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ORIGINAL ARTICLE
Congestive Heart Failure

Outcomes of acute heart failure associated with acute coronary syndrome versus other causes

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Background: **By and large, prior registries and randomized trials have not distinguished between acute heart failure (AHF) associated with acute coronary syndrome (ACS) versus other causes.**
Aims: **To examine whether the treatments and outcomes of ACS-associated AHF are different from non-ACS-associated AHF.**
Methods: **We examined in a prospective, nationwide hospital-based survey the adjusted outcomes of AHF patients with and without ACS as its principal cause.**
Results: **Of the 4102 patients in our national heart failure survey, 2336 (56.9%) had AHF, of whom 923 (39.5%) had ACS-associated AHF. These patients were more likely to receive intravenous inotropes and vasodilators and to undergo coronary angiography and revascularization, but less likely to receive intravenous diuretics. The unadjusted in-hospital, 30-day, one-year, and four-year mortality rates for AHF patients with or without ACS were 6.5% versus 5.0% (*$P = 0.13$*), 10.3% versus 7.5% (*$P = 0.02$*), 26.6% versus 31.0% (*$P = 0.02$*), and 55.3% versus 63.3% (*$P = 0.0001$*), respectively. In the multivariate analysis, the adjusted mortality risk for patients with ACS at the respective time points were 1.46 (0.99–2.10), 1.67 (1.22–2.30), 1.02 (0.86–1.20), and 0.93 (0.82–1.04).**
Conclusions: **Patients with ACS-associated AHF seem to have a unique clinical course and perhaps should be distinguished from other AHF patients in future trials and registries.**

Keywords: Acute heart failure, acute coronary syndrome, outcome

Acute heart failure (AHF) is one of the major reasons for hospital admissions, especially among the elderly (1,2). Large European (3–5) and American (6–7) registries have demonstrated that the in-hospital mortality ranges from 4–7%, and patients surviving hospitalization have approximately 10% risk of dying in the next two months, with even higher rates in selected subgroups.

AHF is a well-described complication of the various forms of the acute coronary syndrome (ACS) (8–12). By and large, prior registries and randomized trials have not distinguished between AHF associated with ACS and AHF associated with other causes (3–7,13–16). We hypothesized that the treatments and outcomes of AHF associated with ACS are different from AHF related to other conditions. To examine this hypothesis, we examined a large cohort of AHF patients enrolled in a national survey of heart failure with up to four years of follow-up.

Methods

We studied all patients with AHF, defined as either acute *de novo* or acute exacerbation of chronic heart failure, that were included in the Heart Failure Survey In Israel (HFSIS), a nationwide hospital-based survey conducted in Israel. The survey recorded data on all patients with acute or chronic heart failure who were admitted to cardiology or internal medicine wards in all 25 public hospitals throughout the country in March to April 2003 and were followed-up for four years. The details of the survey and subsequent sub-analyses have been previously described elsewhere (17–19). The diagnosis of heart failure was based on the presence of the classic symptoms at rest or during exertion and objective evidence of cardiac dysfunction at rest (20).

For each eligible patient, the attending physicians were required to complete a structured questionnaire on

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patient characteristics, in-hospital course and management, pre-hospital and discharge medications, and admission and discharge diagnoses. Participation did not require any amendment in the management or hospital care. The study protocol was approved by the institutional review board of each participating hospital. Death or survival during the four years after the index hospitalization was determined in 99% of patients.

The primary endpoint of the study was all-cause mortality during hospitalization, at 30 days, at one year, and at four years of follow-up, as documented in the database itself (in-hospital charts) or by cross-matching the patient's identification number with the Israel National Population Death Register. As a primary analysis, AHF was analyzed based on its cause; patients whose AHF was associated with ACS versus other causes, including idiopathic, hypertensive, and valvular cardiomyopathies. The diagnosis of ACS as the cause of AHF was determined by the attending physician based on the clinical scenario, biomarker findings, electrocardiographic patterns, and angiographic characteristics, but was not protocol-driven. As an ancillary analysis that aimed towards determining whether ACS *per se* impacted on outcomes or rather the presence of coronary artery disease, we further analyzed patients who did not have ACS and divided them into 2 subgroups; those with known antecedent coronary artery disease and those without.

