Growth differentiation factor 15: a biomarker to guide empagliflozin treatment in acute myocardial infarction?

Óscar M. Peiró, MD, PhD,[a,b,c*] Alfredo Bardají, MD, PhD, [a,b,c] Anna Carrasquer, MD, PhD, [a,b,c] German Cediel, MD, PhD, [a,b,c] Isabel Serrano, MD, [a,c] Gil Bonet, MD, [a,b,c] María Ferrero, MD, [a] Víctor Del-Moral-Ronda, MD, [a] Mar Rocamora-Horrach, MD, [a,c] José Luis Ferreiro, MD, PhD [a,b,c]

a. Department of Cardiology, Joan XXIII University Hospital, Tarragona, Spain.

b. Pere Virgili Health Research Institute (IISPV), Tarragona, Spain.

c. Rovira i Virgili University, Tarragona, Spain.

* Author for correspondence: Óscar M. Peiró. Cardiology Service. Joan XXIII University Hospital. Rovira Virgili University. IISPV. Calle Dr Mallafré Guasch 4. 43005. Tarragona. Spain Tel 0034 977 29 58 34. email: ompeiro.hj23.ics@gencat.cat

1. Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have consistently demonstrated a clear benefit in terms of cardiovascular outcomes in patients with established heart failure (HF), chronic kidney disease and type 2 diabetes. However, the benefits of SGLT2 inhibitors in patients after an acute myocardial infarction (MI) at risk of developing HF are less clear. In the EMPACT-MI trial (Study to Evaluate the Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients with Acute Myocardial Infarction), despite empagliflozin did not significantly reduce the primary endpoint (composite of first hospitalization for HF or all-cause death) in patients with an acute MI and at risk of development of HF, the SGLT2 inhibitor diminished the risk of first and total number of HF hospitalizations [1,2]. Although patients included in the EMPACT-MI trial were required to have at least one enrichment factor (including clinical and analytical parameters known to be associated with hospitalization for HF or even death), these eligibility criteria may have not been perfect in terms of selecting the population that could benefit the most from empagliflozin therapy. An optimal identification of those patients at greater risk after an acute MI is crucial to implement therapeutic strategies, such as SGLT2 inhibitors, that may play a role in preventing the development and progression of HF.

Growth differentiation factor-15 (GDF-15) has been proven useful as a prognostic biomarker for cardiovascular death and hospitalizations for HF after an acute coronary syndrome (ACS) [3]. Besides, the prognostic ability of GDF-15 in HF was demonstrated in a pooled analysis of the EMPEROR trials in which, most interestingly, elevated concentrations of GDF-15 were associated with more pronounced benefits of empagliflozin [4]. Accordingly, GDF-15 might be used to refine the selection of high-risk patients after an acute MI that could benefit from empagliflozin therapy. The aim of the

present study was to evaluate and compare the prognostic performances of GDF-15 versus the inclusion criteria of the EMPACT-MI trial and their discriminative ability to identify subjects at high risk of development of HF in a cohort of patients after an acute MI.

2. Methods

In a prior investigation performed by our group, the long-term predictive ability of GDF-15 for cardiovascular events was observed in a cohort of ACS patients [5]. Briefly, patients admitted in a single center from January 2011 to December 2014 with an ACS who underwent coronary angiography were included and blood samples were collected during the procedure. Plasma GDF-15 was measured by an electrochemiluminescence immunoassay (Elecsys GDF-15, Roche Diagnostics, Basel, Switzerland) and GDF-15 >1800ng/L was classified as high risk based on previously established thresholds [6-7]. Clinical data as well as long-term cardiovascular events were registered by review of electronic medical records. This very same study population was used for the present investigation, but excluding patients with unstable angina or those subjects meeting any exclusion criteria of the EMPACT-MI trial. Patients were classified into two categories, high risk (HRHF) or no high risk of development of HF (NHRHF), according to two models: 1) GDF-15: HRHF if >1800ng/L and NHRHF if ≤1800ng/L; and 2) EMPACT-MI criteria: HRHF if meeting the trial inclusion criteria. The entire cohort was first evaluated with the GDF-15 model and later completely reassessed using the EMPACT-MI model. Cox regression and ROC curve analyses were used to evaluate the prognostic performance and discriminative ability of both models. Multivariable analysis was adjusted by age, diabetes mellitus, hypercholesterolemia, glomerular

filtration rate at admission, significant three vessels stenosis and left ventricular ejection fraction <40% at discharge and type of MI. The primary endpoint was the composite of all-cause death or first hospitalization for HF. The institutional ethical committee approved the study.

