Ischemic Etiology in Advanced Heart Failure: Insight from the HELP-HF Registry

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In patients with advanced heart failure (HF), defined according to the presence of at least one I-NEED-HELP criterium, the updated 2018 Heart Failure Association of the European Society of Cardiology (HFA-ESC) criteria for advanced HF identify a subgroup of patients with HF with worse prognosis, but whether ischemic etiology has a relevant prognostic impact in this very high-risk cohort is unknown. Patients from the HELP-HF registry were stratified according to ischemic etiology and presence of advanced HF based on 2018 HFA-ESC criteria. The primary end point was a composite of all-cause death and HF hospitalization at 1 year. Secondary end points were all-cause death, HF hospitalization, and cardiovascular death at 1 year. Ischemic etiology was a leading cause of HF, in both patients with advanced and nonadvanced HF (46.1% and 42.4%, respectively, p = 0.337). The risk of the primary end point (hazard ratio [HR] 1.31, 95% confidence interval [CI] 1.09 to 1.58) and all-cause mortality (HR 1.37, 95% CI 1.06 to 1.76) was increased in ischemic as compared with nonischemic patients. The risk of the primary end point was consistently higher in ischemic patients in both patients with advanced and nonadvanced HF (advanced HF, HR 1.50 95% CI 1.04 to 2.16; nonadvanced HF, HR 1.25 95% CI 1.01 to 1.56, $p_{interaction}$ = 0.333), driven by an increased risk of mortality, mainly because of cardiovascular causes. In conclusion, ischemic etiology is the most common cause of HF in patients with at least one I-NEED-HELP marker and with or without advanced HF as defined by the 2018 HFA-ESC definition. In both patients with advanced and not-advanced HF, ischemic etiology carried an increased risk of worse prognosis. **(Am J Cardiol 2023;204:268−275)**

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Heart failure (HF) is a worldwide epidemic, affecting >6 million adults in the United States alone.[1] Advanced HF (advHF) is characterized by progressive worsening of symptoms, poor quality of life, and increased risk of mortality; timely referral for advanced therapies, if indicated, should not be delayed, to improve outcomes.[2] In contrast, proper selection of patients who could truly benefit from advanced therapies is mandatory, to avoid futile and expensive treatment to end-stage patients.[3] We recently showed that the 2018 Heart Failure Association of the European Society of Cardiology (HFA-ESC) definition of advHF identifies patients with the worst prognosis in a contemporary, real-world, multicenter high-risk cohort of patients with HF presenting with at least one "I NEED HELP" high-risk marker, being encumbered by an increased risk of all-cause death or HF hospitalization at 1-year follow-up. However, more granularity might help in further improving candidate selection for long-term heart replacement therapies, such as heart transplantation or left ventricular assist device. Coronary artery disease and ischemic cardiomyopathy are highly prevalent in patients with HF and represent an important prognostic factor across all HF stages.[4] Nonetheless, the prevalence and prognostic impact of ischemic etiology on the outcome of patients fulfilling the 2018 HFA-ESC criteria for advHF is still unknown. This study aims to assess clinical characteristics and outcomes of a real-world cohort of patients with HF with at least one "I-NEED-HELP" high-risk marker,[5]

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stratified by ischemic cardiomyopathy as the primary cause of HF, and if the negative prognostic impact of ischemic etiology is maintained in patients who fulfill the 2018 HFA-ESC definition of advHF.[2]

Methods

As previously described,[6] the HELP-HF registry is an observational, retrospective, multicenter registry including 1,149 consecutive patients with acute and chronic HF evaluated at 4 Italian high-volume centers between January 1, 2020, and November 20, 2021. Included patients presented with at least 1 "I-NEED-HELP" high-risk marker[5] and details on the 2018 updated HFA-ESC criteria for advHF were collected; patient fulfilled the 2018 HFA-ESC definition of advHF if all 4 criteria were met.[2] Such criteria included: (1) severe and persistent HF symptoms; (2) severe cardiac dysfunction, defined as a left ventricular ejection fraction (LVEF) ≤30%, isolated right ventricular failure, nonoperable severe valve or congenital abnormalities, or persistently increased levels of natriuretic peptides in the context of HF with mildly reduced ejection fraction (EF) and preserved EF; (3) episodes of congestion, low output syndrome, or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last year; (4) severe impairment of exercise capacity. Institutional review board approval was waived for this registry because of its retrospective design with collection of anonymized data and without any study-specific intervention. Deidentified individual patient data on medical history, clinical presentation, echocardiography and laboratory findings, medical therapy, and clinical outcomes were collected. Congestion and perfusion status at clinical presentation were described according to available guidelines and position statements. American College of Cardiology/American Heart Association HF stage and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) class were reported.[7,8] Follow-up was performed using medical record or telephone contact.