Statistical analysis

Patient characteristics, management during and after hospitalization, and outcomes were compared for subgroups. Medians with 25th and 75th percentiles were reported for continuous variables and frequencies for categorical variables. The Wilcoxon rank-sum tests were used for continuous variables and χ^2 tests were used for categorical variables. All tests were two-sided and values of $P < 0.05$ were considered statistically significant. Kaplan–Meier curves were drawn to exhibit the unadjusted mortality rates.

In the primary analysis, the effect of ACS on mortality was assessed using logistic regression for short-term mortality and proportional hazard regression for long-term mortality. We used stepwise variable selection method in each of the regression models. The models included variables known to result in increased mortality and included age, gender, diabetes, atrial fibrillation, past coronary artery disease, hypertension, smoking, dyslipidemia, peripheral vascular disease, glomerular filtration rate <60 ml/min/1.73m^2, New York Heart Association (NYHA) class III and IV, severe anemia (hemoglobin <10.5 gr/dl for females and <11.5 gr/dl for males), serum urea >86 mg/dl and ACS. Observations with missing covariates were excluded from corresponding adjusted analyses.

The area under the receiver operator curve was used to assess model discrimination. Adjusted odds ratios (OR) or hazard ratios (HR) with their corresponding 95% confidence intervals (CI) and p values were reported. All analyses were carried out using SAS Version 9.1 (SAS Institute, Cary, North Carolina, USA).

In the ancillary analysis, the outcomes were analyzed using only unadjusted mortality rates at the respective time points.

Results

Of the 4102 patients in the entire survey, 2336 (56.9%) had AHF, of whom 923 (39.5%) had ACS during the index hospitalization. Electrocardiographic characterization of the ACS event was available in 318 patients; 171 (53.8%) had ST-elevation ACS. Of the patients with ACS-associated AHF, 503 (54.5%) were admitted with primary heart failure, as compared with patients without ACS, of whom 1095 (77.5%) were admitted with primary heart failure. In general, patients with ACS-associated AHF were older, although the group included a smaller proportion of patients older than 75 years (Table I). ACS patients were more likely to be males, to have risk factors for atherosclerosis, have a history of coronary artery disease and coronary interventions, but less likely to have had atrial fibrillation and clinical heart failure before admission. Upon admission, they were more likely to have lower blood pressure levels and to be in Killip class III-IV, markers for poor prognosis in AHF (7). They were more likely to have lower measured ejection fraction values during the index hospitalization. Troponin assays were applied in only 483 ACS patients and 597 patients without ACS; patients with ACS-associated AHF were more likely to have positive serum troponin assays (48.6% versus 10.9%, $P < 0.0001$). The glomerular filtration rates were similar for both groups, and there was no difference in the incidence of severe renal dysfunction (serum creatinine ≥ 2.75 mg/dl), a marker of poor prognosis in AHF (7). Patients with ACS-associated AHF also less often had plasma urea ≥ 86 mg/dl, a marker for poor prognosis in AHF (7), although the ACS group had median concentration values that were higher. Patients with ACS-associated AHF less often had severe anemia, although the ACS group had lower median hemoglobin concentrations. Patients with ACS-associated AHF had lower white blood cell counts and lower blood glucose levels. There were no differences in sodium levels.

Prior to their hospitalization, patients with ACS-associated AHF were more likely to be treated chronically with aspirin, clopidogrel, and statins, but less likely to receive diuretics, digoxin, and oral anticoagulants (Table II). During their index hospitalization, these patients were more likely to receive intravenous inotropes and vasodilators and to undergo diagnostic coronary angiography (without an ensuing intervention) as well as revascularization procedures, but less likely to receive intravenous diuretics.

At discharge, ACS patients were more likely to be treated with antiplatelet agents, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and statins, and less likely with diuretics, spironolactone, digoxin, calcium-channel blockers, and oral anticoagulants, as compared with non-ACS patients (Table II).

