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Published in:
European Journal of Heart Failure

DOI:
10.1002/ejhf.2431

Publication date:
2022

ESC European Society of Cardiology

European Journal of Heart Failure (2022)
doi:10.1002/ejhf.2431

RESEARCH ARTICLE

Regional differences in precipitating factors of hospitalization for acute heart failure: insights from the REPORT-HF registry

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Received 7 October 2021; revised 5 January 2022; accepted 14 January 2022

Aims Few prior studies have investigated differences in precipitants leading to hospitalizations for acute heart failure (AHF) in a cohort with global representation.

Methods and results We analysed the prevalence of precipitants and their association with outcomes in 18 553 patients hospitalized for AHF in REPORT-HF (prospective international REgistry to assess medical Practice with lOngitudinal obseRvation for Treatment of Heart Failure) according to left ventricular ejection fraction subtype (reduced [HFrEF] and preserved ejection fraction [HFpEF]) and presentation (new-onset vs. decompensated chronic heart failure [DCHF]). Patients were enrolled from 358 centres in 44 countries stratified according to Latin America, North America, Western Europe, Eastern Europe, Eastern Mediterranean and Africa, Southeast Asia, and Western Pacific. Precipitants were pre-with mutually exclusive categories and selected according to the local investigator's discretion. Outcomes included in-hospital and 1-year mortality. The median age was 67 (interquartile range 57–77) years, and 39% were women. Acute coronary syndrome (ACS) was the most common precipitant in patients with new-onset heart failure in all regions except for North America and Western Europe, where uncontrolled hypertension and arrhythmia, respectively, were the most common precipitants, independent of confounders. In patients with DCHF, non-adherence to diet/medication was the most common precipitant regardless of region. Uncontrolled hypertension was a more likely precipitant in HFpEF, non-adherence to diet/medication, and ACS were more likely precipitants in HFrEF. Patients admitted due to worsening renal function had the worst in-hospital (5%) and 1-year post-discharge (30%) mortality rates, regardless of region, heart failure subtype and admission type ($p_{interaction}$ >0.05 for all).

Conclusion Data on global differences in precipitants for AHF highlight potential regional differences in targets for preventing hospitalization for AHF and identifying those at highest risk for early mortality.

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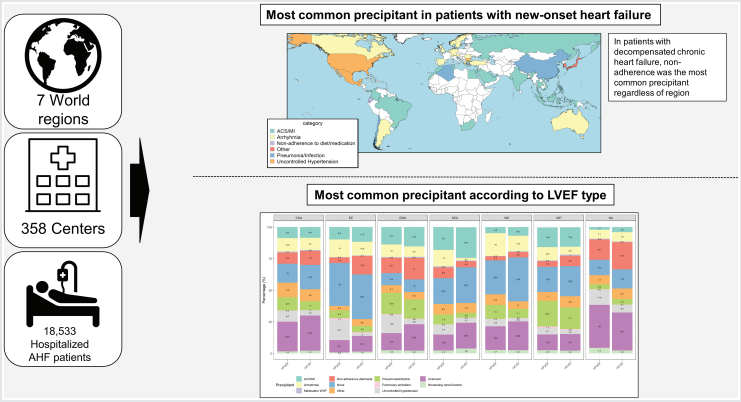
Graphical Abstract



Overview of the methods and results of this study.

Keywords Precipitants • Heart failure • Acute heart failure • HFrEF • HFpEF • Global differences

Introduction

Hospitalization for acute heart failure (AHF) is associated with significant morbidity and mortality.[1] Numerous clinical factors can precipitate hospitalization for AHF, including acute coronary syndromes (ACS)/myocardial infarction (MI), infection, uncontrolled hypertension, arrhythmias, worsening renal function (WRF) and non-adherence to medication or diet.[2–14] Knowledge of the frequency of precipitating factors is essential, as this can inform targets for prevention before hospital admission and treatment during hospitalization. Further, understanding the association between precipitants and mortality may identify a subset of patients who may require intensive management strategies during their inpatient stay.

Several studies have investigated the frequency of factors precipitating AHF hospitalization, yet these were almost exclusively from (Western) Europe and North America.[2,3,5–8,10,11,13,14] Importantly, geographic differences in precipitants according to heart failure (HF) presentation (decompensated chronic HF [DCHF] vs. new-onset HF) and left ventricular ejection fraction (LVEF) type (HF with reduced [HFrEF] vs. mildly reduced [HFmrEF] and preserved ejection fraction [HFpEF]) in patients hospitalized for AHF are poorly described.