In our study, the HELP-HF cohort was stratified according to ischemic cardiomyopathy as the primary etiology of HF. Ischemic etiology definition was based on investigator-reported ischemic HF etiology or the evidence of previous acute myocardial infarction (AMI), percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG), in the absence of any other known cause of HF. Patients with history of AMI, PCI, or CABG were included in the nonischemic group if the primary etiology of HF was reported to be different than ischemic cardiomyopathy. Stratification for fulfillment of the 2018 updated HFA-ESC definition of advHF was also performed and 4 classes of patients were identified resulting from the combination of the 2 stratifications. In ischemic patients, additional analysis stratified by history of AMI was performed.

The primary end point of the study was the composite of all-cause death or HF hospitalization at 1 year. Secondary outcomes were all-cause death, cardiovascular death, and first HF hospitalization, as individual end points, at 1 year.

Continuous variables are presented as mean ± SD or median (interquartile range) and compared with the unpaired Student's *t* test or the Mann−Whitney *U* test, based on their distribution. Normal distribution was checked for all variables using the Shapiro-Wilk test. Categorical variables are presented as numbers and percentages and were compared with the chi-square or Fisher's exact test. Cumulative incidence of the primary end point was reported using the Kaplan−Meier method and compared between groups using the log-rank test for time to the first event. For all end points, follow-up was evaluated at the date of the event or the last available follow-up, which was censored at 1 year. Cox proportional hazards regression analysis was also performed to assess the prognostic impact of ischemic etiology on the primary end point, on all-cause mortality, and cardiovascular mortality in patients fulfilling or not the 2018 HFA-ESC advHF criteria. The impact of ischemic etiology and the 2018 HFA-ESC advHF definition on the occurrence of first HF hospitalization was evaluated using the Fine-Gray hazard method to account for the competing risk of mortality and was plotted using the cumulative incidence function.

Results of the Cox regression analyses are reported as hazard ratio (HR) and 95% confidence interval (CI). Results of the Fine-Gray models are reported as sub-HR (SHR) with 95% CI. Adjusted HR (adjHR) and adjusted SHR and 95% CI in the overall cohort were calculated using multivariable Cox regression, including in the model the covariates with univariable $p < 0.10$ and others considered to be relevant according to the judgment of the investigator (e.g., age and gender).[6] The variables included in the models for each end point are listed in Supplementary Table 1. AdjHRs and 95% CI were not calculated in the subgroups of advanced and not advHF considering their limited sample size and the subsequent risk of type II error. Previous AMI, included in the multivariable model in the main analysis, was not included to avoid collinearity with ischemic etiology of HF. The proportional-hazards assumption was tested using Schoenfeld residuals. Formal interaction tests between ischemic etiology and fulfillment of the 2018 HFA-ESC advHF definition on the primary and secondary end points were performed using Cox regression. All reported p values are 2-sided, and a $p < 0.05$ was considered statistically significant. Statistical analyses were performed using STATA version 17.0 (Stata Corp., College Station, Texas).

Results

In 1,149 patients with HF with at least one "I-NEED-HELP" marker, 494 (43%) had ischemic cardiomyopathy as the primary cause of HF. Of 193 patients who met the 2018 HFA-ESC advHF definition, 89 (46.1%) had ischemic cardiomyopathy as the primary cause of HF, resulting in 4 subgroups of patients: 89 (7.8%) were classified as "ischemic-advanced," 104 (9%) as "nonischemic-advanced," 405 (35.2%) as "ischemic-not advanced" and the remaining 551 (48%) patients as "nonischemic-not advanced" (Figure 1).