3. Results

The initial cohort consisted of 358 patients (characteristics of the study population have been presented previously) [5], of which 52 and 31 subjects were excluded due to unstable angina diagnosis or EMPACT-MI trial exclusion criteria, respectively. Thus, 275 patients were finally included for analysis (73.1% male, 70.6% with non-ST-segment elevation MI and 29.4% with ST-segment elevation MI). Baseline characteristics of both models are shown in table 1. A total of 82 (29.8%) and 60 (21.8%) patients were classified as HRHF according to GDF-15 levels and EMPACT-MI criteria, respectively. According to GDF-15 concentration, a primary endpoint event occurred in 38 (46.3%) patients in the HRHF group and 11 (5.7%) patients in the NHRHF group, with a median follow of 4.9 years. With regard to the second model, following the EMPACT-MI criteria, a primary endpoint event occurred in 26 (43.3%) and in 23 (10.7%) patients in the HRHF and in the NHRHF, respectively. Of note, a stronger association with the composite endpoint (Figure 1) was observed with the GDF-15 model (HR 10.7 [95%CI 5.5–21.0]) compared to the EMPACT-MI model (HR 3.9 [(95%CI 2.2–6.8]). Even after adjustment, patients classified as HRHF according to the GDF-15 model remained strongly associated with the primary endpoint (HR 6.3 [95%CI 2.9–13.3]). The c-index was significantly higher (p=0.004) for the GDF-15 model (0.790 [95%CI 0.726–0.855]) compared with the EMPACT-MI model (0.629 [(95%CI 0.559–0.699]).

Similar results were obtained for the individual endpoint of HF first hospitalization. Elevated levels of GDF-15 were more strongly associated with an increased risk of hospitalization for HF (HR 41.9 [95% CI 5.6–311.1]) than HRHF defined as per EMPACT-MI criteria (HR 5.7 [95% CI 2.2–14.8]), as shown in Figure 1. A superior discrimination ability (p=0.045) was observed for the GDF-15 model compared to the EMPACT-MI criteria model, with c-indices of 0.842 (95% CI 0.779–0.906) 0.697 (95% CI 0.574–0.820), respectively.

4. Discussion

The findings of this investigation can be summarized as follows: GDF-15 is a strong predictor of all-cause death and HF in patients after an acute MI and has a superior discriminative ability to detect patients at high risk of development of HF compared to the inclusion criteria of the EMPACT-MI trial. An accurate identification of patients at high risk of development of HF after an acute MI is key in terms of implementing therapeutic regimens that can improve prognosis. It can be hypothesized that a suboptimal identification of this high-risk subpopulation may have been one of the factors contributing to the lack of benefit of empagliflozin on the primary endpoint in the EMPACT-MI trial.

GDF-15 levels rise significantly after an acute MI, but this increase is considered mild and unrelated to infarct size [6, 8]. In fact, post-MI circulating GDF-15 concentrations tend to remain relatively stable, suggesting they may reflect an underlying chronic disease burden rather than acute instability [9-10]. In this context, elevated GDF-15 levels have been associated with a higher risk of mortality and HF in both short and long-term follow-up [5-10]. However, elevated GDF-15 levels are not associated with recurrent MI or

stroke when measured early after ACS but are linked to a higher incidence of these events in stabilized ACS patients and those with stable atherosclerotic cardiovascular disease [3].

Determining GDF-15 levels in this setting could be useful, since this biomarker may help identify patients at greater risk of mortality and HF after an acute MI, as suggested by the results of the present study, and is also associated with the positive effect of empagliflozin in patients with HF [4]. However, whether the inclusion of GDF-15 in the selection criteria of the EMPACT-MI trial would have changed the primary results of the study is merely speculative. The main limitations of our study are the small sample size and those inherent to a retrospective investigation.