REPORT-HF (Prospective international Registry to assess medical Practice with lOngitudinal obseRvation for Treatment of Heart Failure) is the largest prospective global AHF registry with inclusion from 44 countries across seven world regions. REPORT-HF is thus uniquely positioned to investigate (i) geographic differences in precipitants leading up to hospitalization for AHF, and (ii) the association with HF outcomes. Therefore, this study aims to investigate geographic differences in precipitants of AHF and their association with in-hospital and 1-year all-cause mortality according to LVEF subtype and HF presentation.

Methods

Study design and population

The study population is derived from REPORT-HF. The rationale and design of the REPORT-HF registry have been previously described.[15–17] In short, REPORT-HF was a large, well-characterized global cohort of patients hospitalized for AHF, with either new-onset (first diagnosis) HF or DCHF, as assessed by the clinician/investigator. Patients were excluded if they participated in another clinical trial related to any investigational treatments or did not provide informed consent. A total of 358 hospitals from 44 countries in seven world regions participated in the REPORT-HF registry. Enrolment was completed between 23 July 2014 and 24 March 2017.

This study was performed in accordance with the Declaration of Helsinki.[18] At each participating site, the protocol was approved by either the institutional review board, the ethics committee, or both. Written informed consent was obtained from all patients or a legal representative if permitted.

Definitions and study outcomes

For the current study, the case report form (CRF) asked the investigators to choose from 12 different answers on precipitating factors: ACS/MI, arrhythmias, uncontrolled hypertension, non-adhering to diet, non-adhering to prescribed medications, prescription of medications likely to worsen HF, pneumonia/respiratory tract infection, pulmonary embolism, WRF, other, none, and unknown. Patients listed as non-adhering to diet (n = 621), or medication (n = 999) were combined into one non-adherence group. Data on precipitants was missing in 750 (4%) patients. We combined these patients together with 2918 patients, which had precipitant selected as 'unknown' in the CRF, as a single category. The pre-defined precipitant categories were selected according to the physician investigator's clinical judgement.

These categories, while pre-defined and mutually exclusive, did not include specific quantitative measurements, e.g. there were no specific creatinine/glomerular filtration rate measurements to qualify for 'worsening renal function', nor specific blood pressure measurements to qualify for 'uncontrolled blood pressure'.

Patients with an LVEF of <40% were classified as HFrEF, LVEF of 40%–49% as HFmrEF, and an LVEF of ≥50% as HFpEF. Based on a modified version of the World Health Organization classification, participating countries were stratified into seven regions: Western Europe, Eastern Europe, Western Pacific, Southeast Asia, North America, Central and South America, and Eastern Mediterranean Region and Africa.

Follow-up information was collected at 6 and 12 months after hospital discharge via regular follow-up visits or telephone interviews. Local investigators were asked to ascertain the cause of death and indicate if it either was due to a cardiovascular, non-cardiovascular, or unknown cause. Data on post-discharge mortality were supplemented with locally available death records. The outcomes of interest were in-hospital and 1-year post-discharge mortality.

Statistical analysis

Comparisons of demographic and clinical parameters among HF precipitants or regions were made using χ^2 tests for categorical variables and analysis of variance for continuous variables. Categorical variables were described as numbers and percentages, and continuous variables were expressed as means ± standard deviation or median (25th and 75th percentiles) depending on their distribution. Cox proportional hazards models were used to calculate unadjusted hazard ratios. The precipitating factor with the lowest hazard ratio for the chosen outcome (risk nadir) was used as a reference. Multivariable models were selected based on expert knowledge. The model for 1-year post-discharge mortality included age, sex, hypertension, atrial fibrillation, chronic obstructive pulmonary disease/asthma, chronic kidney disease, coronary artery disease, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), LVEF category (HFrEF, HFmrEF, HFpEF, missing), HF diagnosis (new-onset vs DCHF), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers at discharge, mineralocorticoid receptor antagonists at discharge, beta-blockers at discharge, diuretics at discharge and geographic region. The model for in-hospital mortality included age, sex, hypertension, atrial fibrillation, chronic obstructive pulmonary disease/asthma, chronic kidney disease, coronary artery disease, CABG, PCI, LVEF category, HF diagnosis, systolic blood pressure at admission, heart rhythm at admission and geographic region. We tested for interaction between precipitant and LVEF subtype (HFrEF, HFmrEF, HFpEF) and presentation (new-onset HF vs. DCHF). A two-sided p-value <0.05 was considered statistically significant. Stata SE16 (StataCorp. 2017. Stata Statistical Software: Release 17; StataCorp LLC, College Station, TX, USA) was used for statistical analyses.

Results

Baseline characteristics

The population median age was 67 (interquartile range 57–77) years, and 39% were women. In total, 20% of patients had an unknown precipitant, and 23% had no precipitant. Among known precipitants, ACS was most frequently reported (13%), followed by pneumonia and respiratory tract infection (10%), and arrhythmia (10%). Medication likely to worsen HF (<1%) and pulmonary embolism (<1%) were least frequently reported as precipitant.