As listed in Table 1, ischemic patients were more frequently male (79.6% vs 58%, $p < 0.001$) and had worse cardiovascular risk profile and kidney function (estimated glomerular filtration rate 39 [26 to 59.4] vs 44.4 [28.1 to 61.9] ml/min/1.73 m^2) than nonischemic patients. Most ischemic patients had history of myocardial

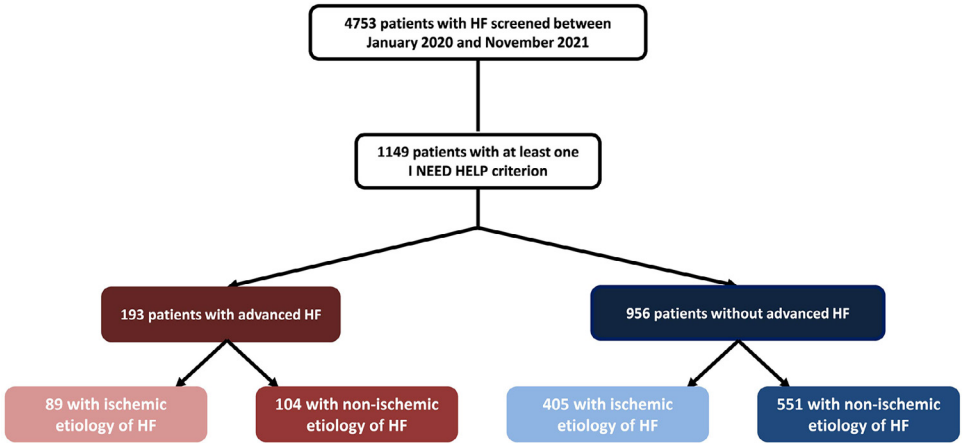

Figure 1. Study flow chart.

revascularization (PCI: 63.2%; CABG: 32.8%) and 72.5% had history of AMI; in nonischemic patients, few underwent PCI, CABG, or had a history of AMI (3.7%, 2.3%, 1.4%). HF with reduced EF (HFrEF) was more prevalent in ischemic patients (65.7% vs 49.6%) and median LVEF was lower than in nonischemic patients (32.7% [25 to 45] vs 40% [25 to 55]). Ischemic patients were more frequently treated with β blockers (82.7% vs 72.5%), whereas other classes of guideline-directed medical therapies did not differ between groups; 42.1% of ischemic patients had an implantable cardioverter defibrillator (ICD) with respect to 21.8% nonischemic patients. Clinical presentation was similar between groups: most patients were included during hospital admission (65.2% vs 69.5%); a minority of patients presented with cardiogenic shock or acute pulmonary edema at inclusion, without differences between groups.

Supplementary Table 2 lists baseline characteristics in ischemic and nonischemic patients who fulfilled the 2018 HFA-ESC definition of advHF. A higher prevalence of cardiogenic shock and pulmonary edema was noted in both groups at inclusion, as compared with the entire population. Beta blockers and angiotensin-receptor neprilysin inhibitors were more frequently prescribed in ischemic-advanced rather than nonischemic-advanced patients; no other difference in guideline-directed medical therapies was found. Baseline characteristic of patients not fulfilling the 2018 HFA-ESC definition of advHF stratified by ischemic etiology of HF are listed in Supplementary Table 3.

Median follow-up was similar between groups (267 [108 to 408] vs 252 [104 to 374] days). The primary end point occurred in 217 ischemic patients (46.6%) versus 230 nonischemic patients (35.1%) (HR 1.31, 95% CI 1.09 to 1.58, p = 0.004; Supplementary Figure 1). Both components of the primary end point occurred more frequently in ischemic than nonischemic patients, although a significant difference was observed only in terms of all-cause death (24.7% vs 18.5%, HR 1.37, 95% CI 1.06 to 1.76, p = 0.015). The assumption of proportional hazards was confirmed, as treatment effect−time interaction was not significant. A trend toward higher risk of hospitalization for HF (SHR 1.24, 95% CI 0.98 to 1.57, p = 0.074) and of cardiovascular death (16.8% vs 12.7%, HR 1.35, 95% CI 1.00 to 1.83, p = 0.054), was observed in ischemic patients as compared with nonischemic patients (Supplementary Figures 2 to 4). Ischemic patients had a trend toward shorter median time to first HF hospitalization after inclusion (183.5 [50 to 328] vs 223 [63 to 350], p = 0.075). The results were largely consistent after adjustment with Cox multivariable regression analysis: ischemic patients had an increased risk of the primary end point (adjHR 1.30, 95% CI 1.06 to 1.59, p = 0.012), and of all-cause death (adjHR 1.44, 95% CI 1.09 to 1.91, p = 0.011), whereas the risk of cardiovascular death (adjHR 1.37, 95% CI 0.97 to 1.93, p = 0.077) and first HF hospitalization (adjusted SHR 1.18, 95% CI 0.92 to 1.53, p = 0.193) did not differ in ischemic and nonischemic patients.