The unadjusted in-hospital, 30-day, one-year, and four-year mortality rates for AHF patients with or without ACS were 6.5% versus 5.0% ($P = 0.13$), 10.3% versus 7.5% ($P = 0.02$), 26.6% versus 31.0% ($P = 0.02$), and 55.3% versus 63.3% ($P = 0.0001$), respectively (Figure 1). In the multivariate analysis, the adjusted OR/HR for mortality for patients with ACS at the respective time points were 1.46 (0.99–2.10), 1.67 (1.22–2.30), 1.02 (0.86–1.20), and 0.93 (0.82–1.04).

Table I. Demographic and clinical characteristics of AHF patients with and without ACS.

Variables	ACS (%) (n = 923)	Non-ACS (%) (n = 1413)	P-value
Age (years)	76 (68–82)	74 (65–82)	0.01
Age >75 years	47.7	52.5	0.02
Female sex	39.9	47.9	0.0001
Diabetes mellitus	57.1	48.1	0.00002
Dyslipidemia	46.2	28.6	<0.0001
Peripheral vascular disease	11.9	8.4	0.006
Smoking	16.0	18.4	0.14
History of atrial fibrillation	21.2	34.3	<0.0001
Coronary artery disease	52.9	38.0	<0.0001
Previous angiography	44.6	18.8	<0.0001
Previous percutaneous coronary intervention	26.9	5.7	<0.0001
Previous bypass surgery	11.7	10.1	0.2
NYHA I	25.2	12.7	<0.0001
NYHA II	36.9	37.6	0.7
NYHA III, IV	37.9	49.7	<0.0001
Left ventricular ejection	59.5	45.0	<0.0001
Fraction <40%			
Killip class III–IV	36.4	29.7	0.0008
Systolic blood pressure (mmHg)	140 (120–160)	142 (122–170)	0.00003
Systolic blood pressure <115 mmHg	18.7	15.7	0.06
Estimated glomerular filtration rate (ml/min/1.73 m^2)	52.4 (36.4–71.3)	52.3 (38.8–73.8)	0.01
Serum urea (mg/dl)	48 (32–75)	45 (28–67)	0.0004
Serum urea ≥86 mg/dl	15.4	19.3	0.02
Serum creatinine (mg/dl)	1.2 (0.90–1.70)	1.2 (0.90–1.60)	0.1
Serum creatinine ≥2.75 mg/dl	5.9	7.6	0.1
Plasma sodium (meq/dl)	139 (136–141)	139 (136–141)	0.5
Plasma sodium <136 meq/l	23.1	23.2	0.9
Plasma glucose (mg/dl)	132 (104–183.50)	148 (115–226)	<0.0001
Hemoglobin (gr/l)	12.0 (10.6–13.4)	12.5 (11.1–13.8)	<0.0001
Severe anemia	23.5	30.0	0.0007
White blood cells (cells/μl)	7240 (1202–9900)	8300 (3060–11600)	0.02

Non-ACS-associated AHF with and without prior coronary artery disease

In order to determine whether ACS *per se* impacted on outcomes or rather the presence of coronary artery disease, we analyzed the outcomes of patients who did not have ACS and divided them into two subgroups; those with known antecedent coronary artery disease and those without. Of the 1413 patients with non-ACS-associated AHF, 537 (38.0%) had a previous history of coronary artery disease. Patients with previously diagnosed coronary artery disease tended to be older, although a smaller proportion of patients were older than 75 years (Table III). They were more likely to be males and to have risk factors for atherosclerosis. Prior to admission patients with previous history of coronary artery disease were more likely to have significant clinical heart failure. Upon admission, they had similar Killip class distributions and blood pressure values as for patients without previous coronary artery disease. They were more likely to have a lower ejection fraction, severe anemia, and a higher glomerular filtration rate while in-hospital. Patients with previously diagnosed coronary artery disease had a lower median plasma urea concentration, although a higher proportion had plasma urea over 86mg/dl. They had lower glucose concentrations and similar plasma sodium and white blood cell concentrations.

Prior to their hospitalization patients with a history of coronary artery disease were more likely to be chronically treated with aspirin, clopidogrel, beta-blockers, ACE inhibitors, spironolactone, furosemide and statins, but less often with oral anticoagulants and calcium-channel blockers (Table IV). While in-hospital, they were more likely to undergo revascularization. Both groups were treated similarly with intravenous inotropes, vasodilators, and diuretics (Table IV). At discharge, patients with previous coronary artery disease were more likely to receive antiplatelet agents, beta-blockers, ACE inhibitors, furosemide, and statins.

Although the patients with previously-diagnosed coronary artery disease had worse baseline characteristics, the unadjusted in-hospital, 30-day, 1-year, and 4-year mortality rates were similar for both subgroups: 5.0% versus 5.0% (P = 0.99), 6.9% versus 8.5% (P = 0.29), 30.2% versus 32.4% (P = 0.36), and 62.1% versus 65.2% (P = 0.23), respectively. These findings indicate that the presence of coronary artery disease *per se* did not impact on outcomes of AHF patients without ACS.

Discussion

Our data, derived from a nationwide, contemporary, hospital-based survey that included 2336 patients with AHF,

Table II. Treatment before, during and after hospitalization in AHF patients with and without ACS.

	ACS (%) (n = 923)	Non-ACS (%) (n = 1413)	P-value
Treatment prior to hospitalization			
Aspirin	60.7	52.9	0.0002
Clopidogrel	6.5	2.9	0.00003
Beta-blockers	48.9	46.2	0.2
ACE inhibitors	48.3	48.7	0.9
Angiotensin receptor blockers	10.2	8.0	0.07
Spironolactone	9.4	15.9	<0.0001
Furosemide	50.1	65.8	<0.0001
Digoxin	10.2	14.6	0.001
Statins	39.8	29.6	<0.0001
Oral anticoagulants	11.1	20.9	<0.0001
Calcium-channel blockers	23.8	27.4	0.06
Alpha-blockers	10.1	12.7	0.06
Treatment during hospitalization			
Intravenous inotropes	12.7	6.1	<0.0001
Intravenous vasodilators	23.4	7.9	<0.0001
Intravenous diuretics	75.1	81.0	0.0006
Percutaneous coronary intervention	44.6	18.8	<0.0001
Diagnostic coronary angiography	8.2	3.7	<0.0001
Treatment after discharge			
Aspirin	80.5	59.6	<0.0001
Clopidogrel	24.3	4.0	<0.0001
Beta-blockers	71.9	54.2	<0.0001
ACE inhibitors	64.6	58.7	0.006
Angiotensin receptor blockers	9.4	10.0	0.6
Spironolactone	18.2	24.8	0.0003
Furosemide	70.5	83.8	<0.0001
Digoxin	13.2	17.2	0.01
Statins	54.5	32.4	<0.0001
Oral anticoagulants	12.5	23.2	<0.0001
Calcium-channel blockers	20.2	27.9	0.0001
Alpha-blockers	9.5	11.6	0.1

demonstrate that AHF was associated with ACS in a substantial proportion of patients (39.5%). These patients were hospitalized primarily with heart failure secondary to ischemia rather than primary heart failure, in contrast to the AHF patients without ACS, who were more likely to have primary heart failure. The demographic and clinical characteristics of ACS-associated AHF patients were significantly different from the other AHF patients, as were the treatments before, during, and after the index hospitalization. The main finding of our analysis was that the adjusted short-term (i.e. up to 30 days) mortality rates for ACS patients were higher, whereas the long-term (i.e. up to four years) mortality rates were not. In an ancillary analysis, patients with non-ACS-associated AHF with and without known antecedent coronary artery disease had similar outcomes, indicating that the presence of coronary artery disease per se did not impact on outcomes of AHF, but rather the acute ischemic event. These findings support our

Table III. Demographic and clinical characteristics of non-ACS-associated AHF patients with and without prior known coronary artery disease (CAD).

Variables	Prior CAD (n = 537)	Without prior CAD (n = 876)	P-value
Age (years)	77 (68.5–83)	75 (68–81)	0.6
Age >75 years	49.3%	54.6%	0.05
Female sex	32.8%	57.8%	<0.0001
Diabetes mellitus	55.4%	43.4%	<0.0001
Dyslipidemia	40.5%	20.8%	<0.0001
Peripheral vascular disease	13.1 %	5.4%	<0.0001
Smoking	24.6%	14.4%	<0.0001
Coronary artery disease	96.8%	39.6%	<0.0001
Previous angiography	41.0%	4.2%	<0.0001
Previous percutaneous coronary intervention	14.5%	0	<0.0001
Previous bypass surgery	25.6%	0	<0.0001
History of atrial fibrillation	31.5%	36.0%	0.08
NYHA I	9.3%	14.9%	0.002
NYHA II	34.4%	39.7%	0.05
NYHA III, IV	56.3%	45.5%	0.00007
Left ventricular ejection Fraction <40%	60.4%	34.0%	<0.0001
Killip class III–IV	30.8%	29.1%	0.5
Systolic blood pressure (mmHg)	142 (120–164)	143 (122–170)	0.2
Systolic blood pressure <115 mmHg	15.9%	15.6%	0.9
Estimated glomerular filtration rate (ml/min/1.73 m^2)	56.4 (38.8–73.3)	48.1 (33.5–67.4)	0.00004
Serum urea (mg/dl)	45 (30–69.5)	54.6 (37–86)	<0.0001
Serum urea ≥86 mg/dl	25.1%	15.5%	<0.0001
Serum creatinine (mg/dl)	1.1 (0.9–1.6)	1.4 (1.1–1.9)	0.008
Plasma sodium (meq/dl)	139 (136–141)	138 (136–141)	0.4
Plasma sodium <136 meq/l	22.9%	23.4%	0.8
Plasma glucose (mg/dl)	128 (102–178)	138 (107–193)	0.001
Hemoglobin (gr/l)	12.1 (10.6–13.5)	12.0 (10.5–13.4)	0.6
Severe anemia	34.0%	27.3%	0.007
White blood cells (cells/μl)	7200 (1174–9850)	7300 (1302–9930)	0.2

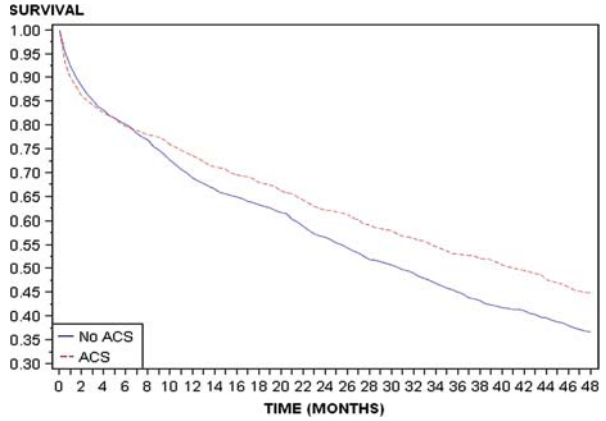

Figure 1. The unadjusted survival of AHF patients with or without ACS.

hypothesis that patients with ACS-associated AHF have a unique clinical course, and thus should be distinguished from other AHF patients in future trials and registries.

Clinical implications

Most of the prior AHF trials and registries have focused on short-term mortality (3–7,13–16). The AHF trials in particular have adopted a one-size-fits-all approach, enrolling all-comers with AHF, including patients with ACS. For example, the large Acute Decompensated Heart Failure National Registry (ADHERE), includes all patients 18 years or older who are admitted to an acute care hospital with a primary or secondary discharge diagnosis of heart failure (7,21,22). Our findings, showing significantly worse short-term outcomes for ACS-associated AHF patients, indicate that the results of trials may be significantly affected by the proportion of patients with ACS-associated AHF. In fact, given that the adjusted 30-day mortality rates for ACS patients were higher by almost 70%, differences in the proportion of ACS patients would probably overshadow any expected drug effect in a trial.

Beyond the epidemiological ramifications of our findings, they may also indicate that the current approach of using similar treatments for AHF in the setting of ischemia and in other settings, the one-size-fits-all approach, may be erroneous. Patients with ACS-associated AHF were more likely to be without overt clinical heart failure before the admission, whereas patients with other causes were more likely to have had long-standing clinical heart failure. Moreover, patients with ACS-associated AHF had different co-morbidities and concomitant treatments. These factors may interact with available and future pharmacological treatments for AHF.

A recent report from the ADHERE registry highlighted the prognostic significance of elevated cardiac troponin levels (21). In our cohort, troponin levels were not routinely examined, but among those patients with available troponin values, the AHF patients with ACS were more likely to have elevated troponin levels. As the authors acknowledged in the report (21), some patients with both heart failure and ACS may have been included in the analysis. Thus, given the significant overlap between the subgroup of ACS patients and the subgroup of elevated troponin AHF patients, our analysis may offer another perspective of a similar subgroup. Moreover, given that the new definition of acute myocardial infarction stressed the importance of cardiac biomarkers for the diagnosis of acute myocardial infarction (23), and that troponin levels may be elevated among AHF patients without ACS (21), it is possible that some of our patients were erroneously categorized as ACS patients, merely because they had elevated troponin levels.

An additional finding demonstrated in our survey is that management of AHF patients may be suboptimal, as manifested by underuse of evidence-based treatments. This is underscored in the subgroup of AHF patients who had ACS, in whom the use of evidence-based treatments was

Table IV. Treatment before, during and after hospitalization in non-ACS-associated AHF patients with and without prior known CAD.

	Prior CAD (%) (n = 537)	Without prior CAD (%) (n = 876)	P-value
Treatment prior to hospitalization			
Aspirin	71.9	40.6	<0.0001
Clopidogrel	5.4	1.3	<0.0001
Beta-blockers	58.2	38.4	<0.0001
ACE inhibitors	54.5	44.9	0.0004
Angiotensin receptor blockers	9.7	6.9	0.06
Spironolactone	18.8	14.0	0.02
Furosemide	76.0	59.2	<0.0001
Digoxin	15.1	14.3	0.7
Statins	44.3	20.5	<0.0001
Oral anticoagulants	17.9	22.8	0.03
Calcium-channel blockers	24.2	29.5	0.2
Alpha-blockers	14.0	11.8	0.2
Treatment during hospitalization			
Intravenous inotropes	6.8	5.6	0.4
Intravenous vasodilators	9.3	7.0	0.1
Intravenous diuretics	81.4	80.8	0.8
Percutaneous coronary intervention	38.7	6.5	<0.0001
Diagnostic coronary angiography	30.0	4.1	0.3
Treatment after discharge			
Aspirin	73.7	50.3	<0.0001
Clopidogrel	7.0	2.0	<0.0001
Beta-blockers	62.3	48.9	<0.0001
ACE inhibitors	60.0	57.9	0.4
Angiotensin receptor blockers	11.7	8.9	0.09
Spironolactone	27.7	22.9	0.05
Furosemide	87.3	81.5	0.01
Digoxin	15.5	18.2	0.2
Statins	44.1	20.1	<0.0001
Oral anticoagulants	19.7	25.5	0.01
Calcium-channel blockers	24.4	30.2	0.02
Alpha-blockers	12.8	10.9	0.3

inadequate. These findings emphasize the need for measures to increase the use of evidence-based treatments, as well as the need for surveys or registries to verify their implementation.

Limitations

Despite the marked differences in baseline characteristics and treatments between AHF patients with and without ACS, it is reassuring that the two groups were not markedly different in terms of high-risk parameters, such as serum urea, serum creatinine, hyponatremia, severe anemia, and admission blood pressure (7). Nevertheless, the groups were very heterogeneous and differed in other aspects, including demographics, clinical history, and therapy. We tried to adjust for this significant caveat partially using multivariate analysis. In addition, data regarding the admission electrocardiogram and serum troponin levels were not available for a large proportion of patients. It is worth mentioning that at the time our survey was performed, troponin assays were not routinely applied for AHF patients. Indeed, in the seminal paper from ADHERE that demonstrated the significance of troponin assays in AHF (21), troponin was examined in only 80.5% of the cohort, and the analysis pertains to a subgroup that comprised only 64.4% of the entire cohort. As compared with other AHF registries (3–7,21,22), the sample size in our registry was relatively small, and hence might be underpowered for drawing firm conclusions. However, the survey is strengthened by the long-term follow-up. Furthermore, the inclusion of almost all patients admitted with AHF during a certain period of time on a national basis avoids the selection bias of the registries mentioned above (3–7,21,22), in which only selected centers participate on a voluntary basis.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the writing and content of the paper.

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