Table 1 shows the baseline characteristics according to the most likely precipitant. Patients with arrhythmia as precipitating factor were the oldest, and those with non-adherence to diet or medications were the youngest. Patients with pulmonary embolism as precipitant were more likely in New York Heart Association class III/IV at discharge than patients with other precipitants. Dyspnoea at rest was most common in patients with pulmonary embolism. Orthopnoea occurred most frequently in admitted with non-adherence to diet/medication, peripheral oedema was most common in patients with WRF, and rales were most common in patients with pneumonia/infection.

New-onset heart failure versus decompensated chronic heart failure

In total, 7902 (43%) patients were admitted with new-onset HF, and 10 651(57%) patients had DCHF. *Figure 1A* shows that patients with new-onset HF most frequently presented with ACS/MI (18%), arrhythmias (11%), and uncontrolled hypertension (8%). Patients with DCHF were mostly admitted due to non-adherence to diet/medication (12%) or pneumonia/respiratory tract infection (10%). Multivariable analyses adjusting for age, sex, hypertension, atrial fibrillation, chronic obstructive pulmonary disease/asthma, chronic kidney disease, coronary artery disease, region and LVEF subtype (online supplementary *Table S1*) show that patients admitted with ACS/MI, arrhythmia, uncontrolled hypertension, pneumonia/infection, or pulmonary embolism had a significantly higher odds ratio for having new-onset HF (p for all <0.05). Patients admitted for non-adherence to diet/medication or medication that can cause or worsen HF had a significantly higher odds ratio for having DCHF (p for all <0.05).

Online supplementary *Table S2* shows the number and percentages of precipitants stratified by region and presentation (new-onset HF vs. DCHF). Having ACS/MI as a precipitant was most common in patients with new-onset HF from the Western Pacific (21%) region, Eastern Mediterranean or African region (22%) and Southeast Asia (27%). Arrhythmia as precipitant was most common in patients with new-onset HF from Eastern (16%) and Western (18%) Europe. Non-adherence to diet or pharmacotherapy was a more common reason for admission in patients with DCHF from Southeast Asia (14%), the Eastern Mediterranean or African region (18%), and North America (23%). Pneumonia or respiratory tract infection was a common precipitant in patients from the Eastern Mediterranean or African region with DHCF (16%) and new-onset HF (13%) and in patients from the Western Pacific with DCHF (20%) and new-onset HF (16%).

Precipitants according to left ventricular ejection fraction subtype

In total, 8904 (48%) patients were admitted with HFrEF, 2871 (16%) patients with HFmrEF and 5168 (28%) patients with HFpEF. *Figure 1B* suggests uncontrolled hypertension was a more likely

Table 1 Baseline characteristics according to most likely precipitant

	ACS/MI	Pneumonia/ infection	Arrhythmia	Non-adherence diet/meds	Other	Uncontrolled hypertension	Worsening renal function	Medication WHF	Pulmonary embolism	None	Unknown
n (%)	2346 (13)	1800 (10)	1776 (10)	1620 (9)	1283 (7)	1112 (6)	423 (2)	112 (<1)	93 (<1)	4320 (23)	3668 (20)
Age, years, median (IQR)	66 (58–75)	69 (58–79)	71 (61–79)	63 (54–72)	66 (54–76)	66 (57–76)	67 (58–75)	68 (56–77)	67 (52–77)	67 (57–77)	68 (58–77)
Race, *n* (%)											
Caucasian	902 (38)	793 (44)	1172 (66)	799 (49)	618 (48)	579 (52)	163 (39)	60 (54)	48 (52)	2528 (59)	1994 (54)
Black	38 (2)	48 (3)	37 (2)	189 (12)	57 (4)	113 (10)	34 (8)	3 (3)	1 (1)	100 (2)	247 (7)
Asian	1184 (50)	730 (41)	360 (20)	370 (23)	431 (34)	256 (23)	166 (39)	37 (33)	36 (39)	1338 (31)	830 (23)
Native American	35 (1)	27 (2)	40 (2)	44 (3)	30 (2)	36 (3)	21 (5)	1 (1)	0 (0)	60 (1)	81 (2)
Pacific Islander	2 (<1)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)
Other	185 (8)	202 (11)	165 (9)	217 (13)	147 (11)	128 (12)	39 (9)	11 (10)	8 (9)	292 (7)	516 (14)
DCHF, *n* (%)	1403 (60)	715 (40)	845 (48)	357 (22)	490 (38)	625 (56)	153 (36)	30 (27)	51 (55)	1874 (43)	1359 (37)
NYHA class at discharge, *n* (%)											
I	414 (18)	180 (10)	203 (12)	180 (11)	136 (11)	212 (19)	30 (7)	18 (16)	7 (8)	304 (7)	338 (9)
II	826 (36)	725 (42)	583 (33)	636 (40)	382 (31)	379 (34)	128 (32)	36 (33)	27 (30)	1173 (28)	860 (24)
III	312 (14)	314 (18)	270 (15)	284 (18)	201 (16)	158 (14)	65 (16)	21 (19)	22 (24)	877 (21)	462 (13)
IV	103 (4)	47 (3)	41 (2)	41 (3)	37 (3)	30 (3)	17 (4)	4 (4)	6 (7)	172 (4)	127 (4)
Missing/unknown	637 (28)	467 (27)	651 (37)	446 (28)	487 (39)	322 (29)	163 (40)	31 (28)	28 (31)	1693 (40)	1789 (50)
LVEF subtype, *n* (%)											
<40	1095 (47)	800 (44)	737 (41)	941 (58)	661 (52)	316 (28)	212 (50)	61 (54)	37 (40)	2183 (51)	1861 (51)
≥40 and <50	537 (23)	273 (15)	287 (16)	204 (13)	166 (13)	175 (16)	62 (15)	17 (15)	15 (16)	635 (15)	500 (14)
≥50	526 (22)	579 (32)	644 (36)	365 (23)	370 (29)	509 (46)	115 (27)	27 (24)	38 (41)	1130 (26)	865 (24)
Unknown	188 (8)	148 (8)	108 (6)	110 (7)	86 (7)	112 (10)	34 (8)	7 (6)	3 (3)	372 (9)	442 (12)
Heart rate, bpm, median (IQR)	88 (75–100)	88 (76–102)	100 (78–125)	87 (75–100)	84 (71–100)	87 (74–101)	81 (71–98)	82 (72–95)	90 (80–108)	83 (71–99)	85 (72–100)
Systolic blood pressure, mmHg, median (IQR)	130 (116–150)	130 (111–146)	130 (112–145)	130 (110–148)	123 (110–140)	168 (144–190)	132 (113–160)	130 (110–140)	120 (110–140)	130 (110–146)	128 (110–147)
Diastolic blood pressure, mmHg, median (IQR)	80 (70–90)	77 (67–88)	80 (70–90)	80 (69–90)	72 (64–83)	92 (80–106)	78 (65–90)	77 (65–85)	76 (70–90)	78 (69–89)	76 (65–87)
Signs and symptoms, *n* (%)											
Dyspnoea at rest	1789 (83)	1464 (86)	1287 (80)	1264 (87)	902 (82)	866 (87)	327 (86)	80 (80)	77 (93)	3149 (80)	2404 (83)
Orthopnoea	1433 (73)	1282 (85)	1132 (77)	1171 (86)	744 (75)	740 (81)	274 (80)	74 (80)	58 (73)	2728 (76)	1998 (77)
Peripheral oedema	1114 (52)	1170 (70)	1170 (70)	1207 (78)	804 (69)	695 (68)	309 (78)	81 (74)	60 (71)	2632 (70)	2163 (71)
Pulmonary rales	1333 (68)	1312 (82)	1072 (70)	1008 (70)	661 (63)	700 (71)	249 (71)	70 (72)	45 (59)	2140 (62)	1693 (63)
Medical history, *n* (%)											
Hypertension	1495 (64)	1126 (63)	1167 (66)	1061 (65)	714 (56)	1016 (91)	300 (71)	68 (61)	55 (59)	2572 (60)	2234 (61)
Atrial fibrillation/flutter	304 (13)	584 (32)	1185 (67)	492 (30)	361 (28)	201 (18)	108 (26)	43 (38)	22 (24)	1345 (31)	1121 (31)
COPD/asthma	237 (10)	426 (24)	223 (13)	258 (16)	184 (14)	169 (15)	58 (14)	12 (11)	16 (17)	560 (13)	512 (14)
Anaemia	1141 (49)	879 (49)	702 (40)	831 (51)	737 (57)	515 (46)	336 (79)	66 (59)	39 (42)	1922 (45)	1561 (43)
Valvular heart disease	148 (6)	372 (21)	502 (28)	355 (22)	411 (32)	145 (13)	83 (20)	32 (29)	11 (12)	983 (23)	637 (17)
Coronary artery disease	2346 (100)	790 (44)	599 (34)	721 (45)	486 (38)	387 (35)	202 (48)	46 (41)	26 (28)	1822 (42)	1504 (41)
Diabetes	1103 (47)	700 (39)	484 (27)	639 (39)	441 (34)	477 (43)	250 (59)	49 (44)	25 (27)	1537 (36)	1362 (37)
CKD	362 (15)	351 (20)	300 (17)	325 (20)	267 (21)	245 (22)	276 (65)	22 (20)	18 (19)	845 (20)	755 (21)
Medication at discharge, *n* (%)											
ACEi/ARB/ARNi	1504 (66)	1090 (64)	1191 (68)	1079 (68)	768 (62)	851 (78)	161 (40)	75 (68)	58 (64)	2824 (67)	2295 (64)
MRA	956 (42)	884 (52)	848 (49)	833 (53)	636 (52)	374 (34)	93 (23)	49 (45)	50 (56)	2382 (57)	1747 (49)
Beta-blockers	1573 (69)	1131 (66)	1343 (77)	1202 (76)	866 (70)	791 (72)	252 (63)	75 (68)	60 (67)	3119 (74)	2631 (74)
Diuretics	1600 (70)	1440 (84)	1453 (83)	1432 (90)	1064 (86)	869 (79)	327 (82)	99 (90)	69 (77)	3739 (89)	3061 (86)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin type II receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DCHF, decompensated chronic heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

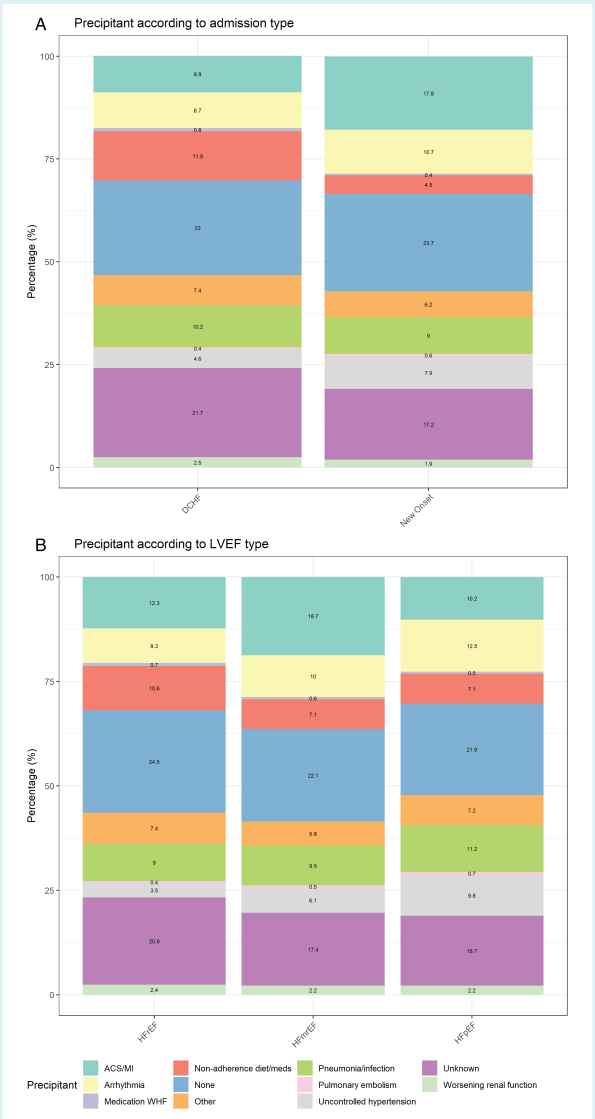


Figure 1 Stacked bar charts depicting percentages of precipitant stratified by admission type (*A*) and heart failure subgroup (*B*). ACS, acute coronary syndrome; DCHF, decompensated chronic heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; WHF, worsening heart failure.

precipitant in HFpEF than HFrEF (10% vs. 4%). In multivariable analyses (online supplementary *Table S1*), patients with HFpEF more commonly had arrhythmia, uncontrolled hypertension, pneumonia or infection and pulmonary embolism as likely precipitants than patients with HFrEF.

Online supplementary *Table S3* shows differences in precipitants according to geographic region and LVEF subtype. ACS/MI was most common in patients with HFmrEF (22%) from the Eastern Mediterranean or African region and patients with HFrEF (24%) or HFmrEF (43%) from Southeast Asia. Arrhythmia as precipitating factor was most common in patients with HFpEF from Western Europe (18%). Non-adherence to diet or medication as precipitant was most common in patients with HFrEF from North America (22%). Pneumonia and infection were more prevalent in the Western Pacific and Eastern Mediterranean or African region, regardless of LVEF subtype.

In-hospital and post-discharge mortality

In total, 451 patients (2.4%) died in hospital. Among 18 102 patients discharged alive, 470 were lost to follow-up, and 3461 (20%) died. *Figure 2* depicts the in-hospital mortality and post-discharge mortality according to precipitant. The cumulative mortality at 1 year was lowest in patients admitted with uncontrolled hypertension and highest in patients with WRF. *Table 2* suggests the in-hospital mortality was lowest in patients hospitalized with uncontrolled hypertension (1%). Patients hospitalized for WRF had the highest in-hospital mortality (5%). Patients hospitalized with pneumonia/infection had an in-hospital mortality rate of 4%. These differences remained statistically significant after correcting for confounders. We did not find a statistically significant interaction between precipitant and geographic region for in-hospital or 1-year post-discharge mortality ($p_{interaction}$ >0.05 for both), suggesting that the association of precipitants with mortality was similar across geographic regions.

The 1-year post-discharge mortality incidence in *Table 2* ranged from 14.2 (95% confidence interval [CI] 12.0–16.7) per 100 patient-years for patients admitted with uncontrolled hypertension to 37.5 (95% CI 31.4–44.9) per 100 patient-years for patients admitted due to WRF. After correction for confounders, relative differences remained highly significant: compared with patients hospitalized with uncontrolled hypertension, patients hospitalized with ACS/MI, non-adherence to diet/medication and WRF had worse 1-year mortality.

Discussion

In this detailed global analysis on the frequency of precipitants for AHF and their association with post-discharge mortality according to region, LVEF subtype, and HF admission type, we found (i) important regional variations in the frequency of precipitants according to LVEF subtype and HF presentation, a significant proportion of which could be mitigated with outpatient surveillance and treatment; and (ii) the type of precipitant was significantly associated with in-hospital and post-discharge mortality (*Graphical Abstract*). Together, our results identify regional specific treatment targets to prevent HF admission and premature death potentially.

Previous reports on the frequency and association with mortality precipitants for patients hospitalized for AHF were predominantly from North America,[2,3,6–8,12,13] and Western Europe.[4,5,9–12,14] Despite being home to most of the world's population, limited studies investigated precipitants to AHF according to LVEF subtype and HF presentation in Asia or the Eastern Mediterranean and African region. Our data suggest ACS/MI is the most common precipitant for AHF regardless of geographic region. Close to a quarter of new-onset HF patients from Southeast Asia and

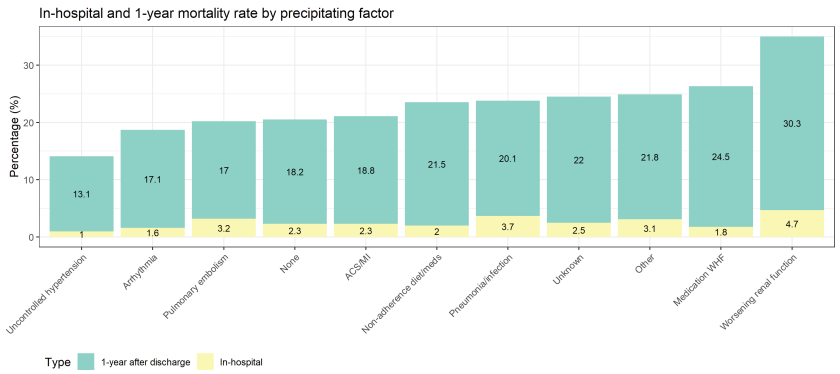


Figure 2 Bar charts depicting prevalence of in-hospital and 1-year post-discharge mortality, stratified by precipitating factor. ACS, acute coronary syndrome; MI, myocardial infarction; WHF, worsening heart failure.

Table 2 Association with in-hospital and 1-year mortality

In-hospital mortality			
	***n* (%)**	**Univariable OR (95% CI) *p*-value**	**Multivariable OR (95% CI) *p*-value**
Uncontrolled hypertension	11 (1.0)	Ref.	Ref.
ACS/MI	54 (2.3)	2.36 (1.23–4.53) 0.010	1.61 (0.82–3.15) 0.165
Arrhythmia	28 (1.6)	1.60 (0.80–3.23) 0.187	0.92 (0.44–1.91) 0.828
Non-adherence med/diet	33 (2.0)	2.08 (1.05–4.14) 0.036	1.23 (0.61–2.49) 0.565
Medication worsening HF	2 (1.8)	1.82 (0.40–8.32) 0.440	1.07 (0.23–4.95) 0.933
Pneumonia/infection	67 (3.7)	3.87 (2.04–7.35) <0.001	2.32 (1.20–4.50) 0.013
Pulmonary embolism	3 (3.2)	3.34 (0.91–12.18) 0.068	2.29 (0.62–8.50) 0.217
WRF	20 (4.7)	5.00 (2.36–10.46) <0.001	2.50 (1.16–5.41) 0.019
Other	40 (3.1)	3.22 (1.64–6.31) 0.001	1.62 (0.81–3.23) 0.175
None	101 (2.3)	2.40 (1.28–4.48) 0.006	1.43 (0.75–2.73) 0.280
Unknown	92 (2.5)	2.56 (1.37–4.83) 0.003	1.31 (0.68–2.51) 0.417
1-year post-discharge mortality			
	Deaths per 100 py (95% CI)	**Univariable HR (95% CI) *p*-value**	**Multivariable HR (95% CI) *p*-value**
Uncontrolled hypertension	14.2 (12.0–16.7)	Ref.	Ref.
ACS/MI	21.3 (19.4–23.5)	1.49 (1.24–1.81) <0.001	1.30 (1.07–1.58) 0.009
Arrhythmia	19.2 (17.1–21.5)	1.35 (1.10–1.65) 0.004	1.12 (0.91–1.39) 0.268
Non-adherence med/diet	24.6 (22.0–27.4)	1.72 (1.41–2.09) <0.001	1.30 (1.07–1.60) 0.010
Medication worsening HF	28.8 (19.6–42.2)	2.01 (1.32–3.05) 0.001	1.52 (0.99–2.32) 0.050
Pneumonia/infection	22.9 (20.5–25.4)	1.60 (1.32–1.95) <0.001	1.21 (0.98–1.48) 0.072
Pulmonary embolism	19.2 (11.6–31.8)	1.35 (0.79–2.30) 0.272	1.29 (0.76–2.21) 0.344
WRF	37.5 (31.4–44.9)	2.60 (2.04–3.33) <0.001	1.62 (1.26–2.09) <0.001
Other	25.0 (22.2–28.3)	1.75 (1.43–2.15) <0.001	1.34 (1.09–1.66) 0.006
None	20.5 (19.1–22.0)	1.44 (1.20–1.72) <0.001	1.20 (0.99–1.44) 0.058
Unknown	25.4 (23.7–27.3)	1.77 (1.48–2.13) <0.001	1.31 (1.09–1.58) 0.004

ACS, acute coronary syndrome; CI, confidence interval; HF, Heart failure; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio; py, patient-years; WRF, worsening renal function.
Multivariable model: age, sex, hypertension, atrial fibrillation, copd/asthma, chronic kidney disease, coronary artery disease, ACEi/ARB at discharge, MRAs at discharge, beta-blockers at discharge and diuretics at discharge.

the Eastern Mediterranean and African region were admitted with ACS/MI, compared to only 7% in Western Europe or 6% in North America. Differences in risk factors and access to high quality care might explain this finding. Risk factors like smoking and hypertension are increasing in prevalence in Southeast Asia and Northern Africa.[19,20] The PURE registry showed that revascularization and treatment for coronary artery disease were less common in lower-income regions, especially in Southeast Asia, possibly precipitating new-onset HF due to untreated and unrecognized ACS/MI.[21] Together, this suggests that preventative measures targeting atherosclerosis like smoking cessation or statins could also prevent hospitalizations for AHF in these regions. Our data suggest cardiac arrhythmia is a common precipitant for patients being admitted for new-onset HF, especially in regions like Western Europe with a high prevalence of atrial fibrillation[17] and elderly patients. This suggests that interventions targeting arrhythmias, like remote monitoring with hand-held devices or smart watches, might be beneficial. Uncontrolled hypertension was common in patients with new-onset HF from North America. The large proportion of African Americans (~50%) enrolled in North America in REPORT-HF, in whom hypertension is a particularly important issue,[22] likely explains this observation. Therefore, more aggressive treatment of hypertension in these patients might prevent or delay acute hospitalization for HF. Close to a quarter of patients in North America with DCHF and 18% of patients in the Eastern Mediterranean or African region were admitted due to non-adherence to diet or medication, highlighting significant areas for improving HF self-care care and education. Our previous study highlighted that non-adherence to diet/medication was a substantial issue in African-Americans.[22] Pneumonia/respiratory tract infection was a common precipitant in the Eastern Mediterranean or North African region and the Western Pacific. This observation might be explained by regional differences in strategies regarding preventive medicine, including flu vaccination.[23]

To our knowledge, this is the first global report on differences in precipitants according to LVEF subtype. A previous study from the Get With The Guidelines-HF (GWTG-HF) database found pneumonia was relatively common among patients with HFpEF and was associated with a longer in-hospital stay.[8] Consistent with findings from the GWTG-HF[8] study, patients with HFrEF were frequently admitted due to non-adherence. Similar to results from the CHARM programme, uncontrolled hypertension was a more critical precipitant in patients with HFpEF than HFrEF.[12]

Differences in precipitants were associated with in-hospital and post-discharge mortality. The cumulative (in-hospital and post-discharge) mortality ranged from 13% in patients with uncontrolled hypertension to 30% in patients with WRF. These results confirm findings from previous studies in North America and Western Europe.[2,8,9,14,24] In OPTIMIZE-HF, uncontrolled hypertension was associated with the lowest mortality and patients with ACS/MI or WRF had the worst mortality.[2] In BIOSTAT-CHF, WRF was most strongly associated with a composite of all-cause death or hospitalisation for HF.[14] We extend these previous results to all global regions included in REPORT-HF: we did not find a significant interaction between precipitants and region, precipitants and LVEF subtype, or precipitants and HF presentation, for in-hospital or 1-year mortality. Our results suggest a unifying global message to identify precipitants amenable to outpatient interventions. A considerable proportion of precipitants in REPORT-HF could be addressed with preventative strategies, including ACS/MI, non-adherence to diet/medication and pneumonia/respiratory tract infection. In many lower-income regions in REPORT-HF, like Southeast Asia, the Western Pacific and the Eastern Mediterranean or Africa, these possibly amenable precipitants constituted a significant proportion of cases, highlighting the unmet need for improved treatment and prevention of hospitalization for AHF.

Study limitations

Our findings describe important global patterns concerning precipitants and their association with in-hospital and post-discharge mortality. However, they should be interpreted considering the following limitations. There is a possible selection bias of the participating sites. Furthermore, patients had to provide informed consent. Sicker patients might not have been included in this registry, which might explain the low in-hospital mortality rates. Patients could be hospitalized due to more than one precipitant. The local investigator determined the main precipitant. Lastly, a significant proportion of precipitants were either classified as 'unknown' or 'none'. This might reflect differences in local documentation or could be a consequence of the study protocol only allowing one precipitant.

Conclusion

Precipitants for AHF hospitalizations vary by region and according to HF presentation (DCHF vs. new-onset HF) and LVEF subtype. ACS, pneumonia or respiratory tract infection and uncontrolled hypertension were common precipitants in patients with new-onset HF globally, especially in Southeast Asia and the Eastern Mediterranean or Africa region. In HFpEF, uncontrolled hypertension was more common than in HFrEF. Precipitants significantly predicted in-hospital and post-discharge mortality globally, irrespective of HF presentation or LVEF subtype. Knowledge of modifiable risk factors precipitating hospitalization for AHF highlights possible region-specific targets for preventing AHF hospital admission and prevention of early mortality.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Funding

The REPORT-HF registry steering committee and investigators thank Novartis for their generosity in funding this large observational registry. J.T is suppored by the National University of Singapore Start-up grant and the Ministry of Education Tier one grant.

Conflict of interest: J.T. reports consultancy fees from Boehringner Ingelheim, Roche diagnostics, Daiichi Sankyo and

Us2.ai; he serves as scientific advisor to Us2.ai and holds a patent (US-10702247-B2) unrelated to the present manuscript. J.G.F.C. reports grants and personal fees from Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Philips, Stealth Biopharmaceuticals, and Torrent Pharmaceuticals; grants, personal fees, and non-financial support from Medtronic, Novartis, and Vifor; personal fees from Myokardia, Sanofi, Servier, and Abbott; and grants and non-financial support from Pharmacosmos and PharmaNord. C.E.A. reports grants and personal fees from Novartis; she further acknowledges non-financial support from the University Hospital Würzburg and the Comprehensive Heart Failure Center Würzburg, and grant support from the German Ministry for Education and Research. U.D. reports research support from AstraZeneca, Pfizer, Boehringer Ingelheim, Vifor, Roche Diagnostics and Boston Scientific and speaker's honoraria and consultancies from AstraZeneca, Novartis and Amgen. M.H. received honoraria as a lecturer from Novartis, Aventis, Amgen, Merck Sharp & Dohme, AstraZeneca, and Merck. S.V.P. reports personal fees from Laboratorios Bago, Laboratorios Ferrer, Abbott–St Jude, Novartis, United Therapeutics, Janssen Cilag, and Servier; and grants from Tecnologia Disruptiva San Pablo. M.G., A.S., and A.O. are or were employed by Novartis. G.F. reports research grants from the EU; committee fees from Novartis related to REPORT-HF; and committee member in trials or registries, sponsored by Servier, Boehringer Ingelheim, Medtronic and Vifor. S.P.C. reports research grants from National Institutes of Health, Agency for Healthcare Research and Quality, American Heart Association, Patient-Centered Outcomes Research Institute and consulting fees from Novartis, Medtronic, Vixiar, and Ortho Clinical. C.S.P.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the advisory board, steering committee, or executive committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, Cytokinetics, WebMD Global, Radcliffe Group, and Corpus; and serves as cofounder and non-executive director of eKo.ai. All other authors have nothing to disclose.

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