5. Conclusions

In conclusion, GDF-15 might have a better discriminative ability than the inclusion criteria of the EMPACT-MI trial to identify those patients at higher risk of death and HF after an acute MI, who might be more appropriate candidates for SGLT2 inhibitor therapy. Our findings must be considered hypothesis-generating and further dedicated studies are warranted in order to discern the true role of GDF-15 (either alone or as component of a score including other parameters) for identification of patients at higher risk of developing HF after an acute MI that, subsequently, may benefit more from implementing therapy with SGLT2 inhibitors.

References

[1] Butler J, Jones WS, Udell JA, et al. Empagliflozin after Acute Myocardial Infarction. N Engl J Med. 390 (2024) 1455-1466. doi:10.1056/NEJMoa2314051

[2] Hernandez AF, Udell JA, Jones WS, et al. Effect of Empagliflozin on Heart Failure Outcomes After Acute Myocardial Infarction: Insights From the EMPACT-MI Trial. Circulation. 149 (2024) 1627-1638. doi:10.1161/CIRCULATIONAHA.124.069217

[3] Kato ET, Morrow DA, Guo J, et al. Growth differentiation factor 15 and cardiovascular risk: individual patient meta-analysis. Eur Heart J. 44 (2023) 293-300. doi:10.1093/eurheartj/ehac577

[4] Ferreira JP, Packer M, Butler J, et al. Growth differentiation factor-15 and the effect of empagliflozin in heart failure: Findings from the EMPEROR program. Eur J Heart Fail. 26 (2024) 155-164. doi:10.1002/ejhf.3078

[5] Peiró ÓM, García-Osuna Á, Ordóñez-Llanos J, et al. Long-term prognostic value of growth differentiation factor-15 in acute coronary syndromes. Clin Biochem. 73 (2019) 62-69. doi:10.1016/j.clinbiochem.2019.07.014

[6] Wollert KC, Kempf T, Peter T, et al. Prognostic value of growth-differentiation factor-15 in patients with non-ST-elevation acute coronary syndrome. Circulation. 115 (2007) 962-971. doi:10.1161/CIRCULATIONAHA.106.650846

[7] Bonaca MP, Morrow DA, Braunwald E, et al. Growth differentiation factor-15 and risk of recurrent events in patients stabilized after acute coronary syndrome: observations from PROVE IT-TIMI 22. Arterioscler Thromb Vasc Biol. 31 (2011) 203-210. doi:10.1161/ATVBAHA.110.213512

[8] Kempf T, Björklund E, Olofsson S, et al. Growth-differentiation factor-15 improves risk stratification in ST-segment elevation myocardial infarction. Eur Heart J. 28 (2007) 2858-65. doi: 10.1093/eurheartj/ehm465.

[9] Eggers KM, Kempf T, Lagerqvist B, et al. Growth-differentiation factor-15 for long-term risk prediction in patients stabilized after an episode of non-ST-segment-elevation acute coronary syndrome. Circ Cardiovasc Genet. 3 (2010) 88-96. doi: 10.1161/CIRCGENETICS.109.877456.

[10] Buljubasic N, Vroegindewey MM, Oemrawsingh RM, et al. Temporal Pattern of Growth Differentiation Factor-15 Protein After Acute Coronary Syndrome (From the BIOMArCS Study). Am J Cardiol. 124 (2019) 8-13. doi: 10.1016/j.amjcard.2019.03.049.

Figure legend

Figure 1. Cumulative incidence of the primary and secondary endpoint by GDF-15 (left) and EMPACT-MI inclusion criteria (right).

Conflict of interest statement

Óscar M. Peiró reports honoraria for lectures from Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Ferrer, NovoNordisk, Sanofi and Viatris Pharmaceutical. José Luis Ferreiro reports a) honoraria for lectures from Eli Lilly Co, Daiichi Sankyo, Inc., AstraZeneca, Pfizer, Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Rovi, Terumo and Ferrer; b) consulting fees from AstraZeneca, Eli Lilly Co., Ferrer, Boston Scientific, Pfizer, Boehringer Ingelheim, Daiichi Sankyo,Inc., Bristol-Myers Squibb and Biotronik; c) research grants from AstraZeneca.

