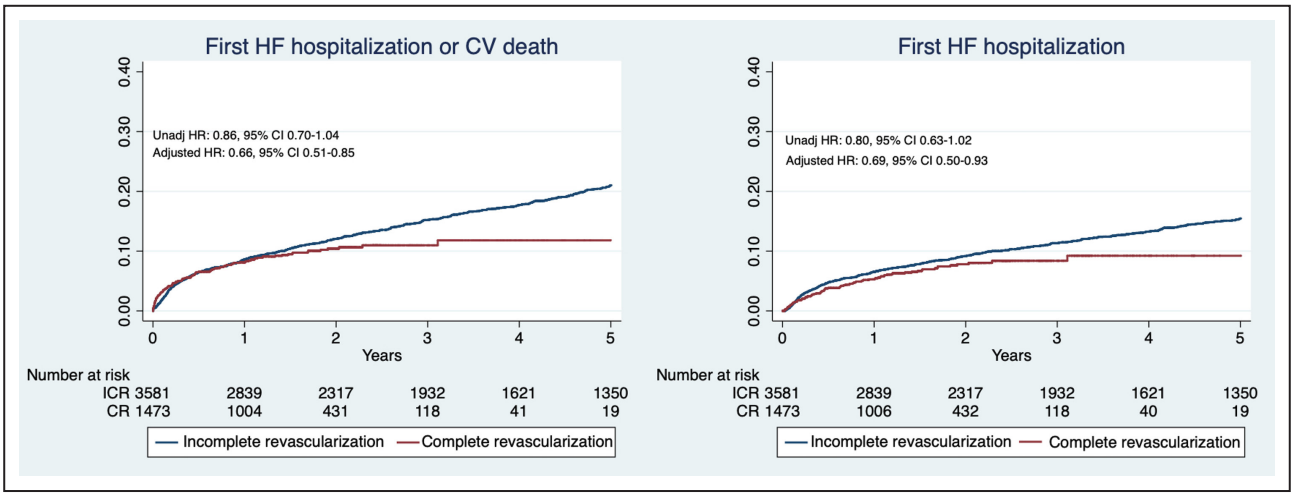

Figure 1. Unadjusted Kaplan–Meier incidence of primary end point (left) and first HF hospitalization (right).
CR indicates complete revascularization; CV, cardiovascular; HF, heart failure; HR, hazard ratio; and ICR, incomplete revascularization.

and 575 (16.3%) in the ICR group underwent the primary end point (*P*<0.001).

In the unadjusted Kaplan–Meier time-to-event curves, the CR group had a nonsignificant lower cumulative incidence of the primary end point compared with the ICR group (hazard ratio [HR], 0.86 [95% CI, 0.70–1.04], *P*=0.12); Figure 1 and Table 2. After multivariate adjustment, the CR was significantly associated with a reduced incidence of the primary end point (HR, 0.66 [95% CI, 0.51–0.85], *P*=0.002; Figure 1 and Table 2). The results were also consistent in the PS matching population (HR, 0.60 [95% CI, 0.45–0.80], Figure 2 and Table 2) and in the IPTW analysis (IPTW HR, 0.43 [95% CI, 0.23–0.80]; Table 2), also in a sensitivity analysis including medications at discharge in the 2 models (Table S2).

Secondary End Points

During follow-up, a first HF hospitalization occurred in 88 (6.3%) patients in the CR group and 415 (11.7%) in the ICR group (*P*<0.001), cardiovascular death in 51 (3.7%) patients in the CR group, and 236 (6.7%) in the ICR (*P*<0.001) and all-cause death in 130 (9.4%) patients in the CR group and 531 (15.0%) in the ICR group (*P*<0.001).

Unadjusted and PS matching adjusted Kaplan–Meier cumulative incidence of first HF hospitalization, cardiovascular death, and all-cause death are reported in Figures 1 through 3 and Figure S4. After multivariate adjustment, CR was associated with a reduced incidence of first hospitalization for HF (adjusted HR, 0.67 [95% CI, 0.49–0.90]), of cardiovascular death (adjusted HR 0.56 [95% CI, 0.38–0.84]) and of all-cause death

Table 2. Univariate and Multivariate Cox HR, PS Matching Adjusted HR and IPTW Adjusted HR of the Primary and Secondary Outcomes in the Whole Population and According to ACS Presentation and LVEF

	Unadjusted Cox HR	*P* value	Adjusted Cox HR	*P* value	PS adjusted HR	*P* value	IPTW adjusted HR	*P* value
All population								
Primary end point	0.86 (0.70–1.04)	0.12	0.66 (0.51–0.85)	0.002	0.60 (0.45–0.80)	<0.001	0.43 (0.23–0.80)	0.008
HF hospitalization	0.80 (0.63–1.02)	0.07	0.69 (0.50–0.93)	0.02	0.64 (0.44–0.91)	0.01	0.39 (0.29–0.55)	<0.001
Cardiovascular death	0.94 (0.69–1.29)	0.71	0.57 (0.38–0.84)	0.005	0.53 (0.35–0.81)	0.003	0.36 (0.20–0.64)	<0.001
All-cause death	1.05 (0.87–1.29)	0.59	0.75 (0.57–0.99)	0.04	0.68 (0.51–0.90)	0.008	0.56 (0.42–0.74)	<0.001
STEMI								
Primary end point	0.81 (0.61–1.07)	0.14	0.59 (0.39–0.89)	0.01	0.66 (0.44–0.99)	0.04	0.63 (0.24–0.80)	0.03
NSTE ACS								
Primary end point	0.91 (0.70–1.19)	0.50	0.71 (0.50–0.99)	0.04	0.54 (0.37–0.80)	0.002	0.35 (0.23–0.55)	<0.001
LVEF >40%								
Primary end point	0.57 (0.44–0.74)	<0.001	0.52 (0.37–0.72)	<0.001	0.45 (0.31–0.63)	<0.001	0.29 (0.20–0.40)	<0.001
LVEF ≤40%								
Primary end point	1.19 (0.82–1.72)	0.37	0.77 (0.46–1.28)	0.31	0.64 (0.37–1.10)	0.11	1.13 (0.57–2.23)	0.73

ACS indicates acute coronary syndrome; HR, hazard ratio; IPTW, inverse probability treatment weighting; LVEF, left ventricular ejection fraction; NSTE, non-ST-elevation; PS, propensity score; and STEMI, ST-elevation myocardial infarction.

