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RESEARCH ARTICLE

Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry

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Aims Several clinical conditions may precipitate acute heart failure (AHF) and influence clinical outcome. In this study we hypothesized that precipitating factors are independently associated with 90-day risk of death in AHF.

Methods and results The study population consisted of 15 828 AHF patients from Europe and Asia. The primary outcome was 90-day all-cause mortality according to identified precipitating factors of AHF [acute coronary syndrome (ACS), infection, atrial fibrillation (AF), hypertension, and non-compliance]. Mortality at 90 days was 15.8%. AHF precipitated by ACS or by infection showed increased 90-day risk of death compared with AHF without identified precipitants [hazard ratio (HR) 1.69, 95% confidence interval (CI) 1.44–1.97, $P < 0.001$; and HR 1.51, 95% CI 1.18–1.92, $P = 0.001$), while AHF precipitated by AF showed lower 90-day risk of death (HR 0.56, 95% CI 0.42–0.75, $P < 0.001$), after multivariable adjustment. The risk of death in AHF precipitated by ACS was the highest during the first week after admission, while in AHF precipitated by infection the risk of death had a delayed peak at week 3. In AHF precipitated by AF, a trend toward reduced risk of death during the first weeks was shown. At weeks 5–6, AHF precipitated by ACS, infection, or AF showed similar risk of death to that of AHF without identified precipitants.

Conclusions Precipitating factors are independently associated with 90-day mortality in AHF. AHF precipitated by ACS or infection is independently associated with higher, while AHF precipitated by AF is associated with lower 90-day risk of death.

Keywords Acute heart failure • Precipitating factor • Mortality • Outcome • Acute coronary syndrome • Atrial fibrillation

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Introduction

Despite major achievements in the treatment of chronic heart failure (HF) with marked improvement in survival, the management of acute heart failure (AHF) remains challenging.[1] One possible explanation of the persistently high mortality in AHF is its phenotypic heterogeneity. AHF is a syndrome defined by changes in symptoms and/or signs of HF, rather than a specific disease.[2] Several conditions are recognized to precipitate AHF, including acute coronary syndrome (ACS), atrial fibrillation (AF), infections, uncontrolled arterial hypertension, and lack of compliance with dietary and drug prescriptions.[3]

Current recommendations for the management of HF advise identification of precipitants of AHF in order specifically to treat the cause(s) of the acute episode (e.g. revascularization for ACS, antiarrhythmic treatment for AF, antimicrobial drugs for infections).[1,4] In marked contrast, decisions about intensity of monitoring and therapy (e.g. patient allocation in a normal ward or an intensive care unit) are rather based on haemodynamic parameters and/or biomarkers with little regard to the underlying precipitants.[1,4]

It is still a matter of debate whether ascertaining precipitating factors of AHF identify patients at particularly high risk of unfavourable outcome in need of more intensive monitoring and therapy. It is equally unknown whether specific precipitants independently affect outcome of AHF patients.[3,5] The aim of the present study was to test the hypothesis that precipitating factors of AHF independently predict the 90-day risk of death of patients admitted for AHF in a large, intercontinental cohort.

Methods

Study population and outcome

The study population is derived from the GREAT registry, an international, prospective observational cohort of 20 598 adult patients with AHF as the main diagnosis for hospital admission. Details on the constitution of the GREAT registry have been previously described.[6] AHF—both new-onset HF and acutely decompensated HF—was defined according to the definition of the European Society of Cardiology (ESC).[4] A total of 4770 patients (23%) included in GREAT were excluded from the present analysis because they were missing data on vital status during 90 days after admission or precipitating factors of AHF. The study population was composed of 15 828 AHF patients from a total of seven countries in both Europe (Czech Republic, Italy, Spain) and Asia (China, Japan, Saudi Arabia, and South Korea) (*Figure 1*).

The primary outcome of the study was 90-day all-cause mortality. Six distinct classes of precipitating factors were considered: ACS, infection, AF, hypertension, non-compliance, and no identified precipitating factor. Patients were assigned to one or more precipitating factors by the treating physicians according to the initial clinical presentation.

The following definitions were used: 'ACS' in the presence of ECG alterations and/or dynamic elevation of standard troponin levels, according to the criteria of the ESC;[7,8] 'infection' in the presence of fever and/or other evidence of infection at presentation (leucocytosis, elevated inflammatory parameters, clinical or microbiological evidence of infection); 'atrial fibrillation' in the presence of AF (new-onset or recurrent) with ventricular response >110/min; 'hypertension' in the presence of elevated systolic blood pressure (>160 mmHg) at presentation; and 'non-compliance' if infringements of dietary or therapeutic recommendation were reported.

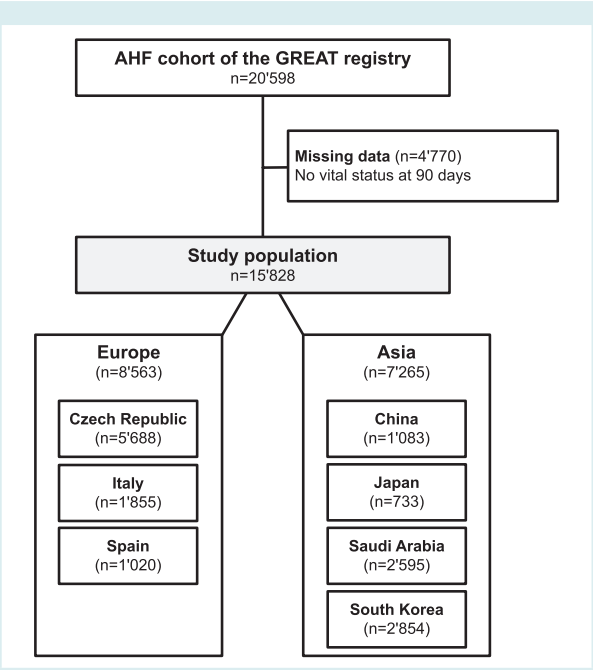

Figure 1 Flowchart of the study population. The study population consisted of a cohort of 15 828 patients with acute heart failure (AHF) for which information on precipitating factors of AHF and vital status at 90 days were available.

Statistical analysis

Values are expressed as median (interquartile range, IQR) or as number (percentage), as appropriate. Group characteristics were compared with the χ^2 test or the Kruskal–Wallis test, as appropriate. Survival was plotted with the Kaplan–Meier curve, and differences between groups were assessed by the log-rank test, with pairwise comparisons if indicated. Univariate and covariate-adjusted Cox proportional hazards regression models were used to estimate the association between the presence of precipitating factors and the 90-day risk of death compared with the absence of identified precipitating factors. Data of patients with more than one precipitating factor were analysed separately.

The covariates included in the regression models were *a priori* selected among baseline variables with known associations with study outcomes:[6] age, gender, left ventricular ejection fraction (LVEF), co-morbidities (history of HF, CAD, diabetes), systolic blood pressure, heart rate, estimated glomerular filtration rate (eGFR), and plasma sodium at admission. The AHEAD score, based on age (≥70 years), history of AF, history of diabetes, anaemia (haemoglobin <120 g/L in women, <130 g/L in men), renal dysfunction (creatinine ≥130 μmol/L), was used to estimate the burden of co-morbidities.[9] When these data were missing, case-wise deletion for that analysis only was used.

We conducted exploratory analyses of the variation in relative hazards of death among those still alive in the cohort by time since admission. Because there was no literature upon which to base *a priori* decisions about functional forms, we used a maximally flexible approach to letting the hazard ratios (HRs) vary over time. We divided

the cohort into seven time periods, balancing roughly even numbers of events without being completely arbitrary: weekly for the first 4 weeks, then biweekly for the next 4 weeks, then combining the remaining weeks of the cohort, and estimated separate HRs for each time period. Because this was an exploratory analysis that could be interpreted in support of several different questions, no adjustment for multiple comparisons was done—as each of the different questions implies different numbers of comparisons—but instead standard confidence intervals (CIs) are reported and interpreted cautiously.

The null hypothesis was rejected with an adjusted two-sided *P*-value <0.05. All analyses were performed with the use of IBM SPSS Statistics, version 21.0 (IBM Corp, Armonk, NY, USA).

Results

Study population

The study population consisted of a cohort of 15 828 AHF patients from seven countries (*Figure 1*). The median age was 71 years and 58% were men. Medical history reported high prevalence of CAD (49%), cardiovascular risk factors (hypertension 66%, diabetes 43%), and co-morbidities (65% of patients had an AHEAD score of ≥2 points). At admission, 46% of patients reported previous history of HF; median LVEF was 38%; and median BNP and NT-proBNP were 866 and 3823 ng/L, respectively. In patients with previous history of HF 14% were in NYHA class I, 27% in NYHA class II, 40% in NYHA class III, and 19% in NYHA class IV. Ten per cent of patients were in cardiogenic shock. Other baseline characteristics of the study population are reported in *Table 1*.

Precipitating factors of acute heart failure

Precipitating factors of AHF were identified in 8784 patients (55%), while in 7044 patients (45%) no specific precipitant could be identified. One single precipitant was identified in 7764 patients (49% of the study population) while in 1020 patients (6% of the study population) a combination of two or more precipitants was identified.

Among the 7764 patients with one single identified precipitant, ACS was the most common cause ($n = 4004$, 52%), followed by AF ($n = 1228$, 16%), infection ($n = 1104$, 14%), uncontrolled hypertension ($n = 831$, 11%), and non-compliance ($n = 597$, 8%). Cardiogenic shock was more frequent in patients with ACS (13%) compared with patients with infection (6%) and non-compliance (5%) ($P < 0.001$). Notable differences in baseline characteristics between the groups of precipitating factors were present (*Table 1*). Of note, elevated plasma troponin concentrations were found in 66% of patients for whom measurement at hospital admission was available ($n = 8061$). In patients with ACS as the precipitating cause, elevated troponin was found in 71% of patients.

Precipitating factors and 90-day mortality

Figure 2 shows that among patients with only one identified precipitant, every precipitating factor was associated with strikingly different 90-day mortalities (log-rank $P < 0.001$). Notably, *Figure 2* shows that compared with patients without identified precipitants, patients admitted with AHF precipitated by ACS or infection showed higher 90-day hazard of death (HR 1.51, 95% CI 1.38–1.66, $P < 0.001$; and HR 1.40, 95% CI 1.21–1.62, $P < 0.001$, respectively). On the other end of the spectrum, patients with AHF precipitated by uncontrolled hypertension or AF showed reduced 90-day hazard of death compared with patients without an identified precipitant (HR 0.56, 95% CI 0.44–0.72, $P < 0.001$; and HR 0.72, 95% CI 0.60–0.86, $P < 0.001$, respectively). The group of patients with AHF precipitated by non-compliance showed an intermediate hazard of death, similar to those of patients without an identified precipitant (HR 0.96, 95% CI 0.77–1.21, $P = 0.74$).

After adjustment for 10 *a priori*-selected prognostic determinants (age, gender, LVEF, history of HF, CAD, diabetes, systolic blood pressure and heart rate at admission, renal function, and plasma sodium at admission), AHF precipitated by ACS or by infection showed persistent increased 90-day hazard of death compared with AHF without identified precipitants (HR 1.69, 95% CI 1.44–1.97, $P < 0.001$; and HR 1.51, 95% CI 1.18–1.92, $P = 0.001$, respectively). Furthermore, AHF precipitated by AF showed lower 90-day risk of death compared with AHF without identified precipitants (HR 0.56, 95% CI 0.42–0.75, $P < 0.001$) (*Figure 3*). The reduced risk of death associated with hypertension as a precipitating factor lost statistical significance after covariate adjustment.

Of note, AHF with more than one identified precipitating factor showed a similar outcome overall to AHF with only one precipitating factor (Supplementary material online, *Figure S1*, log-rank $P = 0.67$).

Subgroup analyses according to world area are reported in the Supplementary material online, *Table S1*. AHF precipitated by ACS was associated with increased 90-day hazard of death in both European and Asian populations, while AHF precipitated by infection was associated with a particularly bad prognosis in Asians.

Patterns of the risk of death during the first weeks after admission

The risk of death associated with different precipitating factors, compared with the absence of identified precipitants, was not homogeneous during the first weeks after admission. As shown in an exploratory analysis in *Figure 4*, the relative hazard of death in AHF precipitated by ACS was the highest during the first week after admission (HR 2.57, 95% CI 2.22–2.99, $P < 0.001$), while in AHF precipitated by infection a delayed peak of the relative hazard of death was shown at week 3 (HR 2.83, 95% CI 1.95–4.12, $P < 0.001$). Conversely, in AHF precipitated by AF, possible reduced risk of death during the first weeks after admission was shown—but that difference was not statistically significant. Notably, at weeks 5–6 and thereafter, AHF precipitated by ACS, infection, or AF showed similar risk of death to that of AHF without identified precipitants (HR 0.93, 95% CI 0.69–1.26, $P = 0.64$; HR 0.91, 95% CI 0.55–1.51, $P = 0.72$; and HR 0.90, 95% CI 0.57–1.43, $P = 0.66$, respectively, for weeks 5–6).

Patients with a high burden of co-morbidities (AHEAD score ≥4 points) showed increased risk of death compared with patients

Table 1 Baseline characteristics of the study population

		One precipitating factor ($n = 7764$)							
	Total ($n = 15\,828$)	ACS ($n = 4004$)	Infection ($n = 1104$)	Atrial fibrillation ($n = 1228$)	Hypertension ($n = 831$)	Non-compliance ($n = 597$)	Combined factors ($n = 1020$)	No factors ($n = 7044$)	*P*-value
Age (years)	71 (61–80)	72 (62–79)	72 (60–81)	73 (62–81)	73 (62–80)	67 (54–76)	66 (56–75)	72 (61–80)	<0.001
Male gender	58%	63%	53%	52%	47%	67%	61%	56%	<0.001
BMI (kg/m^2)	26.1 (23–29.9)	26.1 (23.4–29.3)	24.6 (21.8–28.6)	26.6 (23.5–30.7)	27.7 (24.4–32.5)	27.9 (24.2–32.1)	27.6 (24–31.8)	25.7 (22.6–29.5)	<0.001
Hypertension	66%	67%	64%	62%	89%	60%	78%	62%	<0.001
Diabetes	43%	49%	38%	33%	47%	48%	66%	38%	<0.001
Coronary artery disease	49%	87%	40%	18%	27%	47%	64%	34%	<0.001
Heart failure	46%	25%	55%	43%	38%	83%	61%	54%	<0.001
Atrial fibrillation	30%	15%	37%	68%	22%	32%	22%	33%	<0.001
COPD	16%	11%	19%	18%	19%	14%	8%	19%	<0.001
Systolic BP (mmHg)	130 (110–150)	130 (110–150)	127 (110–145)	130 (113–150)	180 (158–200)	119 (104–136)	135 (110–160)	130 (110–150)	<0.001
Diastolic BP (mmHg)	79 (65–90)	75 (62–85)	73 (62–84)	80 (70–90)	95 (80–110)	70 (60–80)	76 (65–90)	80 (66–90)	<0.001
Heart rate (b.p.m.)	88 (73–105)	88 (73–101)	86 (74–100)	114 (86–135)	90 (75–107)	84 (70–97)	90 (78–106)	85 (72–102)	<0.001
LVEF (%)	38 (27–50)	37 (30–46)	40 (30–55)	44 (30–55)	50 (45–60)	33 (25–42)	40 (30–52)	35 (25–50)	<0.001
Haemoglobin (g/L)	128 (111–142)	130 (113–144)	121 (106–139)	132 (117–144)	127 (111–141)	125 (110–140)	122 (106–139)	128 (112–142)	<0.001
Sodium (mmol/L)	138 (135–141)	138 (135–141)	138 (134–141)	139 (136–141)	139 (136–142)	137 (133–140)	136 (133–139)	139 (136–141)	<0.001
Potassium (mmol/L)	4.1 (3.9–4.6)	4 (3.8–4.5)	4.2 (4–4.7)	4.1 (4–4.6)	4.1 (3.9–4.6)	4.2 (3.9–4.7)	4.1 (3.8–4.6)	4.2 (3.9–4.7)	<0.001
eGFR (mL/min)	54 (38–71)	54 (38–70)	58 (39–80)	57 (43–73)	55 (40–70)	54 (42–71)	51 (36–72)	53 (38–70)	<0.001
Glucose (mmol/L)	7.5 (5.9–10.9)	9 (6.7–13)	7.1 (5.6–9.6)	7 (5.8–9.5)	8.2 (6.1–11.6)	7.3 (5.7–10.1)	8.4 (6.1–12.4)	7 (5.6–9.7)	<0.001
BNP (ng/L)	866 (376–1682)	940 (422–1677)	1007 (463–1665)	591 (336–1362)	1089 (319–2192)	1420 (808–3338)	869 (523–2240)	843 (367–1660)	0.01
NT-proBNP (ng/L)	3823 (1656–8454)	3992 (1428–11018)	3450 (1634–7728)	4406 (2311–8398)	3119 (1344–8871)	5108 (2943–8449)	5370 (2269–9387)	3628 (1575–7941)	0.001
Troponin I (μg/L)	0.05 (0.016–0.2)	0.265 (0.06–3.28)	0.027 (0.01–0.09)	0.05 (0.02–0.161)	0.05 (0.01–0.19)	0.05 (0.02–0.19)	0.145 (0.05–0.83)	0.03 (0.01–0.092)	<0.001
Beta-blocker	40%	42%	39%	34%	43%	67%	72%	32%	<0.001
ACE inhibitor or ARB	61%	58%	56%	58%	67%	71%	70%	60%	<0.001
Diuretic	59%	41%	70%	55%	54%	72%	55%	68%	<0.001
Nitrate	18%	23%	13%	12%	20%	22%	23%	16%	<0.001
Aspirin	44%	48%	27%	33%	43%	61%	69%	40%	<0.001
Statin	34%	33%	23%	24%	33%	53%	60%	31%	<0.001

P-values refer to global comparisons between patients without or with single precipitating factors.
ACS, acute coronary syndrome; BP, blood pressure; eGFR, estimated glomerular filtration rate.

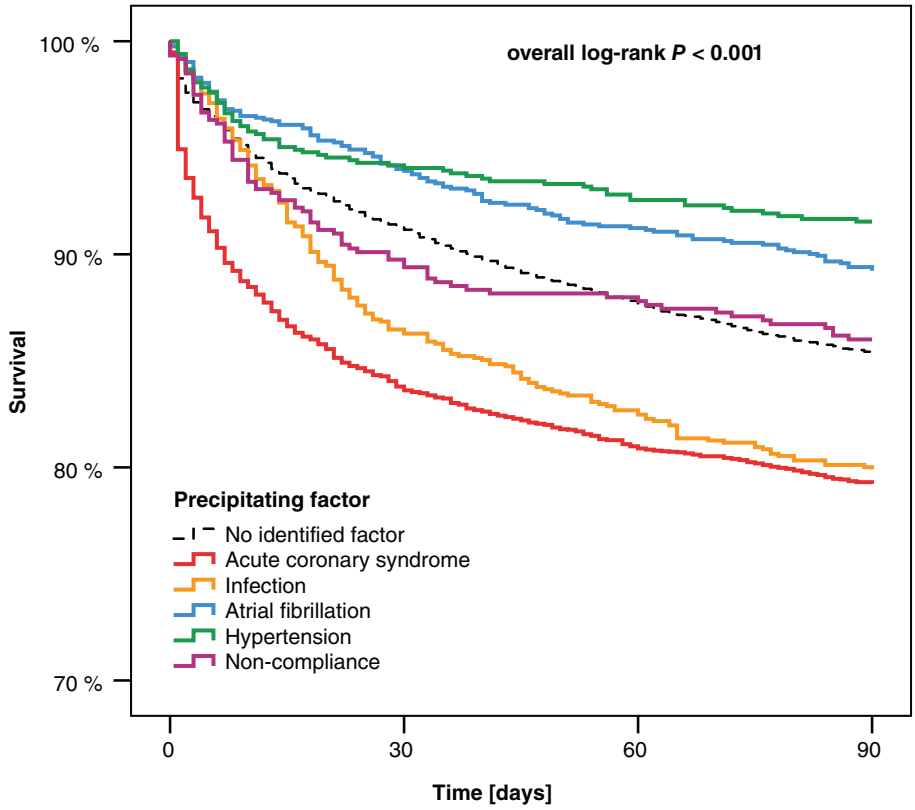

Figure 2 Ninety-day survival according to the presence of identified precipitating factors of acute heart failure (AHF). A difference in 90-day survival according to the presence of identified precipitating factors of AHF was found (overall log-rank $P < 0.001$). Pairwise comparisons with patients without identified precipitating factors showed lower survival in patients with acute coronary syndrome or infection as precipitants of AHF (adjusted log-rank $P < 0.001$ for both), and increased survival in patients with atrial fibrillation or hypertension as precipitants of AHF (adjusted log-rank $P = 0.004$ and $P < 0.001$, respectively). No difference in survival was found in patients with non-compliance as the precipitating factor of AHF.

with fewer co-morbidities (AHEAD score <4 points) during the first weeks after admission. However, as depicted in *Figure 4*, while the association between precipitating factors and risk of death decreased in strength with time since admission, the association between co-morbidities and increased risk of death became closer from week 1 (HR 1.48, 95% CI 1.24–1.76, $P < 0.001$) to weeks 11–13 (HR 2.40, 95% CI 1.73–3.34, $P < 0.001$).

Discussion

Ascertainment of precipitating factors is recommended by current AHF guidelines and, as shown by the present study, allows stratification of 90-day risk of death.[1,4] This study, using a large, intercontinental registry, extends the previously described finding of the North-American OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry and substantially extends the concept to the European and Asian AHF populations.[3] Furthermore, our study, by adjusting for several clinical confounders, shows the independent association of ACS or infection with higher aggregate hazard of death and AF with lower hazard of death—and our exploratory analyses suggest that those relative hazards vary with time since admission in non-trivial ways.

In our large cohort, ACS was shown to be the most common precipitant of AHF, as previously shown in the OPTIMIZE-HF and in the French EFICA (Etude Française de l'Insuffisance Cardiaque Aiguë) registries.[3,10] Previous data showed that ACS complicated by AHF carries a particularly high risk of adverse outcome[11,12] and, similarly, AHF caused by ACS is associated with the highest risk of short-term death, as confirmed by our study.[3,13,14] The unfavourable association between AHF and (ischaemic) myocardial injury is further supported by the analyses of the ADHERE (Acute Decompensated Heart Failure National Registry) study, which reported a marked association between elevated cardiac troponin levels and increased risk of death in AHF.[15] Our study clearly showed that, when ACS precipitates AHF, the risk of death is highest only transiently, during the first week after admission. There is now an urgent need to test whether this early, high risk of death might be reduced through optimal revascularization and/or medical therapy.[16] Timely revascularization might reduce the burden of AHF in ACS patients.[17] A survival benefit of revascularization was shown in the subgroup of AHF patients with cardiogenic shock

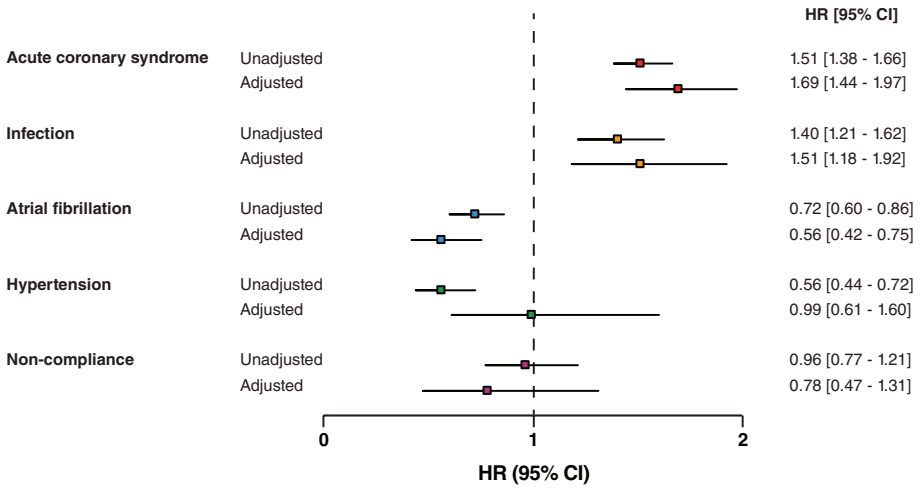

Figure 3 Precipitating factors and 90-day risk of death. Risk of 90-day mortality expressed as hazard ratio (HR) and 95% confidence interval (CI) in the presence of precipitating factors of acute heart failure compared with absence of identified precipitating factors. Adjustment was performed for age, gender, history of heart failure, coronary artery disease, diabetes, systolic blood pressure at admission, heart rate at admission, left ventricular ejection fraction, estimated glomerular filtration rate at admission, and plasma sodium at admission.

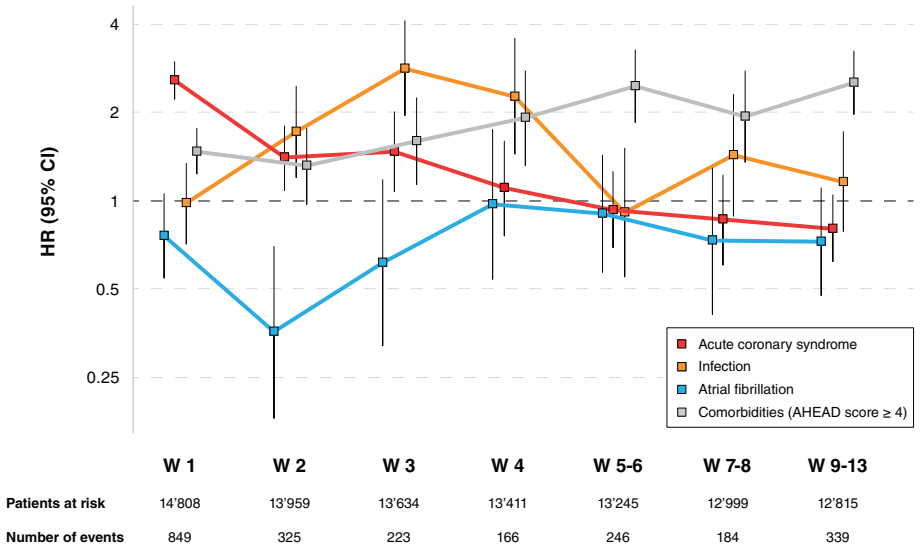

Figure 4 Time-course of risk of death according to precipitating factors and burden of co-morbidities. The weekly risk of death associated with the presence of selected precipitating factors of acute heart failure (red, acute coronary syndrome; orange, infection; blue, atrial fibrillation) compared with absence of identified precipitating factors is expressed as the hazard ratio (HR) and 95% confidence interval (CI). The weekly risk of death associated with the presence of multiple co-morbidities (AHEAD score ≥4 points) compared with score <4 points is depicted in grey.

complicating ACS, but evidence in the larger group of AHF patients without shock is less clear.[18]

The present study also showed high 90-day risk of death when infection precipitated AHF. The generalizability of these results is supported by very recent data from a three-centre registry, showing increased mortality in patients with AHF precipitated by acute pulmonary disease (mostly pneumonia or COPD exacerbation).[5] Moreover, the association of AHF and other non-cardiac acute illness is particularly unfavourable.[19] In the present study, the risk of death was maximal during week 3 after admission, though infection was already recorded at admission for AHF. The delay between hospital admission and death supports the concept of a complex interaction between infection and a combination of endothelial dysfunction, plaque instability, activated coagulation,[20]

volume overload, inflammatory and ischaemic myocardial injury,[21] and arrhythmias,[22] and risk for precipitating other non-cardiac illnesses which may lead to death.[23] It is also possible, however, that this delayed peak may result from a direct focus on the management of the AHF and a relative neglect of the implied sepsis, potentially with suboptimal antibiotic management by clinicians focused on the heart. The interplay between intrinsic physiology and clinician behaviour warrants further study, as infection-triggered AHF is quite common in our cohort and others.

Conversely, our study showed relatively low risk of death when AF precipitated AHF. These observations are in line with those of the Spanish PAPRICA-2 (PApel pronostico de los PRecipitantes de un episodio de Insuficiencia Cardiaca Aguda) study, which showed relatively favourable short-term outcome in AHF precipitated by AF.[13] However, other studies previously described an association between AF, in particular new-onset forms, and increased risk of both short- and long-term mortality in AHF.[24,25] Very recent data showed an association between AF and higher risk of readmission in AH.[26] New-onset AF, through loss of atrial contraction and/or high ventricular rate, may rapidly deteriorate the haemodynamic status and induce AHF even in patients with less severe structural cardiac abnormalities and without major changes in volaemia.[27] However, appropriate antiarrhythmic treatment may rapidly restore haemodynamics without need for intensive treatment with vasodilators and/or diuretics and their potential adverse effects.

Limitations

The present study has notable limitations. Variables included in the survival models were selected among independent predictors of mortality, as previously described in detail.[6] As in any observational study, hidden unmeasured variables might interfere with the results. Nonetheless, random assignment to alternative triggers of AHF is not feasible, and the clinical implication of the study—that ascertainment of precipitating factors may distinguish different risk profiles in AHF—remains prognostically relevant although we have not proven causation. Several differences in the use of oral HF medications at admission were observed. However, the impact of chronic treatment on short-term outcome of AHF patients is less pronounced compared with treatment after admission.[28] We further acknowledge that treatment after admission (including information about coronary revascularization, antimicrobial drugs, and antiarrhythmic therapy) is not reported in our registry and that notable differences around the world may exist.[29,30] However, since recruiting centres are tertiary hospitals with a high level of experience in treating AHF, the observed association between precipitating factors and different outcomes might have been smoothed rather than sharpened.

Moreover, non-compliance with drug and/or dietary recommendation may be more widespread than reported and may have been substantially influenced by heterogeneity in cultural habits in different continents.

In addition, the rather large group of patients without an identified precipitant may include patients with other unrecorded precipitants or may reflect the diagnostic challenge of identifying precipitants of AHF.

Substantial differences may exist between patients with different forms of AHF. However, our cohort included a balanced proportion of patients with new-onset HF and acutely decompensated HF.

Conclusions

Precipitating factors substantially influence 90-day mortality of AHF patients. In particular, AHF precipitated by ACS or infection is independently associated with higher, while AHF precipitated by AF is associated with lower 90-day risk of death. Both these facts, and their time-varying patterns, suggest opportunities for nuanced prognostication and refinements of practice.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Ninety-day survival according to the number of identified precipitating factors of acute heart failure.

Table S1. Precipitating factors and 90-day mortality according to world area.

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