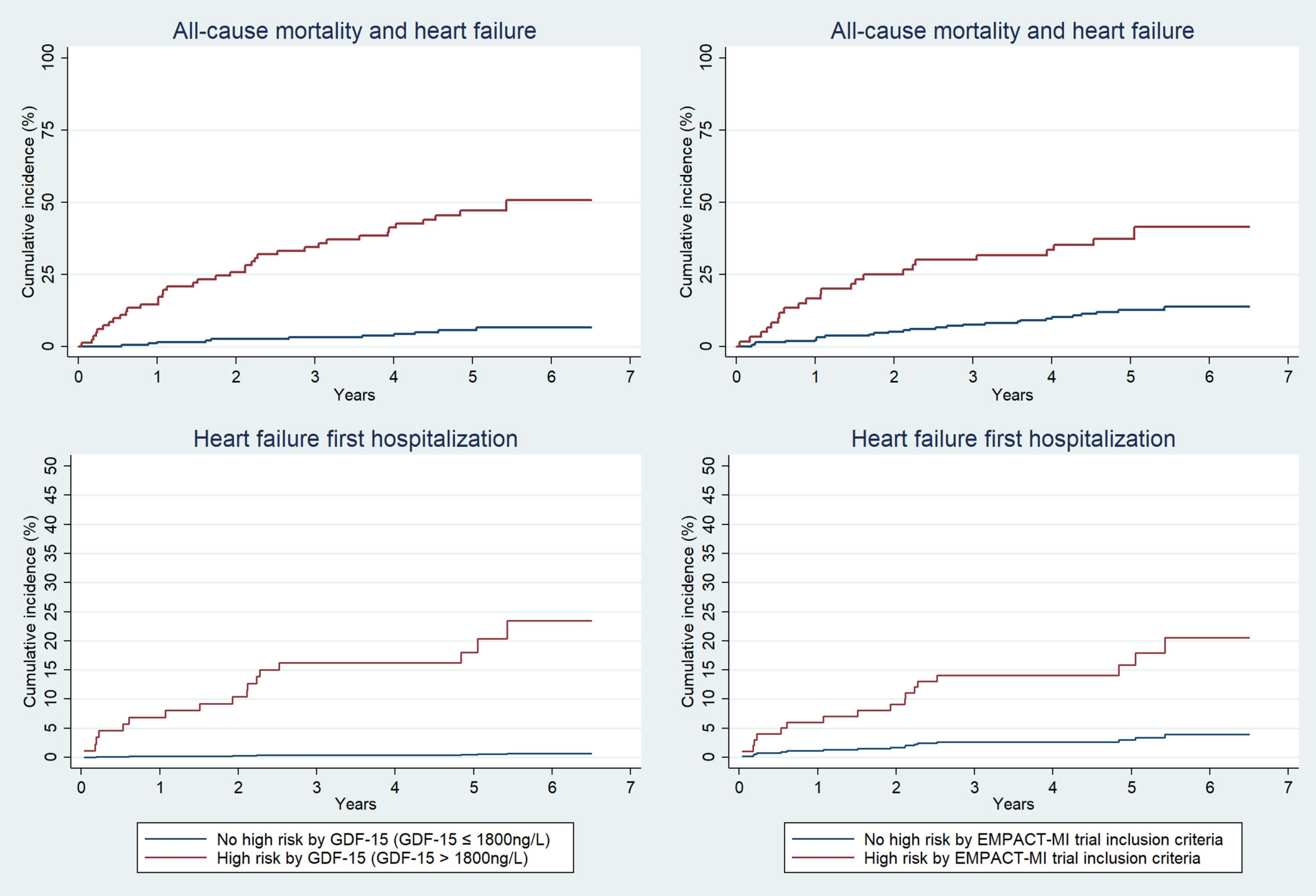
All-cause mortality and heart failure
Cumulative incidence (%)
0
25
50
75
100
0
1
2
3
4
5
6
7
Years
All-cause mortality and heart failure
Cumulative incidence (%)
0
25
50
75
100
0
1
2
3
4
5
6
7
Years
Heart failure first hospitalization
Cumulative incidence (%)
0
5
10
15
20
25
30
35
40
45
50
0
1
2
3
4
5
6
7
Years
Heart failure first hospitalization
Cumulative incidence (%)
0
5
10
15
20
25
30
35
40
45
50
0
1
2
3
4
5
6
7
Years
No high risk by GDF-15 (GDF-15 ≤ 1800ng/L)
High risk by GDF-15 (GDF-15 > 1800ng/L)
No high risk by EMPACT-MI trial inclusion criteria
High risk by EMPACT-MI trial inclusion criteria