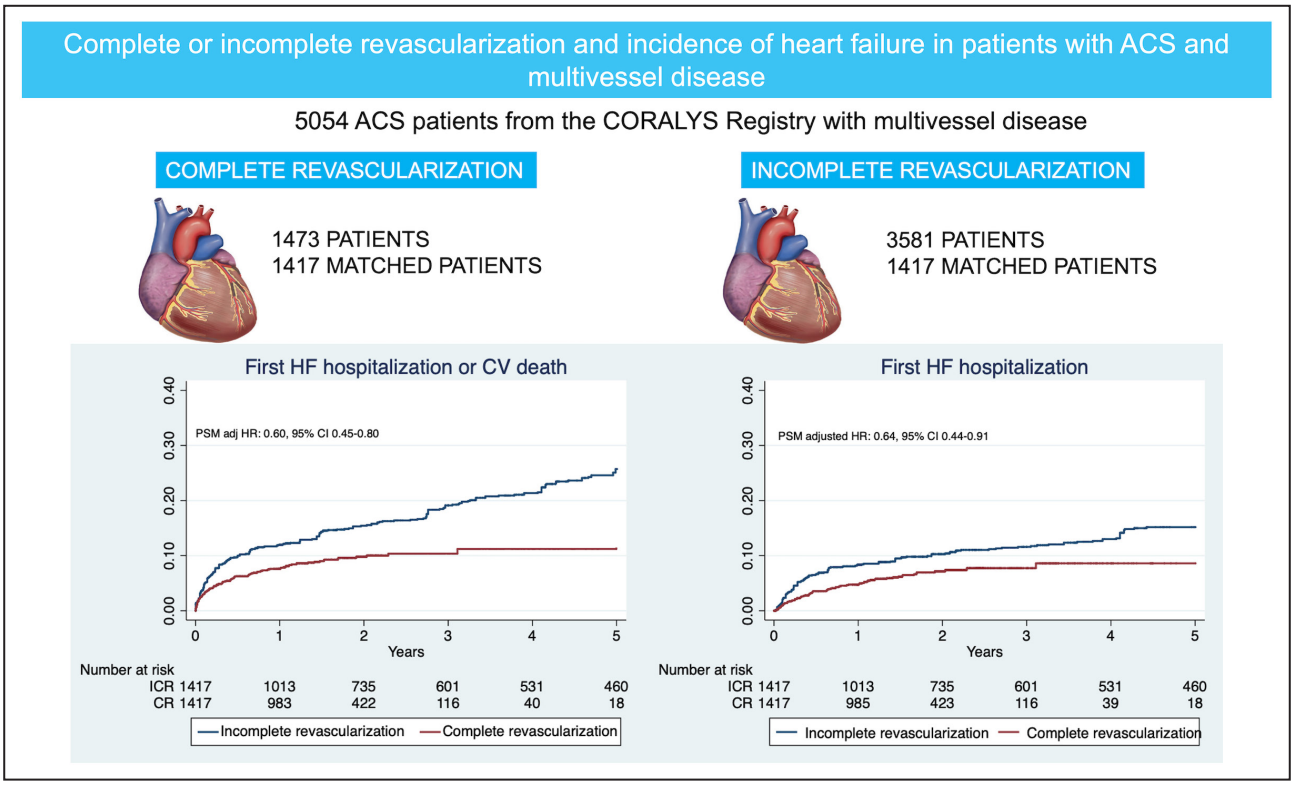

Figure 2. Study summary. Kaplan–Meier incidence of primary end point (left) and first HF hospitalization (right) in the propensity-matched population.
ACS indicates acute coronary syndrome; CORALYS, Incidence and Predictors of Heart Failure After Acute Coronary Syndrome; CR, complete revascularization; CV, cardiovascular; HF, heart failure; HR, hazard ratio; ICR, incomplete revascularization; and PSM, propensity-score matched.

(adjusted HR 0.74 [95% CI, 0.56–0.97]). The results were consistent also in the PS matching population (HR 0.64 [95% CI, 0.44–0.91] for first HF hospitalization, HR 0.53 [95% CI, 0.35–0.81] for cardiovascular death, and HR 0.68 [95% CI, 0.51–0.90] for all-cause death; Figures 2 and 3, Table 2) and in IPTW analysis (IPTW HR, 0.39 [95% CI, 0.29–0.55] for first HF hospitalization, HR, 0.36 [95% CI, 0.20–0.64] for cardiovascular

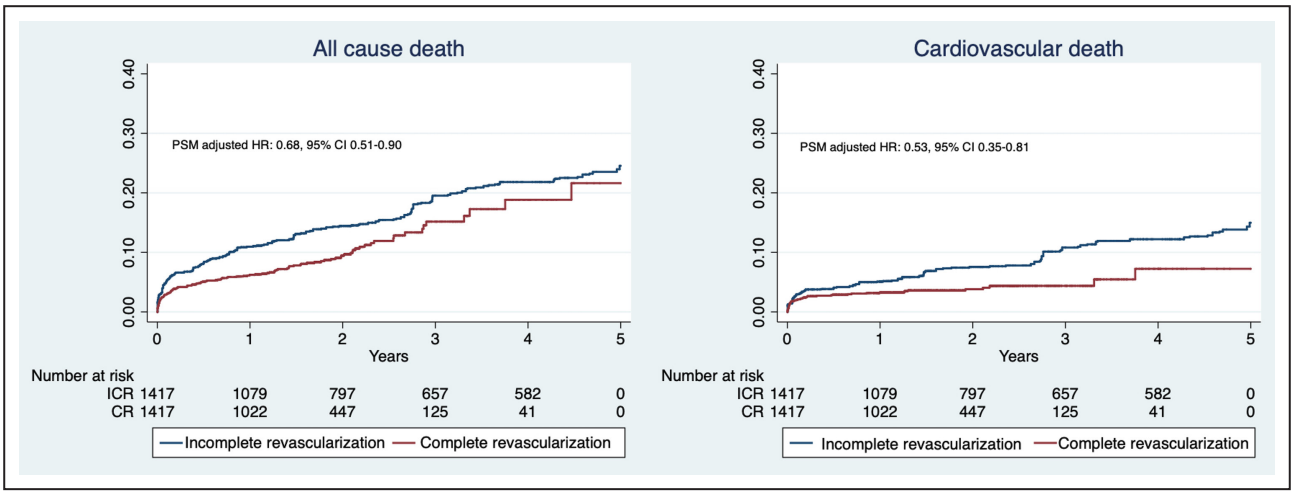

Figure 3. Kaplan–Meier incidence of all-cause death (left) and cardiovascular death (right) in the propensity-matched population.
CR indicates complete revascularization; HR, hazard ratio; ICR, incomplete revascularization; and PSM, propensity-score matched.

death, and HR, 0.56 [95% CI, 0.42–0.74] for all-cause death; Table 2) and also in the model accounting for death as competing risk (Figure S5).

Outcomes According to ACS Presentation and LVEF at Discharge

Incidence of the primary end point according to ACS presentation is reported in Figure 4. After multivariate adjustment, CR was associated with a reduced incidence of the primary end point both in STEMI (HR, 0.59 [95% CI, 0.39–0.89]) and NSTE-ACS (HR, 0.71 [95% CI, 0.50–0.99]). The results were consistent also in the PS matching population (HR, 0.66 [95% CI, 0.44–0.99} for STEMI and HR, 0.54 [95% CI, 0.37–0.80] for NSTE-ACS; Figure 4**)** and (Table 2) and in the IPTW analysis (IPTW HR, 0.63 [95% CI, 0.24–0.80] for STEMI and IPTW HR, 0.35 [95% CI, 0.23–0.55] for NSTE-ACS; Table 2).

Incidence of the primary end point according to LVEF at discharge is reported in Figure 5. After multivariate adjustment, CR was associated with a reduced incidence of the primary end point in patients with LVEF >40% (HR, 0.52 [95% CI, 0.37–0.72]), while no significant benefit was observed in patients with LVEF ≤40% (HR, 0.77 [95% CI, 0.37–1.10], *P* for interaction 0.04). The results were consistent also in the PS matching population (HR, 0.45 [95% CI, 0.31–0.63] for LVEF >40% and HR, 0.64 [95% CI, 0.37–1.10] for LVEF ≤40%; Figure 5 and Table 2) and in IPTW analysis (IPTW HR, 0.29 [95% CI, 0.20–0.40] for LVEF >40% and IPTW HR, 1.13 [95% CI, 0.57–2.23] for LVEF ≤40%; Table 2).

Subgroup Analysis

Subgroup analysis regarding the impact of CR on primary end point is reported in Figure 6. No evidence of interaction between CR and other baseline characteristics both clinical and procedural was identified after adjusting for multiple comparisons (Bonferroni test) except for the presence of CKD at baseline (*P* for

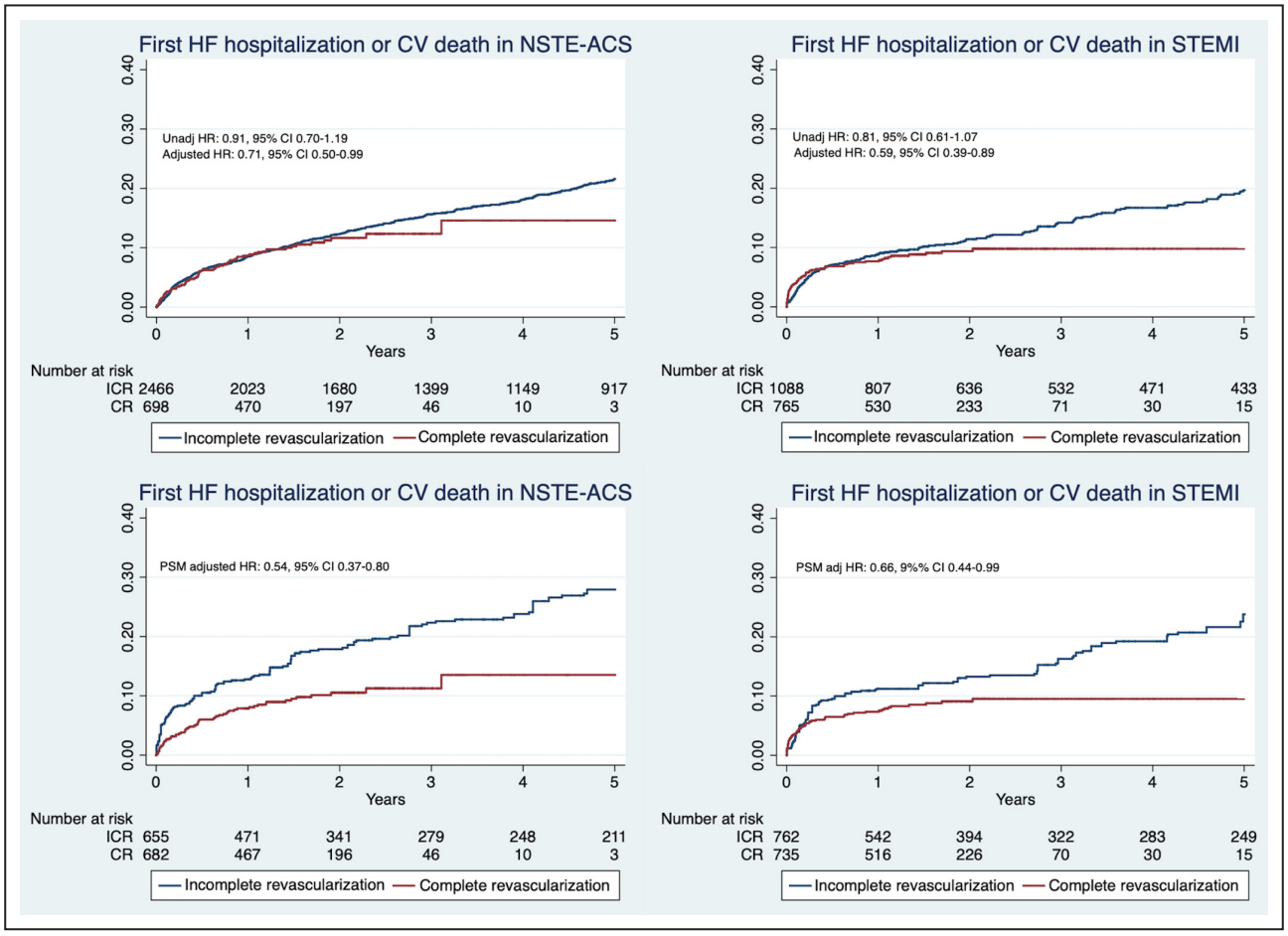

Figure 4. Kaplan–Meier incidence of primary end point and first HF hospitalization according to ACS presentation in the whole population (upper part) and in the propensity-matched population (lower part).
ACS indicates acute coronary syndrome; CR, complete revascularization; CV, cardiovascular; HF, heart failure; HR, hazard ratio; ICR, incomplete revascularization; NSTE, non-ST-elevation; PSM, propensity-score matched; and STEMI, ST-elevation myocardial infarction.

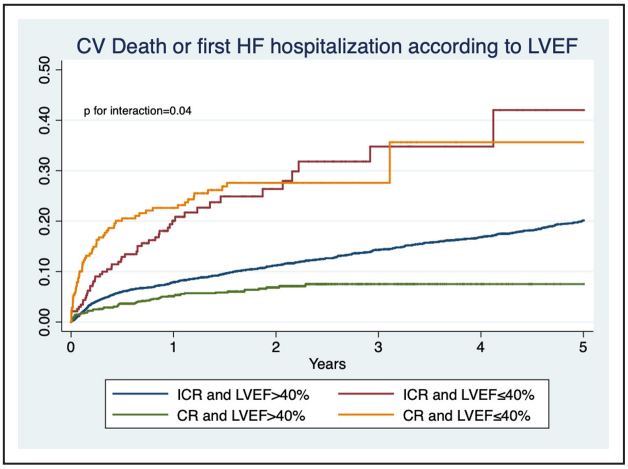

Figure 5. Unadjusted Kaplan–Meier incidence of primary end point according to LVEF.
CR indicates complete revascularization; CV, cardiovascular; HF, heart failure; ICR, incomplete revascularization; and LVEF, left ventricular ejection fraction.

interaction <0.001), LVEF ≤40% (*P* for interaction 0.04), sex (*P* for interaction 0.03), and PCI access (*P* for interaction 0.02). Incidence of the primary end point according to age and sex is reported in Figure S6.

DISCUSSION

In this work, encompassing 5054 patients with multivessel disease included in the CORALYS registry, we sought to estimate the impact of CR on the incidence of cardiovascular death and HF hospitalization among patients admitted for ACS without evidence of prior HF.

The main findings of our work can be summarized as follows: (1) After multivariate adjustment, CR was associated with a reduced incidence of the primary end point of first HF hospitalization or cardiovascular death and of all the secondary end points of first HF hospitalization, cardiovascular death, and all-cause death; (2) the benefit of CR was consistent in STEMI and NSTE-ACS and in patients with LVEF >40%, while no significant benefit was observed in patients with LVEF ≤40%.

In recent years, there has been growing evidence supporting CR in patients with ACS and multivessel disease. In the STEMI subset, CR of nonculprit lesions has been clearly associated with a reduced rate of death, MI, and ischemia-driven revascularization in patients with multivessel disease.[4,5]

For the NST-ACS subset, the evidence that a CR is associated with improved outcomes is more uncertain.[9,19] While data from dedicated randomized controlled trials are scant, 2 large observational multicenter studies showed that single-stage CR appears to be superior to culprit-only vessel PCI in terms of long-term mortality rates, supporting the evidence of a CR also in the NSTE-ACS population, which has a IIA C recommendation in the latest 2020 NSTE-ACS ESC guidelines.[6,7,9–11,14,20] Our results in the NSTE-ACS group confirm these data, and support the evidence that a CR, when feasible, should be achieved in all patients with ACS and multivessel disease, both in the STEMI and NSTE-ACS subset, to reduce the incidence of death, both overall and from cardiovascular causes.

However, the finding that a CR could entail a reduced risk of a first hospitalization for HF among patients without previously impaired myocardial contractility is somewhat new and no previous studies specifically investigated this topic so far.[12] Secemsky et al recently reported a reduction of HF hospitalization in patients younger than 65 years with STEMI undergoing CR from the National Cardiovascular Data Registry and CathPCI Registry, although such benefit was slightly not significant after multivariate adjustment, preventing definite conclusions to be drawn.[21]

In our analysis instead, we found that CR was significantly related with a 34% lower incidence of the primary end point of cardiovascular death or first HF hospitalization and a one-third lower incidence of first HF hospitalization during the follow-up, irrespective of ACS presentation (STEMI versus NSTE ACS).

In ACS, a CR is usually performed to prevent subsequent atherothrombotic events related to plaque progression of a nonculprit lesion. It can be speculated that such benefit is mediated by the prevention of recurrent acute MI, which is associated with further myocyte necrosis and myocardial remodeling.[4,5] However, this is likely not to be the only mechanism subtending the negative impact of nonculprit lesions in the ACS setting. Nonculprit lesions indeed may jeopardize a large amount of myocardium, which can be exposed to chronical ischemia and therefore enter a state of hibernation. This may also entail a negative remodeling of the involved nonculprit segment, therefore leading to LVEF impairment and progressive development of HF.[12,22] In this context CR, combined with optimal medical therapy, could prevent this process, significantly reducing the risk of future hospitalizations for HF. Thus, future multicenter studies and randomized controlled trials are needed to investigate and confirm these hypotheses.

Interestingly, at baseline, patients undergoing CR and ICR were substantially different. Patients treated with CR indeed had fewer comorbidities but a more severe clinical presentation during the ACS, including a higher prevalence of STEMI, cardiogenic shock, higher Global Registry of Acute Coronary Events (GRACE) score and KILLIP class and a lower LVEF. This could explain the absence of a significant difference in adverse outcome at follow-up between the 2 groups in the unadjusted analysis.

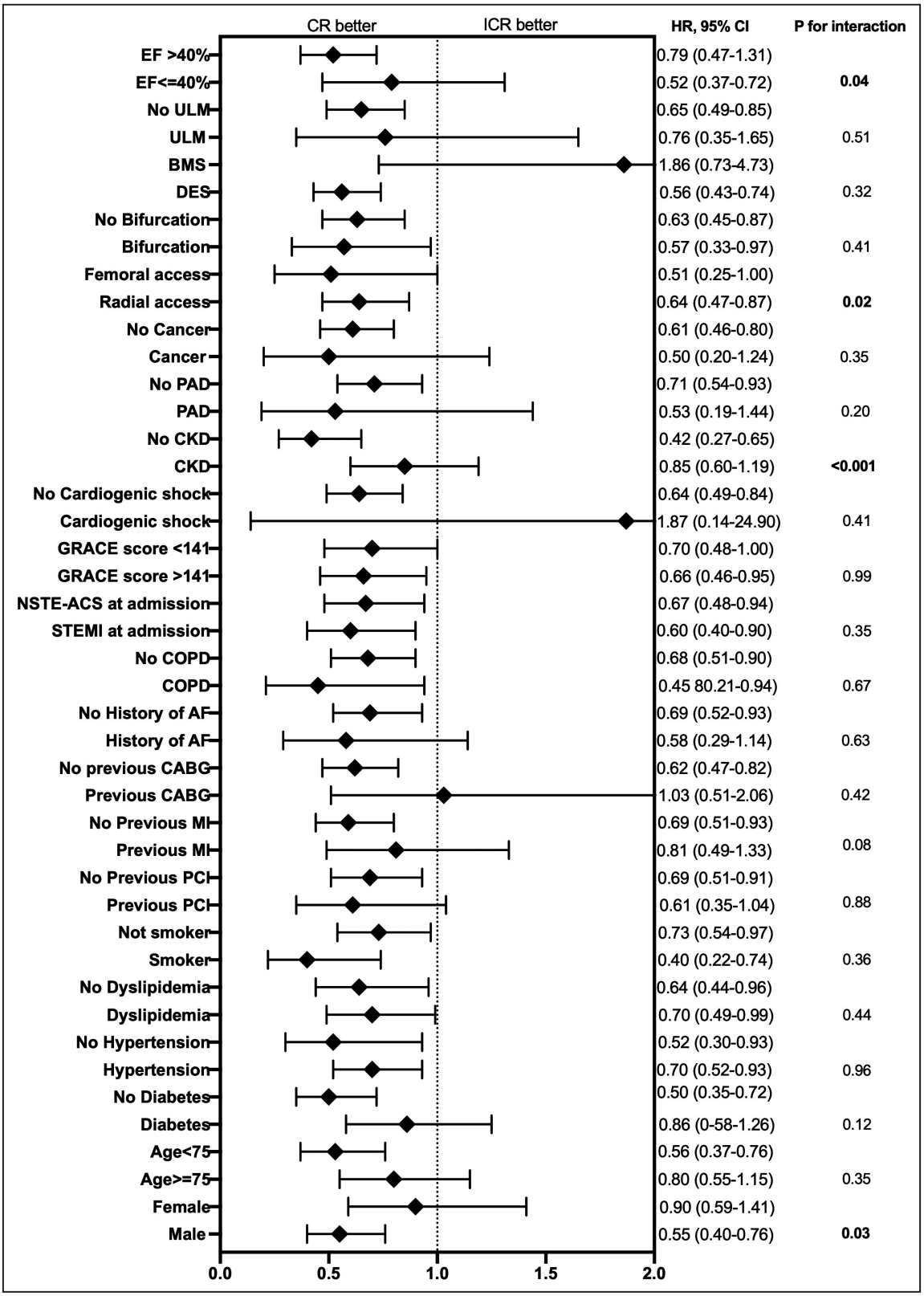

Figure 6. Subgroup analysis on the impact of CR on primary end point.
ACS indicates acute coronary syndrome; AF, atrial fibrillation; BMS, bare metal stent; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CR, complete revascularization; DES, drug-eluting stent; EF, ejection fraction; GRACE, Global Registry of Acute Coronary Events; HR, hazard ratio; ICR, incomplete revascularization; MI, myocardial infarction; NSTE, non-ST-elevation; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; and ULM, unprotected left main.

However, after multivariate adjustment and in the PS matched analysis, CR was strongly associated with reduced adverse outcome. Indeed, this was in line with a patient-oriented approach, suggesting that in a real-world setting, CR is achieved most often in patients with fewer comorbidities and more severe acute presentation. Current ongoing trials are assessing the impact of CR in older patients with more comorbidities.[23] On the other hand, CR, especially when performed during the index procedure, can lead to undesired procedural complications and to a larger administration of contrast medium, impairing outcomes especially in more frail patients. In our study, the presence of CKD at baseline was found to have a significant interaction with the primary end point, supporting the fact that this subset of patients might not benefit from a more extensive treatment. Further evidence is needed to investigate the impact of CKD on PCI strategies in patients with ACS and multivessel coronary artery disease.

Finally, in our analysis, the benefit of CR was consistent in patients with LVEF >40%, while a similar benefit was not observed in the subgroup with LVEF ≤40% (*P* for interaction 0.04). Data about the impact of CR in patients with ACS and reduced LVEF are scant, especially in the context of NSTE-ACS.[24] The CULPRIT shock trial showed that an immediate multivessel PCI in patients with ACS and acute cardiogenic shock is associated with higher rates of death and renal failure as compared with culprit-only PCI, but real-world data are in contrast.[25–27] However, in our analysis, only a small proportion of patients had cardiogenic shock at presentation.

Our results, although being hypothesis generating due to the relatively low number of patients enrolled with LVEF ≤40%, are in line with a recent published analysis of the Grand-drug-eluting stent (DES) registry, including 1314 patients with STEMI with multivessel disease, in which a benefit of CR in terms of reduced major adverse cardiovascular event and cardiovascular death was not observed for patients with LVEF ≤40%.[28]

Although the subgroup analysis of some of the major STEMI trials did not show a possible interaction between CR and LVEF, patients with low LVEF were poorly represented in these trials. Furthermore, no clear evidence for NSTE-ACS is available.[4,5] The nonsignificant benefit observed in lower LVEF could have a physiological basis. Patients with reduced LVEF after a MI usually have large akinetic necrotic cardiac territories caused by the index event. In this subset, the potential benefit of CR is widely limited, and the negative remodeling cannot be prevented by revascularization of cardiac vessels related to other myocardial territories. Dedicated randomized controlled trials are warranted to investigate the benefit of CR with PCI in patients with reduced LVEF and ACS.

LIMITATIONS

Our study has several limitations. First, despite the large sample size, this was not a randomized controlled study and although we used multivariate analysis and PS matching, baseline characteristics of the 2 populations were different and a potential bias due to the effect of unmeasured and unknown variables cannot be excluded. Participating centers were all located in Europe; therefore, our results may not be generalizable to non-European countries. In the whole cohort, the percentage of multivessel disease was lower than reported in the literature (34%) and the presence of multivessel disease was not assessed by a central core-laboratory, suggesting the possibility of an underreporting. Furthermore, despite a high proportion of patients discharged on optimal medical therapy, the use of HF medication at discharge was not standardized. Moreover, our study does not address the issue of whether complete revascularization needs to be performed during the index procedure or as a staged procedure and, therefore, timing of complete revascularization remains an important limitation of this article, although data in the literature are contrasting and future evidence is needed to address this topic.[29,30] Finally, no data about a physiology-driven approach to nonculprit lesions in the included patients were recorded.

CONCLUSIONS

In patients with ACS (both STEMI and NSTE-ACS) and multivessel disease, CR reduced the risk of the primary end point of first hospitalization for HF and cardiovascular death, as well as first HF hospitalization, and cardiovascular and overall death. When feasible, CR should be performed in all patients with ACS to reduce the incidence of HF and death at follow-up. Future studies are needed to assess the evidence of CR in low LVEF and CKD.

ARTICLE INFORMATION

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Affiliations

Division of Cardiology, "Città della Salute e della Scienza di Torino" Hospital, Department of Medical Sciences, University of Turin, Italy (F.B., G.M., O.D.F., G. Giannino, A. Borin, D.M., E.E., G. Gallone, G.M.D.F., F.D.); Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland (W. Wanha, P.D., M.G., W. Wojakowski); Fondazione IRCCS Policlinico San Matteo, Coronary Care Unit, Pavia, Italy (S.L., C.M.); Hospital Universitario Álvaro Cunqueiro, Vigo, Spain (S.R.R., M.M., E.A.-A.); Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano Isontina, University of Trieste, Italy (E.F., G. Sinagra); Dipartimento di Scienze Cliniche Internistiche, Anestesiologiche e Cardiovascolari, Sapienza Università di Roma, Roma, Italy (M. Mancone, G. Sardella); IRCCS S. Maria Nascente-Fondazione Don Carlo Gnocchi ONLUS, Milan, Italy (N.M.); 1st Department of Cardiology, Medical University of Warsaw, Warszawa, Poland (Z.H., M.M.); Cardiology Department, Parma University Hospital, Parma, Italy (N.G., D.T.); U.O. di Cardiologia Clinica ed Interventistica, Istituto Clinico Sant'Ambrogio, Milan, Italy (A.I.); Cardiovascular Research Team, San Carlo Clinic, Milan,

Italy (B.C.); Fondazione Ricerca e Innovazione Cardiovascolare, Milan, Italy (B.C.); Cardiovascular Institute, Hospital Clinico San Carlos, Madrid, Spain (I.J.N., M.F.); Division of Cardiology, San Luigi Gonzaga University Hospital, Orbassano, Turin, Italy (M.B.); Division of Cardiology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy (L.B.); University of Milan, Milan, Italy (L.B.); Cardiovascular Institute, Azienda Ospedaliero Universitaria di Ferrara, Cona, Italy (F.M., G.C.); Division of Cardiology, Ospedale Cardinal G. Massaia, Asti, Italy (A.T., M.S.); Department of Cardiology, Sant'Andrea Hospital, Vercelli, Italy (F.U.); Interventional Cardiology Unit, Cardiovascular Department, Fondazione Poliambulanza Istituto Ospedaliero, Brescia, Italy (A. Buono); and Department of Medical Sciences, University of Turin, Italy (M.P.).

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Disclosures

None.

Supplemental Material

Appendix S1.
Data S1
Tables S1–S2
Figures S1–S6

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Supplemental Material

Appendix S1. Complete list of Contributors:

-Federico Conrotto MD, Pierluigi Omedè MD, Matteo Michelone, Pierluigi La Croce; Division of Cardiology, Department of Internal Medicine, Città della Salute e della Scienza, Turin

-Laura Montagna MD, Division of Cardiology, San Luigi Gonzaga University Hospital, Orbassano, Turin, Italy.

-Stefano Carugo Prof. Division of Cardiology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; University of Milan, Milan, Italy

-Emanuele D'Aniello Cardiovascular Institute, Azienda Ospedaliero-Universitaria di Ferrara, Cona

-Karim Jamhour Hospital Universitario Álvaro Cunqueiro, Vigo, Spain

-Giulia Gagno Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano Isontina, University of Trieste, Trieste, Italy.

-Paolo Severino Dipartimento di Scienze Cliniche Internistiche, Anestesiologiche e Cardiovascolari, Sapienza Università di Roma, Roma

-Giulia Magnani, Andrea Denegri Cardiology Department, Parma University Hospital, Parma, Italy

-Gaetano di Palma, Cardiovascular Research Team, San Carlo Clinic, Milano, Italy; Fondazione Ricerca e Innovazione Cardiovascolare, Milano, Italy.

Data S1.

Supplemental Methods

Missing data rate. From the original dataset, Rows with endpoints missing (either one or both) have been dropped (191 patients), reducing the number of samples to 14322. The vast majority of missing values are found in a small features subset of features, so we established a 20% cutoff: all features exceeding this percentage of missing values are excluded from the analysis. This decision eliminated 24 features, leading to a 34-variables dataset. The rows have a mean of 0.9982% of missing values, with a peak of 15.625%. These missing values percentages are treatable by the imputation process, and thus no rows were dropped.

Imputation. At this point, the dataset presents rows missing some values, making up 0.94% of the total observations. The imputation method chosen for this setting is the Fully Conditional Specification, where a separate mode iteratively imputes each incomplete variable: this is a multivariate imputation method allowing for imputing numerical and categorical features since an ad-hoc model imputes each variable. The precise algorithm chosen is MICE. The Bayesian Linear Regression method has been chosen for imputing numerical features, Logistic Regression for binary features, Polytomous Logistic Regression for unordered categorical variables, and the Proportional Odds Model for ordered categorical ones. Lastly, rows that have become identical during the imputation are removed to reduce redundant information: this led to removing three rows and a final dataset made up of 14219 rows.

Table S1: Baseline characteristics differences in the propensity matched population

	Incomplete revascularization (n=1417)	Complete revascularization (n=1417)	P value
Age (years)	67.4	67.3	0.82
Female sex	0.23	0.21	0.24
Hypertension	0.67	0.63	0.11
Diabetes	0.26	0.26	0.64
Dyslipidemia	0.49	0.49	0.88
PAD	0.08	0.08	0.89
Current Smoking	0.31	0.33	0.30
eGRF <60ml/min	0.28	0.29	0.77
Previous MI	0.20	0.21	0.43
Previous CABG	0.06	0.05	0.46
Previous PCI	0.20	0.21	0.43
Atrial fibrillation	0.10	0.09	0.65
Prior Stroke	0.03	0.04	0.31
Prior Major Bleeding (BARC3-5)	0.009	0.015	0.13
Cancer	0.13	0.13	0.91
COPD	0.08	0.08	0.68
STEMI at admission	0.52	0.54	0.31
Cardiogenic shock at admission	0.03	0.04	0.54
Killip class >2	0.16	0.16	0.61
GRACE score >140	0.25	0.25	0.93
ULM disease	0.14	0.13	0.87
Bifurcation involvement	0.26	0.22	0.11
LVEF<50% at discharge	0.44	0.44	0.91
ACE-I/ARB at discharge	0.80	0.79	0.52
Beta-blockers at discharge	0.87	0.82	0.10
Statin at discharge	0.96	0.95	0.15

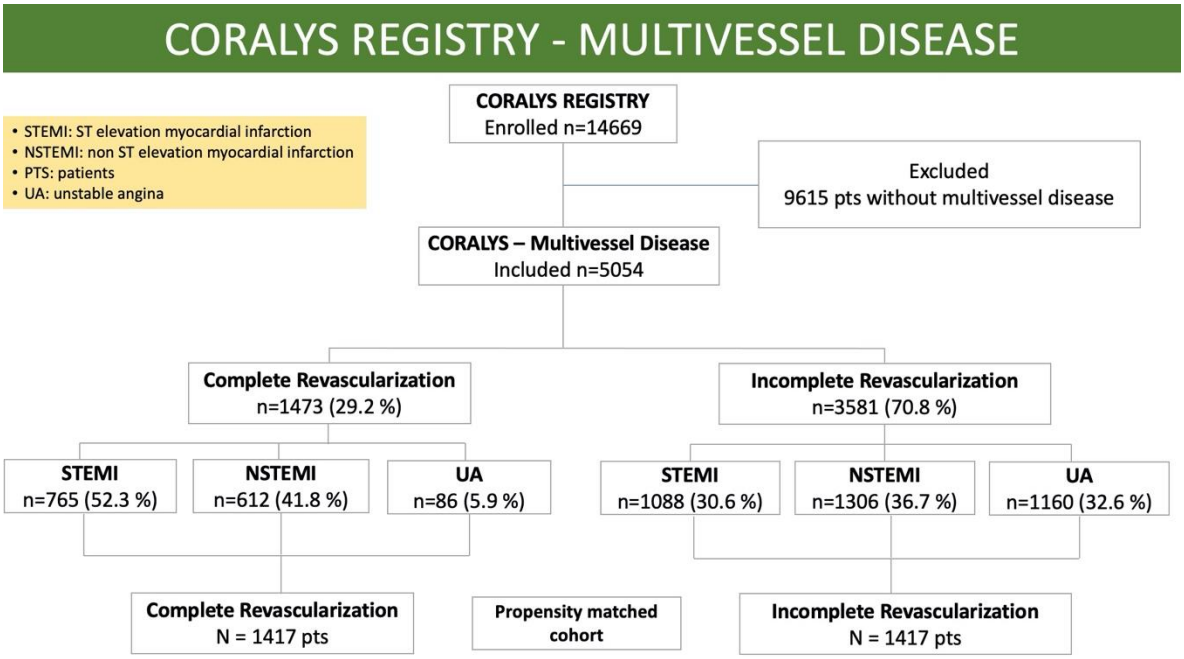
ACE-I=angiotensin converting enzyme inhibitors, ACS=acute coronary syndrome, AF=atrial fibrillation, ARB=angiotensin receptor blocker, CABG=coronary artery bypass graft, COPD=chronic obstructive pulmonary disease, eGFR=estimated glomerular filtration rate, LVEF=left ventricular ejection fraction, MI=myocardial infarction, PAD=peripheral artery disease, PCI=percutaneous coronary intervention, STEMI=ST-elevation myocardial infarction, ULM=unprotected left main

Table S2: PS matching adjusted HR and IPTW adjusted HR of the primary and secondary outcomes including medication at discharge in the models.

All Population				
	PS Adjusted HR	**P value**	**IPTW adjusted HR**	**P value**
Primary endpoint	0.52 (0.39-0.70)	<0.001	0.43 (0.23-0.80)	0.008
HF hospitalization	0.53 (0.37-0.76)	0.01	0.39 (0.29-0.55)	<0.001
CV death	0.48 (0.31-0.76)	0.003	0.36 (0.20-0.64)	<0.001
All-cause death	0.68 (0.49-0.94)	0.02	0.56 (0.42-0.74)	<0.001

ACS= acute coronary syndrome, CV=cardiovascular, CR=complete revascularization, HF=heart failure, HR=hazard ratio, ICR= incomplete revascularization, IPTW=inverse probability treatment weighting, LVEF=left ventricular ejection fraction, NSTE=Non-ST-elevation, PS= propensity score, STEMI=ST-elevation myocardial infarction

Figure S1: The CORALYS Registry and the study cohort



NSTE=Non-ST-elevation, PTS= patients, STEMI=ST-elevation myocardial infarction, UA=unstable angina

Figure S2: Participating centers in the CORALYS registry

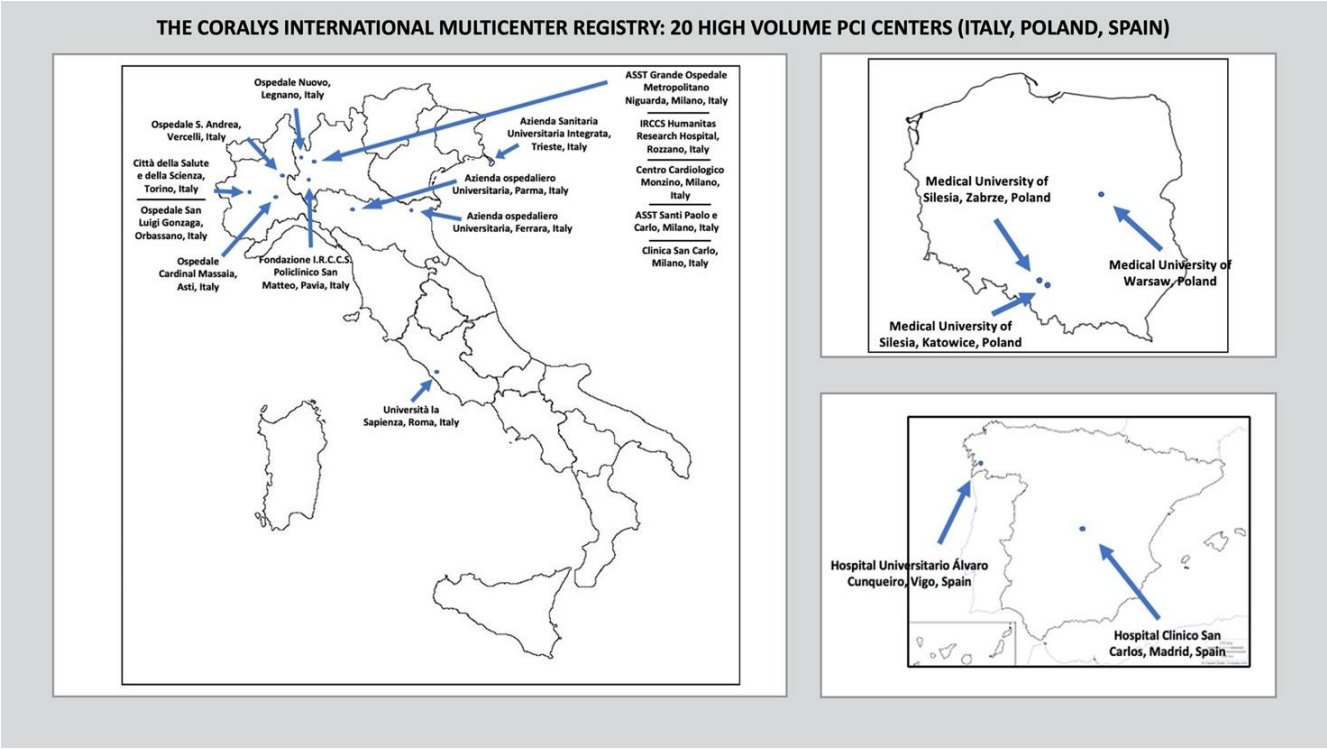


Figure S3: Distribution of Propensity Scores. Propensity score distribution for patients with incomplete and complete revascularization demonstrating good overlap between groups.

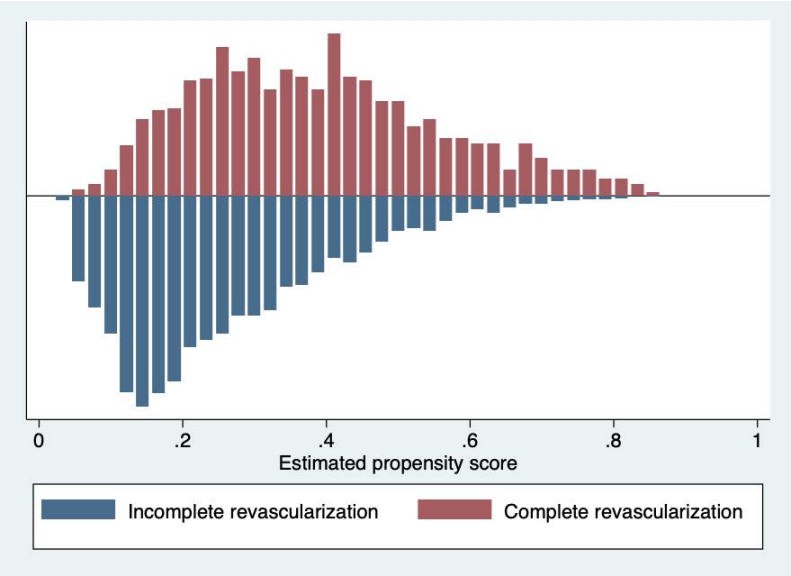
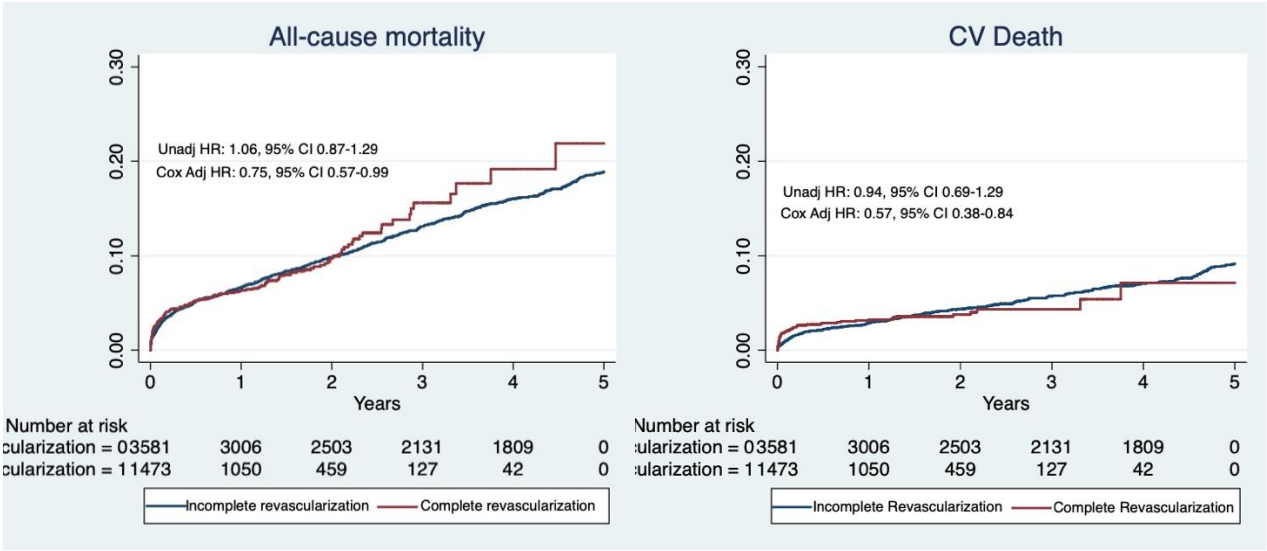
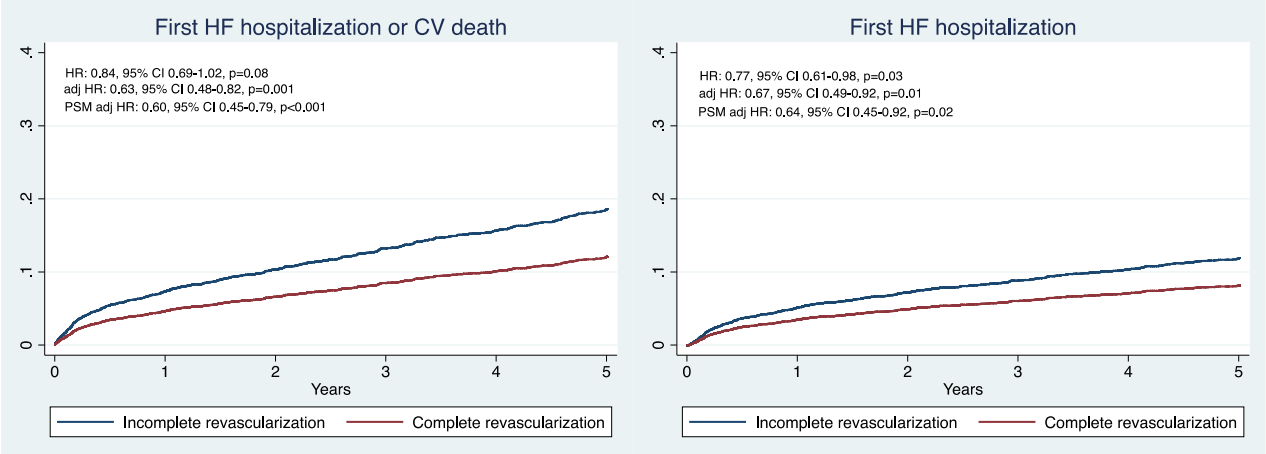


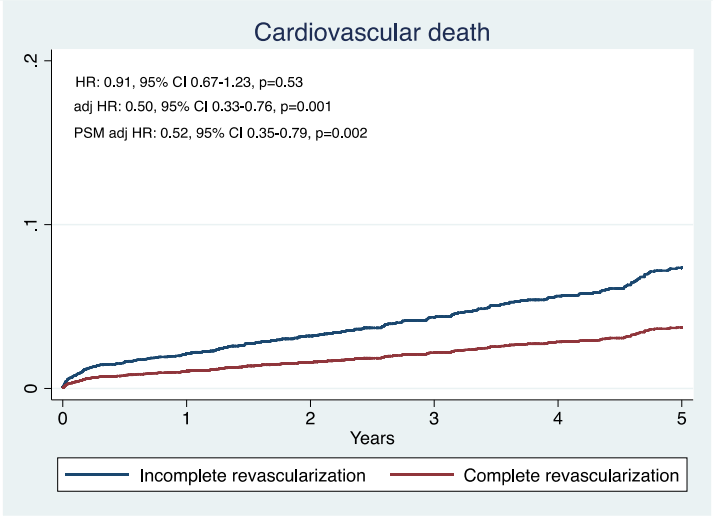
Figure S4: Unadjusted Kaplan Meier incidence of all-cause death (left) and cardiovascular death (right)



CI=confidence interval, HR=hazard ratio

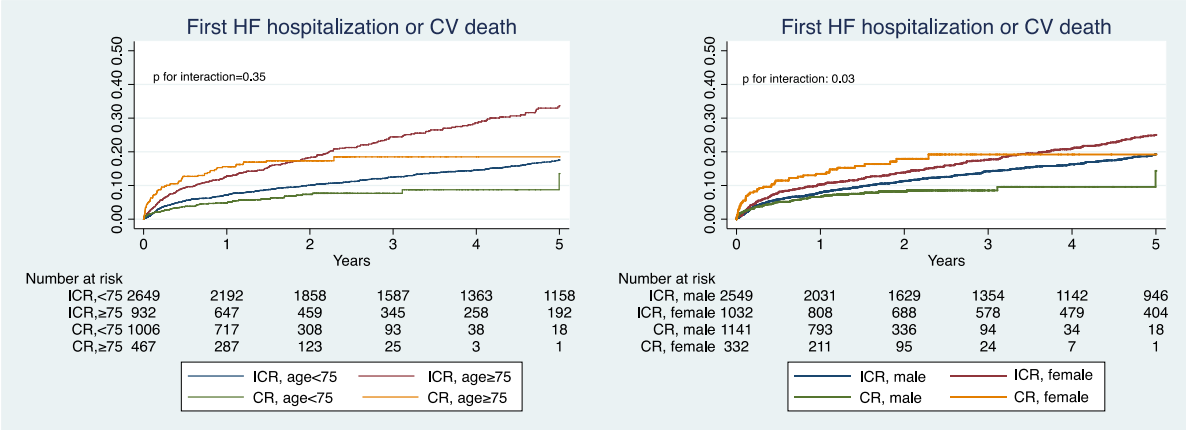
Figure S5: Cumulative incidence of the primary endpoint, first HF hospitalization and CV death in the competing risk model. Univariate, multivariate and propensity-score matching HR in the competing-risk model, showing consistent results with the main analysis.





CI=confidence interval, CV=cardiovascular, HF=heart failure, HR=hazrad ratio, PSM=propensity matched

Figure S6: Unadjusted Kaplan Meier incidence of the primary endpoint according to age (left) and sex (right).



CV=cardiovascular, CR=complete revascularization, HF=heart failure, ICR= incomplete revascularization