After stratifying for fulfillment of the 2018 HFA-ESC definition of advHF, higher occurrence of the primary end point was observed in ischemic-advanced patients rather than nonischemic-advanced patients (67.4% vs 41.6%, HR 1.50 95% CI 1.04 to 2.16, p = 0.029). Conversely, the 2 groups did not differ in terms of risk for all-cause death (41.6% vs 39.4%, HR 1.12 95% CI 0.72 to 1.74, p = 0.630), cardiovascular death (36% vs 35.6%, HR 1.06, 95% CI 0.67 to 1.71, p = 0.786) and first HF hospitalization (SHR 1.39, 95% CI 0.86 to 2.28, p = 0.178; Figure 2). The primary end point occurred more frequently also in ischemic-not advanced patients compared with nonischemic-not advanced patients (38.8% vs 31.6%, HR 1.25 95% CI 1.01 to 1.56, p = 0.040). The former group also showed an increased risk of all-cause death (21% vs 14.5%, HR 1.47, 95% CI 1.08 to 1.99, p = 0.014) and of cardiovascular death (12.6% vs 8.4%, HR 1.52, 95% CI 1.02 to 2.26, p = 0.039), whereas the cumulative incidence of first HF hospitalization was comparable (SHR 1.19, 95% CI 0.91 to 1.56, p = 0.212). No significant interaction was found in groups for all the end points (all p >0.05; Figure 3). Ischemic-advanced patients had a trend toward shorter median HF hospitalization-free days after inclusion than nonischemic-advanced patients (59, 21 to 179 vs 92, 30.5-336, p = 0.065).

In 494 ischemic patients, 358 (72.5%) had a previous AMI; of them, 75 patients (21%) fulfilled the HFA-ESC 2018 definition of advHF. In 136 ischemic patients without history of AMI, 14 (10.3%) fulfilled the HFA-ESC definition of advHF (Supplementary Table 4). The risk of the primary outcome, all-cause death, and cardiovascular death

Table 1
Baseline characteristics in the HELP-HF cohort (n=1149), stratified by ischemic etiology

	Ischemic (n=494)		Non-ischemic (n=655)		p value
Age, yo	77	(70-83)	78	(68-83)	0.870
Female, n	101	(20.5%)	275	(42%)	<0.001
Dyslipidemia, n	342	(69.3%)	267	(40.8%)	<0.001
Diabetes mellitus, n	241	(48.8%)	206	(31.5%)	<0.001
PAD, n	135	(27.3%)	70	(10.7%)	<0.001
Prior stroke/TIA, n	83	(16.8%)	90	(13.7%)	0.150
Prior AF, n	266	(53.9%)	375	(57.3%)	0.250
Prior MI, n	358	(72.5%)	22	(2.3%)	<0.001
Prior PCI, n	312	(63.2%)	24	(3.7%)	<0.001
Prior CABG, n	162	(32.8%)	9	(1.4%)	<0.001
Prior valve surgery, n	47	(9.5%)	92	(14.5%)	0.020
Prior percutaneous valve procedure, n	39	(7.9%)	41	(6.3%)	0.280
Prior myocarditis, n	1	(0.2%)	21	(3.2%)	<0.001
Prior device implantation, n	272	(55.1%)	261	(39.9%)	<0.001
Prior ICD, n	208	(42.1%)	143	(21.8%)	<0.001
Chronic kidney disease, n	322	(65.2%)	328	(50.1%)	<0.001
Dialysis, n	19	(3.9%)	9	(1.4%)	0.007
History of cancer, n	126	(25.5%)	150	(22.9%)	0.300
ADL/IADL impairment, n	154	(33.5%)	185	(29.7%)	0.190
De novo, n	62	(12.6%)	125	(19.1%)	0.003
NYHA III-IV, n	317	(64.2%)	421	(64.3%)	0.971
Cardiogenic shock, n	65	(13.2%)	88	(13.4%)	0.891
Acute pulmonary edema, n	62	(12.6%)	91	(13.9%)	0.507
Peripheral edema, n	280	(56.7%)	393	(60%)	0.258
Inpatients, n	322	(65.2%)	455	(69.5%)	0.124
IV diuretics, n	328	(66.4%)	450	(68.7%)	0.408
Inotropes/vasopressors*, n	120	(32.3%)	153	(33.6%)	0.295
Need of CRRT*, n	25	(7.8%)	20	(4.4%)	0.048
ICU admission*, n	99	(30.8%)	152	(33.4%)	0.435
Need of MCS*, n	25	(7.8%)	22	(4.8%)	0.092
Need of ventilation*, n	87	(27%)	104	(22.9%)	0.184
BMI, kg/m^2	25.6	(23-29.1)	25.8	(22.8-29.7)	0.980
SBP at inclusion, mmHg	120	(105-140)	120	(106.5-140)	0.249
MAP at inclusion, mmHg	86.7	(76.7-96.7)	86.7	(77-98.3)	0.154
HR at inclusion, bpm	72	(63-84)	77	(65-90)	<0.001
Lactate at inclusion, mmol/L	1.5	(1.1-2.3)	1.6	(1.1-2.7)	0.549
BNP, pg/ml	655	(354-1333)	593.5	(217-1208)	0.184
Hemoglobin, g/dL	11.8	(10.5-13.1)	12.2	(10.7-13.7)	0.003
GFR, ml/min/1.73 m^2	39.0	(26-59.5)	44.4	(28.1-61.9)	0.010
Max daily IV furosemide, mg†	375	(120-540)	250	(120-520)	0.496
Max inotropic score*	0	(0-3)	0	(0-2)	0.345
Length of stay, days*	10	(6-16)	10	(6-15)	0.890
Months since HF diagnosis, n	36	(6-96)	24	(1-84)	0.020
LVEF, %	32.8	(25-45)	40	(25-55)	<0.001
LVEF <40%	324	(65.7%)	325	(49.6%)	<0.001
MR moderate-to-severe, n	306	(64.2%)	377	(59.1%)	0.086
RV dysfunction, n	207	(43.9%)	275	(43.0%)	0.785
TR moderate-to-severe, n	242	(52%)	343	(54.6%)	0.399
sPAP, mmHg	45	(35-55)	45	(35-55)	0.378
TAPSE, mm	17	(14-20)	17	(15-21)	0.018
RV/PA gradient, mm/mmHg	0.35	(0.3-0.5)	0.4	(0.3-0.5)	0.020
Beta blocker, n	407	(82.7%)	475	(72.5%)	<0.001
ACEi, n	103	(21%)	142	(21.7%)	0.761
ARB, n	64	(13%)	82	(12.5%)	0.806
ARNI, n	92	(18.7%)	104	(15.9%)	0.209
MRA, n	273	(55.5%)	357	(54.5%)	0.740
SGLT2-i, n	27	(5.5%)	27	(4.1%)	0.287

* Only for inpatients.

† Only for patients receiving IV diuretics.

ACEi = ACE inhibitors; ADL = activity of daily living; AF = atrial fibrillation; ARB =angiotensin receptor blockers; ARNI = angiotensin receptor neprylisin inhibitors; BMI = body mass index; CABG = coronary artery bypass graft; CRRT = continuous renal replacement therapy; GFR = glomerular filtration rate (according to CKD-EPI equation); HR = heart rate; IADL = intermediate activity of daily living; ICU = intensive care unit; IV = intravenous; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; MCS = mechanical circulatory support; MI = myocardial infarction; MR = mitral regurgitation; MRA = mineralcorticoid receptor antagonist; NYHA = New York Heart Association class; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; RV = right ventricular; RV/PA= right ventricular to pulmonary artery; SBP = systolic blood pressure; SGLT2-i = sodium glucose contrasporter 2 inhibitor; sPAP = systolic pulmonary arterial pressure; TIA = transient ischemic attack; TR = tricuspid regurgitation.

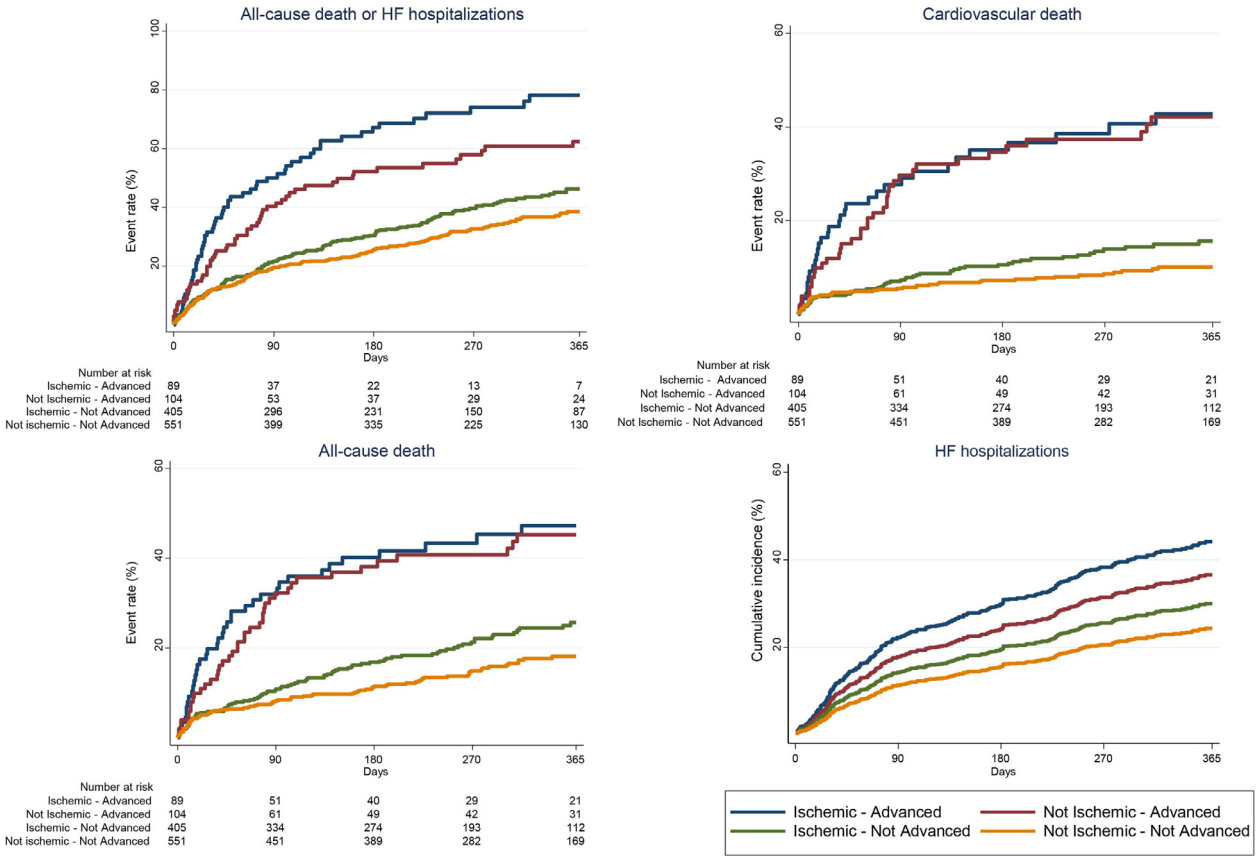

Figure 2. Outcomes stratified by the presence of ischemic cardiomyopathy as primary etiology of HF and fulfillment of the HFA and ESC 2019 updated definition of advanced HF. *SHR are reported for HF hospitalization.

was significantly increased in ischemic patients with previous AMI as compared with those without it, whereas the risk of HF hospitalization did not differ in ischemic patients with or without previous AMI. The primary outcome was consistently increased in all patients with previous AMI, whereas no difference in the risk of first HF hospitalization was observed. Adverse events during follow-up in the overall cohort and in patients fulfilling or not the ESC-HFA definition of advHF, stratified by ischemic etiology, are reported in Supplementary Tables 5 to 7.

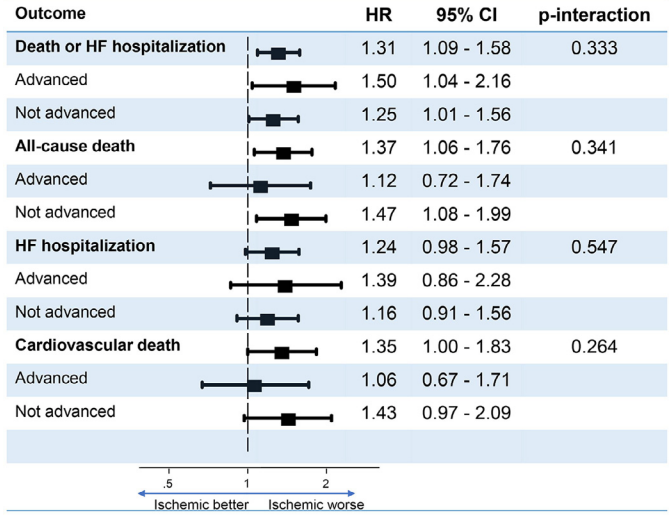

Figure 3. Forest plot for the outcomes of interest, reporting interaction between subgroups.

Discussion

The main results of this sub-analysis of the HELP-HF registry are: (1) Ischemic cardiomyopathy is the primary etiology of HF in approximately half patients with at least one high-risk I NEED HELP marker. A similar proportion was found in patients who fulfilled all criteria of the 2018 HFA-ESC definition of advHF; (2) Ischemic etiology carried an increased risk of all-cause death and HF hospitalization in both advanced and not-advanced patients according to the 2018 HFA-ESC definition.

Despite recent reduction in overall prevalence of ischemic HF, likely related to improvement in prevention and acute management of AMI and the effectiveness of long-term medical therapy, ischemic heart disease (IHD) still represents the leading etiology of HF worldwide.[9–11] In our cohort, IHD was identified as the main cause of HF in 43% of patients, and a similar prevalence was observed in patients fulfilling the updated 2018 HFA-ESC definition of advHF. Clinical characteristics in our population are in line with those reported in previous studies focused on HF because of ischemic cardiomyopathy[12] and confirm advHF as a disease of older patients.[13] Ischemic patients demonstrated an overall higher burden of risk factors and co-morbidities, as seen by increased prevalence of dyslipidemia, diabetes mellitus, peripheral artery disease, and worse kidney function. Despite comparable clinical presentation at admission, need for intensive care unit admission, and advanced support with mechanical circulatory support or ventilation, ischemic etiology was associated with worse prognosis, since the first months after the index presentation, both in terms of all-cause mortality and HF hospitalization. Our results confirm the known negative prognostic impact that IHD carries in patients with HF,[13–20] but it is worth noting it is the first time that ischemic etiology is directly evaluated in this advanced population. Multiple reasons may underlie the increased risk for adverse events in patients with IHD as primary HF etiology. First, multi-organ involvement, extensive atherosclerosis, and multi-site vascular dysfunction, and the relevant burden of co-morbidities, may expose patients to more frequent recurrence of various cardiovascular events, as appreciated also by a reduced time free from HF hospitalization. Of note, no difference in PCI, CABG, and valvular interventions after inclusion was observed; therefore, hemodynamic decompensations seem to be related to broader atherosclerotic burden and organ dysfunction, considering the higher prevalence of peripheral artery disease and worse renal function as compared with nonischemic patients, rather than repetitive coronary events. Second, several studies reported that patients with HF with IHD had limited benefit from drug and resynchronization therapy, and mitral repair in case of secondary mitral regurgitation.[15,21–24] Our results are consistent with those from several randomized trials: despite similar rate of guideline-directed medical therapy prescription, and even more frequent use of β blockers and angiotensin-receptor neprilysin inhibitors, ischemic patients have an increased risk of all-cause death and HF hospitalization. Of note, prescription rate of sacubitril-valsartan was comparable with recently published evidence,[25] whereas a small percentage of patients was treated with sodium-glucose co-transporter 2-inhibitor because of the time period in which patients were included. Therefore, the reduced prognostic impact of guideline-directed medical therapy should lead to consider ischemic patients with advHF for left ventricular assist device, heart transplantation, or palliative care earlier than their nonischemic counterparts. Third, patients with HFrEF, who are at similar[26,27] or even higher mortality risk than patients with HF with preserved EF,[28] were more prevalent in our subgroup of patients with ischemic HF. This is consistent with previous studies, showing that ischemic etiology of HF is more prevalent in HFrEF rather than in HF with preserved LVEF and impacts mostly on patients with HFrEF.[4,17] It is worth noting that a recent large-scale retrospective study that enrolled only patients fulfilling the 2018 HFA-ESC definition of advHF does not support such difference in outcomes by LVEF,[13] although HF etiology was not directly addressed: coronary artery disease was highly prevalent in such population (around 70% of patients) but was not defined whether it was just a bystander. Lastly, the higher rate of ICD recipients in ischemic patients might reflect a worse spectrum of HF, characterized by lower LVEF, possibly previous malignant arrhythmias, and wider fibrotic burden, despite differences in ICD use in the 2 subgroups may be driven by local practice[29] and its efficacy on the prevention of all-cause death, especially in nonischemic patients,[30] is debated. The impact of ischemic etiology was also evaluated after stratifying for fulfillment of the 2018 HFA-ESC definition of advHF: application and fulfillment of all 4 criteria identify a subgroup of patients at increased risk of adverse outcomes[6] and such difference is maintained also after stratifying for ischemic etiology. Ischemic-advanced patients have worse prognosis than their ischemic counterparts not fulfilling all 4 criteria. Even in patients with advHF, despite the limited sample size of this subgroup, it may be appreciated an increased risk of the primary composite outcome in those with ischemic cardiomyopathy as primary etiology of HF. Despite possible underpowering related to the small number of patients in both advanced groups, it is possible to speculate that, even once disease progresses and advHF is reached, IHD still provides increased risk for patient survival; this is likely inherent in the double burden of disease, which seems to be maintained also in this population. Lastly, in ischemic patients, those with previous AMI are at even increased risk, as a history of AMI carries a worse prognosis with respect to ischemic cardiomyopathy because of chronic coronary syndrome. Overall, our results suggest that ischemic etiology carries a negative prognosis in patients with advHF and should prompt earlier referral to advanced therapies or palliative care.

The main limitations of our study are the retrospective observational nature, absence of external outcomes adjudication, and lack of extended follow-up, which is because of the will to enroll a contemporary cohort and is mitigated by high composite event rate. Moreover, the definition of ischemic etiology was investigator-reported and excluded patients with previous coronary revascularization and/or myocardial infarction and another known cause of HF, which however may have led to a slight underestimation of prevalence and prognostic the impact of IHD in our population. In addition, the limited sample size of patients fulfilling the 2018 HFA-ESC definition of advHF may have limited the power to detect an impact for ischemic etiology

in the subgroup analysis, and of history of AMI. Lastly, the use of sodium-glucose transporter 2 inhibitors in our cohort was limited, in light of the time period in which the study was conducted.

In conclusion, in our contemporary, real-world, multicenter cohort of patients with HF with at least one high-risk "I-NEED-HELP" criterion, ischemic etiology carries a worse prognosis in terms of all-cause mortality and HF hospitalization; this impact is relevant also in the very high-risk subgroup of patients fulfilling the 2018 updated HFA-ESC definition of advHF, especially in case of history of AMI. Prompt identification and careful evaluation of such patients should be performed. Prospective studies are needed to better define the casualty of the association, potential confounders, and strategies to ameliorate outcomes of ischemic patients with advHF.

Declaration of Competing Interest

Dr. Stolfo reports personal fees from Novartis, Merck, GSK, and Acceleron outside of the submitted work. Dr. Merlo reports personal fees from Pfizer, Novartis, Novo Nordisk, and Vifor Pharma outside of the present work. Dr. Sinagra reports consulting fees from Novartis, Impulse Dynamics, and Biotronik, and speaker and honoraria from Novartis, Bayer, AstraZeneca, Boston Scientific, Vifor Pharma, Menarini, and Akcea Therapeutics outside of the submitted work. Dr. Metra received personal consulting honoraria of minimal amount from Abbott, Amgen, Bayer, Edwards Therapeutics, LivaNova, and Vifor Pharma for participation in advisory board meetings and executive committees of clinical trials. The remaining authors have no competing interests to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2023.07.114.

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