Table 1. Baseline characteristics

Variable	GDF-15 model			EMPACT-MI criteria model		
	NHRHF (N=193)	HRHF (N=82)	P Value	NHRHF (N=215)	HRHF (N=60)	P Value
Demographics						
Age, years	59.7 (51.4-69.3)	72.7 (64.0-79.2)	<0.001	62.6 (52.9-72.3)	68.4 (58.2-78.6)	0.007
Male sex	150 (77.7)	51 (62.2)	0.008	160 (74.4)	41 (68.3)	0.347
Cardiovascular risk factors						
Current smoker	86 (44.6)	15 (18.3)	<0.001	83 (38.6)	18 (30.0)	0.222
Hypertension	112 (58.0)	67 (81.7)	<0.001	135 (62.8)	44 (73.3)	0.130
Diabetes mellitus	54 (28.0)	47 (57.3)	<0.001	61 (28.4)	40 (66.7)	<0.001
Hypercholesterolemia	100 (51.8)	58 (70.7)	0.004	120 (55.8)	38 (63.3)	0.298
Obesity (BMI ≥30 kg/m^2)	53 (29.4)	21 (28.4)	0.865	56 (27.9)	18 (34.0)	0.384
Medical history						
Myocardial infarction	28 (14.5)	23 (28.1)	0.008	30 (14.0)	21 (35.0)	<0.001
Heart failure	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Cerebrovascular disease	4 (2.1)	13 (15.9)	<0.001	11 (5.1)	6 (10.0)	0.220
Peripheral arterial disease	6 (3.1)	19 (23.2)	<0.001	14 (6.5)	11 (18.3)	0.005
Chronic kidney disease	3 (1.6)	11 (13.4)	<0.001	9 (4.2)	5 (8.3)	0.195
PCI	17 (8.8)	11 (13.4)	0.248	21 (9.8)	7 (11.7)	0.667
Cardiac surgery	4 (2.1)	2 (2.4)	1.000	5 (2.3)	1 (1.7)	1.000
Physical examination at admission						
Systolic arterial pressure (mmHg)	140 (125-154)	135 (122-152)	0.588	140 (128-155)	130 (117-146)	0.009
Atrial fibrillation/flutter	4 (2.1)	7 (8.5)	0.019	6 (2.8)	5 (8.3)	0.066
Killip class > I	8 (4.2)	20 (24.4)	<0.001	5 (2.3)	23 (38.3)	<0.001
Laboratory analysis at admission						
Glycemia (mg/dL)	119 (100-156)	148 (110-218)	<0.001	117 (99-153)	161 (125-215)	<0.001
eGFR (mL/min per 1.73 m^2)	91 (76-102)	60 (49-81)	<0.001	87 (68-99)	78 (58-94)	0.040
LDL cholesterol (mg/dL)	104 (84-125)	89 (69-110)	<0.001	104 (81-123)	90 (69-108)	0.008
HDL cholesterol (mg/dL)	38 (33-44)	37 (29-46)	0.587	37 (31-45)	38 (31-43)	0.914
Coronary angiography						
Significant three vessels stenosis	31 (16.1)	24 (29.3)	0.012	34 (15.8)	21 (35.0)	0.001
PCI	145 (75.1)	59 (72.0)	0.582	159 (74.0)	45 (75.0)	0.870
LVEF at discharge						
LVEF <40%	8 (4.2)	16 (19.5)	<0.001	0 (0.0)	24 (40.0)	<0.001
Discharge diagnostic						
STEMI	60 (31.1)	21 (25.6)	0.362	61 (28.4)	20 (33.3)	0.456
NSTEMI	133 (68.9)	61 (74.4)	0.362	154 (71.6)	40 (66.7)	0.456

High risk of heart failure (HRHF) or no high risk of development of heart failure (NHRHF), according to two models: 1) GDF-15: HRHF if >1800ng/L and NHRHF if ≤1800ng/L; and 2) EMPACT-MI criteria: HRHF if meeting the EMPACT-MI trial

inclusion criteria. Data represent the number (percentage) or median (interquartile range). BMI indicates body mass index; PCI: percutaneous coronary intervention; eGFR indicates estimated glomerular filtration rate; LDL: low-density lipoprotein; HDL: high-density lipoprotein; LVEF: left ventricle ejection fraction; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction.