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IncidenCe and predictOrs of heaRt fAiLure after acute coronarY Syndrome: The CORALYS registry

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ABSTRACT

Background: Previous studies investigating predictors of Heart Failure (HF) after acute coronary syndrome (ACS) were mostly conducted during fibrinolytic era or restricted to baseline characteristics and diagnoses prior to admission. We assessed the incidence and predictors of HF hospitalizations among patients treated with percutaneous coronary intervention (PCI) for ACS.

Methods and results: CORALYS is a multicenter, retrospective, observational registry including consecutive patients treated with PCI for ACS. Patients with known history of HF or reduced left ventricular ejection fraction (LVEF) were excluded. Incidence of HF hospitalizations was the primary endpoint. The composite of HF hospitalization or cardiovascular death, and cardiovascular and all-cause death were the secondary endpoints. Predictors of HF hospitalizations and the impact of HF hospitalization on cardiovascular and all-cause death were assessed by means of multivariable Cox proportional hazards model.14699 patients were included. After 2.9 ±

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1.8 years, the incidence of HF hospitalizations was 12.7%. Multivariable analysis identified age, diabetes, chronic kidney disease, previous myocardial infarction, atrial fibrillation, pulmonary disease, GRACE risk-score ≥ 141, peripheral artery disease, cardiogenic shock at admission and LVEF ≤40% as independently associated with HF hospitalizations. Complete revascularization was associated with a lower risk of HF (HR 0.46,95%CI 0.39–0.55). HF hospitalization was associated with higher risk of CV and all-cause death (HR 1.89,95%CI 1.5–2.39 and HR 1.85,95%CI 1.6–2.14, respectively).

Conclusions: Incidence of HF hospitalizations among patients treated with PCI for ACS is not negligible and is associated with detrimental impact on patients' prognosis. Several variables may help to assess the risk of HF after ACS.

1. Introduction

Prompt reperfusion strategies as primary Percutaneous Coronary Intervention (pPCI) along with improvements in PCI devices and medical therapies for Coronary Artery Disease (CAD) significantly improved the prognosis of patients suffering Acute Coronary Syndromes (ACS) (1–4). However, the increased survival rate after ACS may be associated with higher incidence of late myocardial infarction (MI) complications such as the development of Heart Failure (HF) (5) which is expected to rise due to ageing population (6). Several studies investigated the incidence of HF after ACS, but they were most performed during the fibrinolytic era or focused on specific pattern of ACS such as ST-segment myocardial infarction (STEMI) or on in-hospital outcomes. Among patients enrolled in the GRACE registry, 12% were admitted for HF over 3.8 years of follow-up: however, PCI was performed only in less than half of patients (7). A sub-analysis of the HORIZONS-AMI trial showed an incidence of HF complicating ACS of 5.1% at two years among selected STEMI patients and identified several cardiovascular risk factors (i.e. diabetes and dyslipidemia) along with female sex and reduced left ventricular ejection fraction (LVEF) as predictors of HF onset (8). An accurate detection of predictors of HF development among real life ACS survivors is required to identify high-risk patients that could benefit from the implementation of intensive preventive measures and stricter follow-up strategies.

In this context, the introduction of novel therapeutic options for patients suffering from HF (9,10) and the spread of remote monitoring reinforce the need for an updated identification of predictors of HF and associated prognosis after ACS. For this purpose, we designed the "IncidenCe and predictOrs of heaRt fAiLure after acute coronarY Syndrome (CORALYS) study" to assess the incidence of HF and the clinical features associated with the development of this adverse event across a contemporary cohort of patients suffering from ACS and treated with PCI.

2. Methods

2.1. Study design

The CORALYSIS registry (NCT 04895176) is an international, multicenter, retrospective, observational study including consecutive patients admitted for ACS in 16 European Centers from 2015 to 2020. Where required, study investigators received approval from their local institutional boards or ethic committees. Patients were considered eligible for inclusion in the registry if all the following criteria were met a) age > 18 years-old; b) Confirmed diagnosis of ACS, including STEMI, non-ST segment myocardial infarction (NSTEMI) or unstable angina (UA) at discharge; c) treatment of ACS with PCI.

Patients with a known history of congestive heart failure (CHF), previous HF hospitalizations or reduced left ventricular ejection fraction (LVEF <50%) before the index hospitalization for ACS were excluded.

2.2. Definitions

Demographics, clinical and main angiographic characteristics were retrospectively retrieved and abstracted on pre-specified electronic forms. The presence of cardiovascular risk factors, atrial fibrillation, chronic obstructive pulmonary disease (COPD), malignancies, peripheral artery disease (PAD) and the history of previous MI or myocardial revascularizations and stroke was retrieved from medical history records. Chronic kidney disease was defined as an estimated glomerular filtration rate < 60 ml/min/1.73 m2 according to Modification of Diet in Renal Disease (MDRD) equation. The diagnoses of STEMI, NSTEMI and cardiogenic shock at admission were defined according to the current European Society of Cardiology guidelines definitions (11,12) and they were retrospectively assessed and retrieved from patients' medical history records and hospital discharge letters. Major bleedings were defined as Bleeding Academic research Consortium 3,5 bleedings (13).

Multivessel disease was defined as more than one coronary vessel with critical stenosis (≥ 70% diameter stenosis at angiographic evaluation or FFR ≤ 0.8/iFR ≤ 0.89 at invasive physiological assessment in non-culprit vessels). Complete revascularization was defined as no residual critical stenosis in any coronary vessel after PCI. Left ventricular ejection fraction (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)] and classified as moderate (between 35 and 45%).

PCI was performed according to the standard local practice in accordance with practice guidelines established by the European Society of Cardiology (ESC) (14). 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 (ACEi/ARB) and mineralocorticoid receptor antagonist (MRA), if indicated. 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.

2.3. Endpoints

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, was the primary endpoint. The composite of first hospitalization for HF or cardiovascular (CV) death, along with all-cause death and CV death alone (15) were the secondary endpoints. Further, clinical and procedural predictors of the primary end point along with the impact of HF hospitalization on all-cause and CV death were assessed.

2.4. Statistical analysis

Continuous and categorical variables are reported as mean and standard deviation or median and interquartile range (IQR) and as frequencies and percentages, respectively.

Differences in clinical and procedural features between patients who experienced an HF admission at FU and those who did not were assessed with One-way Analysis of Variance (ANOVA) and chi-square test for continuous and categorical variables, respectively.

Backward stepwise multivariable Cox proportional hazards model, censored at first HF hospitalization or at latest available follow-up, was used to identify clinical and procedural predictors of HF hospitalizations. The initial model included 21 variables, namely: age, sex, hypertension, diabetes mellitus, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), previous MI, previous coronary revascularization, atrial fibrillation, admission diagnosis (STEMI vs NSTEMI), GRACE score $\geq$ 141, cardiogenic shock at admission, ULM or multivessel disease, complete revascularization, smoking status (non smokers vs current/previous smokers), left ventricular ejection fraction <40%, peripheral artery disease (PAD), malignancies and discharge therapy (B blockers, ACE-inibhitors/angiotensin receptor blockers, statins). A model including variables with missing data above 50% of the sample (namely mineralocorticoid receptor antagonists, impaired post-procedural TIMI flow on culprit vessel and left ventricular end-diastolic diameter) was performed as sensitivity analysis. To account for the potential impact of variables acting as colliders and mediators within the Cox proportional hazard model obtained with the backward stepwise approach, we performed further models by removing significant variables in a one-by-one fashion and according to clinical plausibility to confirm the validity and the proportion of the association between a specific variable and the primary endpoint. The calibration and the discrimination ability of the model was assessed with the Hosmer–Lemeshow statistic and the *p* value was obtained comparing the statistic to a chi-squared distribution with Q-2 degrees of freedom (where Q indicates the number of groups). The performance of the model was also assessed via Receiver Operating Characteristic Area Under the Curve (ROC-AUC) analysis.

The principal model plus HF hospitalization, censored at death occurrence or at latest available follow-up, was used to assess the impact of the endpoint on the occurrence of all-cause and CV death. Only significant variables at a value of $P < 0.05$ were retained in the final models. Kaplan-Meier analysis were also produced to compare the incidence of all-cause death and CV death stratified according to HF hospitalizations. Analyses were performed with SPSS® Statistics v24 and STATA v17 (StataCorp, College Station, Texas).

3. Results

3.1. Incidence of HF and all-cause or cardiovascular death

14,699 patients were retrospectively enrolled in the CORALYS registry. Data about HF hospitalizations and survival status were respectively available for 14,507 (98.7%) and 14,527 (98.8%) patients. Over a mean follow-up of 2.9 ± 1.8 years, the cumulative incidence of hospitalizations for HF was 12.7%. The median time to hospitalization for HF after discharge was 1.05 years (IQR 0.29–2.58). 16.2% of patients either were hospitalized for HF or died from cardiovascular causes, while the incidence of all-cause death and CV death was 14.9% and 5.3%, respectively. Incidence of the primary and the secondary outcomes are graphically resumed in Fig. 1 and Supplementary Fig. 1.

3.2. Baseline features according to HF occurrence

Baseline features according to the incidence of the primary outcome are reported in Table 1. Compared with patients who did not develop HF, the group of patients hospitalized for HF at follow-up were older (69.6 ± 10.3 vs 64.4 ± 11.7) and were more frequently women (37.7% vs 30.6%, $p < 0.0001$). A higher prevalence of cardiovascular risk factors (hypertension 84.9% vs 72.5%, diabetes 44.8% vs 28.8%, all $p < 0.0001$) and comorbidities was observed in this subgroup (peripheral artery disease 4.4% vs 2.5%; COPD 8.7% vs 4.9%; CKD 29% vs 16.5%, atrial fibrillation 10.5% vs 4.9%, all $p < 0.0001$). Patients experiencing an admission for HF at follow-up were more likely to have had a previous MI (38.2% vs 24.6%, $p < 0.0001$) and a percutaneous or surgical revascularization as compared with those not developing HF. An admission diagnosis of STEMI was more common in patients without HF (30.7% vs 21.4%, $p < 0.0001$). A higher GRACE score was observed in the HF group (GRACE score 126.9 ± 29 vs 114.7 ± 25, p < 0.0001). Angiographic features are resumed in Table 2. Extent of coronary artery disease was greater in HF patients as outlined by a higher prevalence of multivessel disease or ULM involvement (41.8% vs 36.9%, $p = 0.001$). However, a complete revascularization was more frequently achieved in patients without HF events at follow-up (29.5% vs 17.5%, $p < 0.0001$). Left ventricular ejection fraction at discharge was significantly lower among patients with HF hospitalizations (48.2 ± 7.3% vs 51.58 ± 7.4%, $p < 0.0001$) who were also more likely to be discharged on beta-blockers (88% vs 85.3%, $p = 0.010$) and MRA (37.6% vs 18.6%, p < 0.0001) as compared with non-HF patients. Suboptimal procedural outcome (TIMI flow grade on culprit vessel) was more frequent among patient who developed HF as compared with patients who did not (post-procedural TIMI flow on culprit vessel <3, 10.6% vs 5.5%, $p = 0.002$).

3.3. Predictors of HF hospitalization

The multivariable analysis identified 11 predictors of HF hospitalization: age, diabetes mellitus, CKD, previous MI, atrial fibrillation, COPD, GRACE risk score $\geq$ 141, PAD, cardiogenic shock at admission and moderately reduced LVEF at discharge, Table 3. Complete revascularization was associated with a reduced risk of the primary endpoint (HR 0.46, 95%CI 0.39–0.55, $p < 0.0001$). Such finding was confirmed in the sensitivity analyses, after excluding all other significant variables in

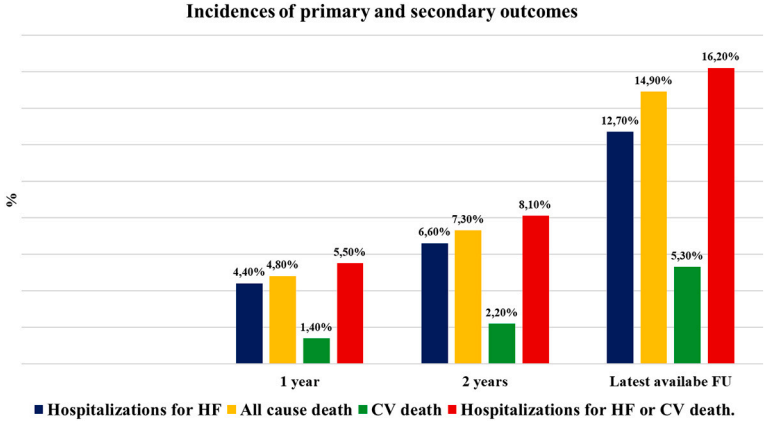

Fig. 1. Incidence of primary and secondary outcomes. HF: heart failure; CV: cardiovascular death.

Table 1
Baseline features according to the occurrence of HF hospitalization at follow-up.

	Overall (n = 14,699)	No Hospitalization for HF (n = 13,282)	Hospitalization for HF (n = 1225)	P value
Age	65.1 ± 11.7	64.4 ± 11.7	69.6 ± 10.3	< **0.0001**
Women	4578 (31.1%)	4060/13282 (30.6%)	462/1225 (37.7%)	< **0.0001**
Hypertension	10,800 (73.5%)	9625/13282 (72.5%)	1040/1225 (84.9%)	< **0.0001**
Dyslipidemia	8654 (58.9%)	7814/13282 (58.8%)	748/1225 (61.1%)	0.129
Smoking status				< **0.0001**
- Non smoker	8950 (60.9%)	8028/13281 (60.4%)	833/1225 (68%)	
- Current smoker	2806 (19.1%)	2602/13281 (19.6%)	148/1225 (12.1%)	
- Previous smoker	2942 (20%)	2651/13281 (20%)	244/1225 (19.9%)	
Peripheral artery disease	416 (2.8%)	334/13275 (2.5%)	54/1220 (4.4%)	< **0.0001**
Diabetes Mellitus	4416 (30%)	3824/13282 (28.8%)	549/1225 (44.8%)	< **0.0001**
- on insulin	1167 (8%)	1012/13258 (7.6%)	141/1225 (11.5%)	< **0.0001**
Previous MI	3781 (25.7%)	3260/13279 (24.6%)	468/1225 (38.2%)	< **0.0001**
Previous PCI	4333 (29.5%)	3802/13276 (28.6%)	480/1225 (39.2%)	< **0.0001**
Previous CABG	1509 (10.3%)	1253/13280 (9.4%)	243/1225 (19.8%)	< **0.0001**
Prior stroke	277 (1.9%)	234/13281 (1.8%)	28/1225 (2.3%)	0.188
Prior Major bleedings	111 (0.8%)	97/13282 (0.7%)	12/1223 (1%)	0.331
Cancer				< **0.0001**
- previous	1908 (13.3%)	1726/12996 (13.3%)	155/1148 (13.5%)	
- on treatment	1932 (13.5%)	1739/12996 (13.4%)	183/1148 (15.9%)	
COPD	781 (5.3%)	656/1382 (4.9%)	107/1225 (8.7%)	< **0.0001**
eGFR	80.6 ± 22.3	81.3 ± 22.0	72.2 ± 23.4	< **0.0001**
CKD (eGFR < 60 ml/min/ 1.73 m2)	2552 (17.7%)	2154/13040 (16.5%)	349/1203 (29%)	< **0.0001**
Systolic blood pressure (on admission)**	139.4 ± 17.9	139.5 ± 17.9	139.6 ± 16.2	0.83
Atrial Fibrillation		653/13234 (4.9%)	128/1218 (10.5%)	< **0.0001**
- paroxysmal	610 (4.2%)	509/13234 (3.8%)	91/1218 (7.5%)	
- persistent	49 (0.3%)	38/13234 (0.3%)	10/1218 (0.8%)	
- permanent	140 (1%)	106/13234 (0.8%)	27/1218 (2.2%)	
Admission diagnosis				< **0.0001**
- STEMI	4332 (30.1%)	3983/12984 (30.7%)	262/1223 (21.4%)	
- NSTEMI	4825 (33.5%)	4291/12984 (33%)	440/1223 (36%)	
- UA	5241 (36.4%)	4710/12984 (36.3%)	521/1223 (42.6%)	
GRACE score	115.8 ± 26.2	114.7 ± 25.4	126.1 ± 29.9	< **0.0001**
- GRACE score ≥ 141	2043 (13.9%)	1682/13282 (12.7%)	302/1225 (24.7%)	< **0.0001**
Cardiogenic Shock at admission	186/ 14697 (1.3%)	166/13280 (1.3%)	17/1225 (1.4%)	0.679
LVEF at discharge	50.6 ± 9.3	51.58 ± 7.38	48.21 ± 7.26	< **0.0001**
LVEF < 40%	1096 (7.5%%)	933/13122 (7.1%)	128/1224 (10.5%)	< **0.0001**
LVEDV at discharge *	106.6 ± 35.1	35.13 ± 0.6	37.69 ± 2.85	0.398
Therapy at discharge				
- Beta blockers	12,218/ 14293 (85.5%)	11,014/12918 (85.3%)	1069/1215 (88%)	**0.010**
- ACE i/ ARB	10,049/ 12602 (79.7%)	8991/11236 (80%)	917/1188 (77.2%)	**0.021**
- Statins	12,968/ 13982 (92.7%)	11,701/12626 (92.7%)	1093/1177 (92.9%)	0.811
- MRA	1531/ 7531 (20.3%)	1254/6743 (18.6%)	237/630 (37.6%)	< **0.0001**

Legend: MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non ST-segment elevation myocardial infarction; UA: unstable angina; LVEF: left ventricular ejection fraction; LVEDV: left ventricle end-diastolic volume; ACE-i: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; MRA: mineralocorticoid receptor antagonists. Significant values in bold

* Data available for 3371 patients.

** Data available for 1399 patients.

a one by-one-one fashion (see supplementary tables 1–6 and 8–12). In particular, the exclusion of potential colliders or mediators from the model such as previous MI, CKD and cardiogenic shock on admission confirmed an independent association between complete revascularization and the primary outcome with similar HR and confidence intervals as compared to main model. Moderately reduced LVEF at discharge was the most important predictor of HF hospitalizations (HR 2.48, 95%CI 1.97–3.11, $p < 0.0001$) followed by CKD (HR 2.22, 95%CI 1.89–2.61, $p < 0.0001$). The significant association of LVEF<40% with the primary outcome was confirmed also after excluding variables one by one from the main model, including the exclusion of potential mediators such as AF (HR 1.86, 95%CI 1.51–2.29, $p < 0.0001$, see supplementary table 7) or colliders as cardiogenic shock on admission (HR 1.81, 95%CI 1.47–2.22, $p < 0.0001$). Similarly, the association of CKD with the incidence of HF hospitalization was confirmed after removing potential colliders as diabetes mellitus (HR 1.84, 95%CI 1.59–2.13, $p < 0.0001$, see supplementary table 5), and vice-versa (see supplementary table 6). Age was associated with a 2.5% increase of HF hospitalization for every one-year increase (HR 1.02, 95%CI 1.02–1.03, p < 0.0001). The independent association of cardiogenic shock on admission with the risk of HF hospitalization that was observed with the stepwise Cox proportional hazard model (HR 1.88, 95%CI 1.1–3.2, $p = 0.020$), was not confirmed in the sensitivity analyses performed by excluding significant variables on a one-by-one fashion. The main model showed satisfactory calibration and discrimination at the Hosmer–Lemeshow statistic, with low differences between observed and predicted cases ($p = 0.09$, see supplementary table 13). The model also yielded moderate accuracy in predicting the primary endpoint throughout the cohort (ROC AUC 0.703, 95%CI 0.689–0.717), see supplementary fig. 2.

The same variables resulting from the stepwise model were associated with an increased risk of *HF hospitalization or CV death*, along with STEMI as admission diagnosis, smoking, multivessel or left main disease and malignancy. Complete revascularization, along with beta-blockers,

Table 2
Procedural features according to the occurrence of HF hospitalization at FU.

	Overall (n = 14,699)	No Hospitalization for HF (n = 13,282)	Hospitalization for HF (n = 1225)	P value
ULM disease	952 (6.5%)	877/13282 (6.6%)	60/1225 (4.9%)	**0.020**
Multivessel disease	5054 (34.4%)	4434/13282 (33.4%)	503/1225 (41.1%)	**<0.0001**
Complete revascularization*	1397/5054/ (28.3%)	1309/4434 (29.5%)	88/503 (17.5%)	**<0.0001**
ULM or multivessel disease	5553/14699 (37.6%)	4902/13282 (36.9%)	512/1225 (41.8%)	**0.001**
Bifurcation lesion	1332 (9.1%)	1176/13282 (8.9%)	118/1225 (9.6%)	0.360
Time from symptoms onset to admission (h)	11.94 ± 23.6	11.9 ± 23.8	12.9 ± 14.2	0.157
Pre procedural TIMI flow (culprit vessel)				**0.010**
- 0	2613/6685 (39.1%)	2362/5647 (39.7%)	209/602 (34.7%)	
- 1	634/6685 (9.5%)	565/5647 (9.5%)	61/602 (10.1%)	
- 2	650/6685 (9.7%)	583/5947 (9.8%)	47/602 (7.8%)	
- 3	2788/6685 (41.7%)	2437/5947 (41%)	285/602 (47.3%)	
Post procedural TIMI flow (culprit vessel)				**0.001**
				0.002
- 0	59/3662 (1.6%)	48/3292 (1.5%)	10/218 (4.6%)	
- 1	30/3662 (0.8%)	24/3292 (0.7%)	4/218 (1.8%)	
- 2	119/3662 (3.2%)	108/3292 (3.3%)	9/218 (4.1%)	
- 3	3454/3662 (94.3%)	3112/3292 (94.5%)	195/218 (89.4%)	
- Post procedural TIMI flow < 3	208/3662 (5.7%)	180/3292 (5.5%)	23/218 (10.6%)	

Legend: HF: heart failure; ULM: unprotected left main; TIMI: thrombolysis in myocardial infarction; h = hours. Significant values in bold. * rates of complete revascularization were computed on patients with multivessel disease.

Table 3
Multivariable predictors of HF hospitalization and HF hospitalization or CV death (results of Cox proportional hazard models).

	HF hospitalization			HF hospitalization or CV death		
Variable	HR	95% CI	P value	HR	95% CI	P value
Age (1 year increase)	1.02	1.02–1.03	< 0.0001	1.03	1.02–1.04	< 0.0001
Previous MI	1.23	1.08–1.40	0.002	1.26	1.09–1.45	0.02
LVEF ≤ 40%	2.48	1.97–3.11	< 0.0001	2.54	2.07–3.12	< 0.0001
Diabetes mellitus	1.51	1.34–1.72	< 0.0001	1.50	1.34–1.67	< 0.0001
CKD	2.22	1.89–2.61	< 0.0001	2.24	1.94–2.59	< 0.0001
Atrial fibrillation	1.68	1.35–2.08	< 0.0001	1.37	1.11–1.68	0.03
COPD	1.70	1.36–2.12	< 0.0001	1.59	1.30–1.94	< 0.0001
GRACE score ≥ 141	1.39	1.17–1.66	<0.0001	1.45	1.24–1.70	< 0.0001
PAD	1.86	1.36–2.53	< 0.0001	1.51	1.13–2.02	0.005
Cardiogenic shock at admission	1.88	1.10–3.20	0.020	2.10	1.39–3.18	<0.0001
Complete revascularization	0.46	0.39–0.55	< 0.0001	0.47	0.40–0.55	< 0.0001
Smoking previous or current			NS	1.17	1.03–1.31	0.011
ULM or multivessel disease			NS	1.20	1.07–1.35	0.001
STEMI as admission			NS	1.17	1.02–1.35	0.022
Malignancy			NS	1.50	1.25–1.81	<0.0001
Beta blockers at discharge			NS	0.78	0.67–0.92	0.003
Statin at discharge			NS	0.81	0.67–0.98	0.040
ACE-i at discharge			NS	0.84	0.73–0.96	0.009

Legend: LVEF: left ventricular ejection fraction; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; PAD: peripheral artery disease; ULM: unprotected left main; STEMI: ST-segment elevation myocardial infarction; ACE: angiotensin converting enzyme. HR: hazard ratio; CI: confidence intervals.

statins and ACE inhibitors at discharge were associated with a lower risk of such composite endpoint at follow-up (Table-3).

Results of the sensitivity analysis performed including in the model variables with missing data above 50% of the sample, are presented in supplementary Table 14, confirming most of the significant association and showing the prognostic impact of impaired post-procedural TIMI flow on the culprit vessel (HR 2.44, 95%CI 1.15–5.02, $p = 0.020$).

3.4. Impact of HF hospitalization on prognosis

The incidence of all-cause death and CV death was significantly higher among patients experiencing HF hospitalization compared with patients who did not (CV death: 28.6% vs 7.8%; all cause death: 35.4% vs 11.9%, both p log rank<0.0001), as shown in in Fig. 2. After multivariable adjustment, the development of HF at follow-up remained independently associated with impaired survival both due to an increased risk of CV death (HR 1.89 95%CI 1.5–2.39, $p < 0.0001$) and all-cause death (HR 1.85,95%CI 1.60–2.14, p < 0.0001) (see *supplementary table 15* for full list of predictors of all-cause and CV death).

4. Discussion

The main findings of the CORALYS registry, enrolling 14,699 patients admitted for ACS and treated with PCI to investigate the incidence and predictors of HF hospitalization after such index event, can be resumed as follows:

1) Despite prompt revascularization with PCI, the incidence of HF hospitalizations is still not negligible (well over 4% per year) among patients with no previous history of HF or LV dysfunction and admitted for ACS.
2) Several variables were identified as independent predictors of HF hospitalizations at FU, mostly including classic cardiovascular risk factors (age, diabetes mellitus), comorbidities (atrial fibrillation, COPD, CKD, PAD, previous MI) and clinical complexity at admission (high-risk GRACE score and presentation as cardiogenic shock). Moderately reduced LVEF at discharge was the most powerful predictor of HF hospitalization, while complete coronary revascularization was associated with a reduced risk of this event.

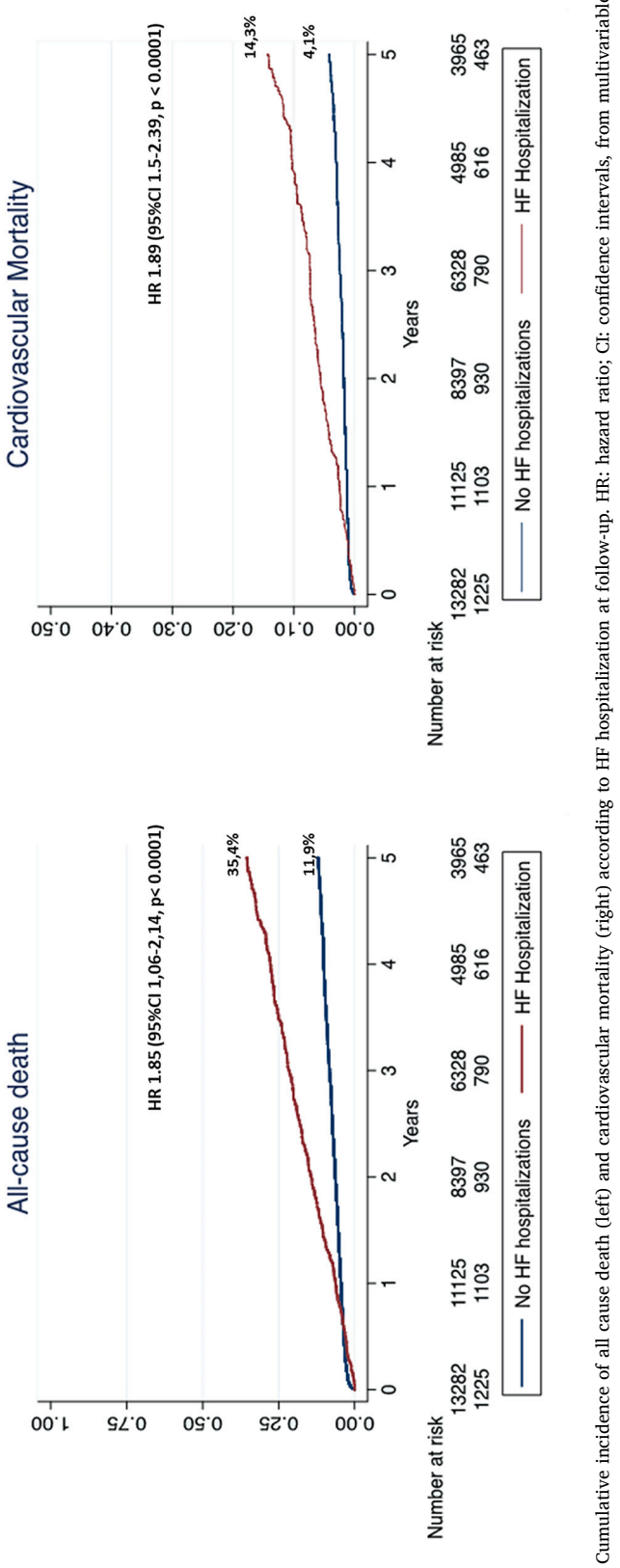

Fig. 2. Cumulative incidence of all cause death (left) and cardiovascular mortality (right) according to HF hospitalization at follow-up. HR: hazard ratio; CI: confidence intervals, from multivariable analysis.

3) The predictors of HF hospitalization, together with STEMI at admission, smoking and malignancy, were also associated with the combined endpoint of HF hospitalizations or CV death at follow-up. Beta-blockers, statin and ACE-I at discharge were instead associated with a lower risk of such composite endpoint.
4) After multivariable adjustment, HF hospitalization was significantly associated with an increased risk of all-cause and CV death at subsequent follow-up.

Our findings offer a contemporary picture of coronary artery disease implications. Indeed, while prompt and revascularization has substantially improved survival of patients with ACS, the risk of late adverse events such as HF remains significant. Previous studies showed discordant results with respect to the incidence of HF after discharge for ACS. In the CARE study, authors reported a global incidence of HF of 6.3% over five years, with a linear pattern rate of 1.3%/year (16). On the other hand, a large nation-wide cohort study showed that the incidence of HF discharge is highest in the first months and up to one year after MI discharge, thereby dropping at a stable rate of 1.3%–2.2% per year, which is in line with our findings (17). This is in line with our findings showing 4.4% incidence of HF hospitalizations at one year, 6.6% at two years and 12.7% at the latest available FU. Differences in study findings are largely influenced by differences in patients' populations and study definitions, thus hampering a direct comparison. However, the increasing incidence of HF hospitalizations in the modern PCI era may reflect the increased proportion of aged patients with multiple comorbidities surviving an index ACS event, therefore being exposed to late complications. In line with this hypothesis and with previous findings, we found age and several chronic illnesses such as CKD and diabetes mellitus to be independently associated with HF hospitalization in our cohort (18–20). Reduced LVEF at discharge, likely mirroring a larger infarct size, more extensive coronary artery disease and less cardiac reserve was the most powerful predictor of HF hospitalization at follow-up consistent with previous evidence. The association between PAD and hospitalization and poor outcomes among patients with HF had been previously described (21). Although PAD and HF share risk factors, the persistence of such association despite extensive adjustment suggests an intrinsic effect of PAD on HF hospitalization, whose mechanism should be further investigated. Similarly, new-onset or pre-existing atrial fibrillation may reflect atrial pressure increase or adverse myocardial remodeling, thereby supporting the association of the arrythmia with the risk of HF after MI (18,22).

In previous studies focusing on the prognosis of patients with HF and concomitant COPD, the latter was consistently an independent predictor of death and HF hospitalizations when reported in multivariable models (23). We found that suffering from chronic pulmonary disease among patients experiencing ACS was associated with higher hospitalizations for HF. One possible pathophysiological link may lie in the chronic low-grade systemic inflammation characterizing COPD, that may contribute to progression of atherosclerosis and adverse cardiovascular events (24). Further, common respiratory infections are frequently associated with heart decompensation at admissions, along with right ventricular involvement with associated peripheral congestion (25).

Of interest, previous studies showed discordant findings about the association of female sex with HF risk after AMI(16;18;19). The absence of such relationship in the present registry may suggest that this issue could be partly related to historical suboptimal hospital care of female patients including an underuse of revascularization (26) and that disparities have been hopefully overcome in the modern practice. The impact a previous MI on the risk of incident HF was reported by several studies and confirmed in our analysis (8,20,27). A preexisting systolic dysfunction has been frequently advocated as the most probable mechanism subtending such excess of risk. We confirmed this association despite the fact that patients with impaired LVEF were excluded in this study. This finding points to the role of additional potential mechanisms such as residual subclinical ischemia after MI and diastolic

dysfunction.

The association of complete revascularization with a reduced risk of HF and HF or CV death among an unselected cohort of ACS patients is among the most interesting findings of this study. Complete revascularization proved superior to culprit-only PCI in reducing the risk of cardiovascular death or MI among STEMI patients with multivessel disease (28). Indirect evidence supports the benefit of complete revascularization also among NSTE-ACS patients being associated with decreased mortality (29). However, the suggestion that complete revascularization may be associated with a lower risk of HF hospitalization among patients without previously impaired myocardial contractility is novel. Possible underlying mechanisms include the prevention of recurrent acute MI (30) and the prevention of residual myocardial ischemic areas, associated with contractile dysfunction (31).

In order to identify patients most likely to benefit from intensive management, international guidance recommends the use of validated prognostic scores. McAllister et Al. showed that the GRACE risk score, commonly used to predict the risk of impaired prognosis among patients admitted for ACS, could also have a role for the identification of patients at risk of HF (7). Our results confirm and extend such finding in a larger real-world cohort. However, there is still an unmet need to draw score specifically conceived for this purpose.

Drugs modulating neurohormonal systems as ACE-I and beta-blockers were associated with a reduced risk of HF hospitalization or CV death but not HF hospitalization alone in our cohort. Despite these medications, along with MRA, represent a standard of care for patients with ACS and LVEF <40% to reduce CV mortality (class I A ESC guidelines recommendation) (11), their use among all ACS patients regardless of LVEF is still debated (32,33) and thereby supported by a lower class of recommendation. In our multivariable model, including adjustment for LVEF <40%, ACE-I and beta blockers, but not MRA, still preserved an independent association with a reduced risk of HF or CV death.

Finally, our results confirm and extend to a contemporary cohort existing evidence showing an association between HF complicating MI and prognosis (34). Despite advancements in management of both these conditions, we found HF to be associated with a near two-fold increased risk of CV death despite adjustment for key confounders. Further, HF after ACS was also associated with overall mortality. Despite the precise mechanism for this association is yet to be determined, there is evidence supporting the concept of HF as a marker of frailty and as a mirror of worsening of chronic diseases (35). Taken together our results indicate that patients experiencing ACS should be carefully assessed at discharge for potential late adverse events such as HF. Although adequate follow-up should be offered to all, patients suffering from chronic illnesses and with impaired LVEF at discharge would deserve stricter and tailored screening, likely including remote monitoring. In line with the finding that HF hospitalizations are associated with an increased risk of death, further efforts should be made to offer optimal medical treatment to patients deemed at high risk. In this sense, age and comorbidities should not be considered a deterrent for the prescription of novel therapies for HF as these patients are supposed to receive the highest benefit in terms of prevention. The association of complete revascularization with a reduced risk of HF should be considered as hypothesis generating in line with the observation design of this registry. Our findings may prompt to account for HF as a relevant endpoint in adequately designed trials assessing the role of complete vs culprit-only revascularization.

4.1. Limitations

The findings of the present study should be considered in the context of some limitations. First, this registry has a retrospective, observational design. Despite the large sample size, a potential bias due to the effect of unmeasured (i.e infarct size and location) and unknown variables cannot be excluded. Among the others we acknowledge that data about patients' compliance to discharge therapies were not available. We acknowledge that HR reported in the main analyses should be considered conditional and susceptible to "Table 2 fallacy" (36). Despite we sought to account for variables acting as colliders and mediators through multiple sensitivity analysis, the effect of unmeasured confounding may persist. In this context, we highlight that the association of cardiogenic shock on admission with the primary outcome was no longer significant after removing each single variable from the main model. From a clinical point of view this may be related to the high mortality rate of these patients consequently limiting the impact of this variable. From a statistical point of view this may represent an example of "fallacy", as described above.

Further, the definition of the main outcome was mostly based on the retrospective evaluation of electronic medical records. However, the results of this study show that the diagnosis of HF used in the present analysis is associated with a significant prognostic value. Further, despite a high proportion of patients discharged on optimal medical therapy, the use of heart failure medication at discharge was not standardized. Lastly, patients were enrolled in this registry over a 5-year period. During this period, there has been a progressive introduction of new HF therapies in clinical practice. Our study was not designed to evaluate the impact of such pharmacological treatments on HF incidence. The incidence of heart failure may be therefore lower in more contemporary cohorts. However, to date the rate of prescription of these drugs is still suboptimal, mainly due to reimbursement issues across European countries. In this context, our results could help to identify the patients who benefit the most from more effective pharmacologic agents.

5. Conclusions

In the contemporary PCI era HF is still a frequent complication after ACS and is associated with impaired prognosis. Several independent predictors of HF hospitalization, including chronic illnesses and impaired LVEF at discharge may help identify patients at risk deserving intensive treatment and follow-up. Conversely, complete revascularization is associated with a reduced risk of HF hospitalization and CV death.

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None.

Data availability statement

The data underlying this article are available in the article and in its online supplementary material.

Declaration of Competing Interest

None declared.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.10.146.

References

[1] E.C. Keeley, J.A. Boura, C.L. Grines, Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials, Lancet 361 (9351) (2003) 13–20.

[2] F. D'Ascenzo, M. Iannaccone, G. Saint-Hilary, M. Bertaina, S. Schulz-Schüpke, C. Wahn Lee, et al., Impact of design of coronary stents and length of dual

antiplatelet therapies on ischaemic and bleeding events: a network meta-analysis of 64 randomized controlled trials and 102735 patients, Eur. Heart J. 38 (42) (2017) 3160–3172.
[3] O. De Filippo, F. D'Ascenzo, S. Raposeiras-Roubin, E. Abu-Assi, M. Peyracchia, P. P. Bocchino, et al., P2Y12 inhibitors in acute coronary syndrome patients with renal dysfunction: an analysis from the RENAMI and BleeMACS projects, Eur Heart J Cardiovasc Pharmacother. 6 (1) (2020) 31–42.
[4] B. Gencer, F. Mach, S.A. Murphy, G.M. De Ferrari, K. Huber, B.S. Lewis, et al., Efficacy of Evolocumab on cardiovascular outcomes in patients with recent myocardial infarction: a Prespecified secondary analysis from the FOURIER trial, JAMA Cardiol. 5 (8) (2020) 952–957.
[5] V.L. Roger, Epidemiology of heart failure, Circ. Res. 113 (6) (2013) 646–659.
[6] J.A. Ezekowitz, P. Kaul, J.A. Bakal, P.W. Armstrong, R.C. Welsh, F.A. McAlister, Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction, J. Am. Coll. Cardiol. 53 (1) (2009) 13–20.
[7] D.A. McAllister, N. Halbesma, K. Carruthers, M. Denvir, K.A. Fox, GRACE score predicts heart failure admission following acute coronary syndrome, Eur. Heart J. Acute Cardiovasc. Care 4 (2) (2015) 165–171.
[8] D.J. Kelly, T. Gershlick, B. Witzenbichler, et al., Incidence and predictors of heart failure following percutaneous coronary intervention in ST-segment elevation myocardial infarction: the HORIZONS-AMI trial, Am. Heart J. 162 (4) (2011) 663–670.
[9] M. Vaduganathan, J.L. Januzzi Jr., Preventing and treating heart failure with sodium-glucose co-transporter 2 inhibitors, Am. J. Cardiol. 124 (Suppl. 1) (2019) S20–S27.
[10] P.K. Kuchulakanti, ARNI in cardiovascular disease: current evidence and future perspectives, Futur. Cardiol. 16 (5) (2020) 505–515.
[11] J.P. Collet, H. Thiele, E. Barbato, O. Barthélémy, J. Bauersachs, D.L. Bhatt, et al., 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, Eur. Heart J. 42 (14) (2021) 1289–1367.
[12] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G.F. Cleland, A.J.S. Coats, et al., 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)developed with the special contribution of the heart failure association (HFA) of the ESC, Eur. Heart J. 37 (27) (2016) 2129–2200.
[13] R. Mehran, S.V. Rao, D.L. Bhatt, C.M. Gibson, A. Caixeta, J. Eikelboom, et al., Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium, Circulation. 123 (23) (2011) 2736–2747.
[14] F.J. Neumann, M. Sousa-Uva, A. Ahlsson, F. Alfonso, A.P. Banning, U. Benedetto, et al., 2018 ESC/EACTS Guidelines on myocardial revascularization, Eur. Heart J. 40 (2) (2019) 87–165.
[15] K.A. Hicks, J.E. Tcheng, B. Bozkurt, B.R. Chaitman, D.E. Cutlip, A. Farb, et al., 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association task force on clinical data standards (writing committee to develop cardiovascular endpoints data standards), J. Am. Coll. Cardiol. 66 (4) (2015) 403–469.
[16] E.F. Lewis, L.A. Moye, J.L. Rouleau, F.M. Sacks, J.M. Arnold, J.W. Warnica, et al., Predictors of late development of heart failure in stable survivors of myocardial infarction: the CARE study, J. Am. Coll. Cardiol. 42 (8) (2003) 1446–1453.
[17] G. Sulo, J. Igland, S.E. Vollset, O. Nygård, M. Ebbing, E. Sulo, et al., Heart failure complicating acute myocardial infarction; burden andtiming of occurrence: a nation-wide analysis including 86 771 patients from the cardiovascular disease in Norway(CVDNOR) project, J Am Heart Assoc 5 (2016), e002667, https://doi.org/10.1161/JAHA.115.002667.
[18] E.F. Lewis, E.J. Velazquez, S.D. Solomon, A.S. Hellkamp, J.J. McMurray, J. Mathias, et al., Predictors of the first heart failure hospitalization in patients who are stable survivors of myocardial infarction com-plicated by pulmonary congestion and/or left ventricular dysfunction: a VAL-IANT study, Eur. Heart J. 29 (2008) 748–756.
[19] J. Wellings, J.B. Kostis, D. Sargsyan, J. Cabrera, W.J. Kostis, Risk factors and trends in incidence of heart failure following acute myocardial infarction, Am. J. Cardiol. 122 (1) (2018) 1–5.
[20] P.G. Steg, O.H. Dabbous, L.J. Feldman, A. Cohen-Solal, M.C. Aumont, J. Lopez-Sendon, et al., Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the global registry of acute CoronaryEvents (GRACE), Circulation 109 (2004) 494–499.
[21] S.C. Inglis, A. Hermis, S. Shehab, P.J. Newton, S. Lal, P.M. Davidson, Peripheral arterial disease and chronic heart failure: a dangerous mix, Heart Fail. Rev. 18 (4) (2013) 457–464.
[22] K. Chadda, S. Goldstein, R. Byington, J.D. Curb, Effect of propranolol after acute myocardial infarction in patients with congestive heart failure, Circulation 73 (1986) 503–510.
[23] N.M. Hawkins, M.C. Petrie, P.S. Jhund, G.W. Chalmers, F.G. Dunn, J.J. McMurray, Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology, Eur. J. Heart Fail. 11 (2) (2009) 130–139.
[24] D.D. Sin, S.F. Man, Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease, Circulation. 107 (2003) (1514–151).
[25] M.S. Nieminen, D. Brutsaert, K. Dickstein, H. Drexler, F. Follath, V.P. Harjola, et al., EuroHeart failure survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population, Eur. Heart J. 27 (2006) 2725–2736.
[26] S. Arora, G.A. Stouffer, A.M. Kucharska-New-ton, A. Qamar, M. Vaduganathan, A. Pandey, et al., Twenty-year trends and sex differences in young adults hospitalized with acute myocardial infarction, Circulation 139 (2019) 1047–1056.
[27] Desta L, Jernberg T, Lofman I, Hofman-Bang C, Hagerman I, Spaak J et al. Incidence, temporal trends, and prognostic impact of heart failure com-plicating acute myocardial infarction. The SWEDEHEART Registry (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies): a study of 199,851 patients admitted with index acute myocardial infarctions, 1996 to 2008 JACC Heart Fail 2015; 3: 234–242.
[28] R. Pavasini, S. Biscaglia, E. Barbato, M. Tebaldi, D. Dudek, J. Escaned, et al., Complete revascularization reduces cardiovascular death in patients with ST-segment elevation myocardial infarction and multivessel disease: systematic review and meta-analysis of randomized clinical trials, Eur. Heart J. 41 (42) (2020) 4103–4110.
[29] K.S. Rathod, S. Koganti, A.K. Jain, Z. Astroulakis, P. Lim, R. Rakhit, et al., Complete versus culprit-only lesion intervention in patients with acute coronary syndromes, J. Am. Coll. Cardiol. 72 (17) (2018) 1989–1999.
[30] S.R. Mehta, D.A. Wood, R.F. Storey, R. Mehran, K.R. Bainey, H. Nguyen, et al., COMPLETE trial steering committee and investigators. Complete revascularization with multivessel PCI for myocardial infarction, N. Engl. J. Med. 381 (15) (2019) 1411–1421.
[31] P. Giannuzzi, C. Marcassa, P.L. Temporelli, M. Galli, U. Corrà, A. Imparato, et al., Residual exertional ischemia and unfavorable left ventricular remodeling in patients with systolic dysfunction after anterior myocardial infarction, J. Am. Coll. Cardiol. 25 (7) (1995) 1539–1546.
[32] S. Bangalore, G. Steg, P. Deedwania, K. Crowley, K.A. Eagle, S. Goto, et al., REACH registry investigators. Beta-blocker use and clinical outcomes in stable outpatients with and without coronary artery disease, JAMA 308 (2012) 13401349.
[33] S. Yusuf, P. Sleight, J. Pogue, J. Bosch, R. Davies, G. Dagenais, Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients, N. Engl. J. Med. 342 (2000), 145153.
[34] Y. Gerber, S.A. Weston, M. Enriquez-Sarano, C. Berardi, A.M. Chamberlain, S. M. Manemann, et al., Mortality associated with heart failure after myocardial infarction: a contemporary community perspective, Circ Heart Fail. 9 (1) (2016), e002460, https://doi.org/10.1161/CIRCHEARTFAILURE.115.002460.
[35] J.A. Ezekowitz, P. Kaul, J.A. Bakal, P.W. Armstrong, R.C. Welsh, F.A. McAlister, Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction, J. Am. Coll. Cardiol. 53 (2009) 13–20.