Mode of Death After Acute Heart Failure Hospitalization
– A Clue to Possible Mechanisms –

Kishan S. Parikh, MD; G. Michael Felker, MD; Marco Metra, MD

Heart failure continues to be a leading cause of hospitalization worldwide, and acute heart failure (AHF) carries significant risk for short-term morbidity and mortality. Despite many trials of potential new therapies for AHF, there have been very few advances over the recent decades. In this review, we will examine mortality during and after AHF hospitalization, with an emphasis on available data on mode of death (MOD). We will also review data on the timing of different MOD after AHF and the effect of specific therapeutics, as well as what is known about the contribution of specific pathophysiological mechanisms. Finally, we discuss the potential utility of further study of MOD data for AHF and its application to drug development, risk stratification, and therapeutic tailoring to improve short- and long-term outcomes in AHF. (Circ J 2016; 80: 17–23)

Key Words: Acute heart failure; Hospitalization; Mode of death

The prevalence of heart failure (HF) in the developed world is projected to substantially increase over the next years. Although overall survival has improved over time, it is still estimated that approximately 50% of people diagnosed with HF will die within 5 years.1–4 Acute heart failure (AHF) is a clinical syndrome with varying inciting factors and presents either de novo or as an acute decompensation of chronic HF.5,6 Despite intensive treatment and improvement in symptoms, patients hospitalized with AHF still carry a substantial 10–20% mortality risk over the next 6 months.5,7–9 However, aside from continuation of β-blocker therapy when tolerated, no medical therapies or management strategies to date have definitively been shown to have beneficial effects on outcomes.1,4,10–12 A better understanding of the causes of AHF-associated deaths may provide the needed insights into the underlying mechanisms in a way that may lead to improved outcomes.

Association of Increased Mortality With AHF Hospitalization
The hospitalization for AHF is a landmark event in the clinical course of patients with HF and is associated with a sharp increase in mortality.1,2 This is especially notable considering that mortality during the HF hospitalization itself is relatively low, of the order of 3–7%. In the recent HF Pilot Survey (ESC-HF Pilot) of the EURObservational Research Program, patients were subdivided into ambulatory outpatients with chronic stable HF and patients hospitalized for AHF. Patients with chronic HF had an annual all-cause mortality of 7.2%, with an annual hospitalization rate of 31.9%. These rates increased to 17.4% and 43.9%, respectively, in patients hospitalized for AHF.13 Similarly, the annual mortality rates of the patients in the Italian HF survey (IN-HF) were 5.9% in chronic outpatients with HF, and 19.2% and 27.7% in the patients hospitalized for either new-onset or chronic decompensated HF, respectively.14 Longitudinal prospective clinical trials have shown similar results. Compared with stable ambulatory patients, patients hospitalized for HF show a dramatic increase in their risk of dying and this is independent of the baseline ejection fraction (EF), with no difference between patients with reduced EF (HFrEF) and those with preserved EF (HFpEF).15–17 This risk of death decreases exponentially in the months following discharge, but remains 3–4-fold higher even at 12–18 months after the initial hospitalization.15,18,19 HF hospitalizations are therefore associated with an increased risk of long-term death, too, and this effect on patients’ prognosis is similar to that described for acute coronary syndrome or stroke.17,18 Thus, improving post-discharge mortality risk in AHF patients remains a major unmet need in current clinical practice. A better understanding of the modes of death (MOD) of AHF patients may lead to better insights and new treatments.

MOD in AHF
In general, there is surprisingly little data available on MOD in AHF. Although large HF registries have provided substantial data on the overall clinical presentation, treatments, and outcomes of patients with AHF, they tend to provide little data on MOD, because the cause of death in registries is typically not systemically assessed. Clinical trials, on the other hand,
cated cases of death in a similar population. After the trial, the rate of concordance between events reported by the clinical events committee and international site investigators using case report forms was analyzed. Of 911 enrolled patients, there were 151 deaths at 24 weeks (16.5% mortality rate). A cardiac cause of death was agreed upon 74% of the time ($\kappa=0.40$, McNemar $P=0.001$), and non-cardiac cause of death was agreed upon 87% of the time ($\kappa=0.40$, McNemar $P=0.001$).

Although these results suggest reasonably good consistency between investigator reported and centrally adjudicated MOD in HF patients, they provide a rationale for the use of adjudication where feasible to ensure the greatest degree of consistency and accuracy.

**Prior Studies**

Among the prior AHF studies, the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST)^9,28 and Relaxin for the Treatment of Acute Heart Failure Mortality Rates in Selected Studies

| Study                  | Patients (n) | Mortality          | Published MOD data |
|------------------------|--------------|--------------------|--------------------|
|                        |              | In-hospital | Post-discharge       |                     |
| ASCEND-HF^8             | 7,141        | –          | 13% (6 months)      | No                  |
| EVEREST^9               | 4,133        | 3%         | 26% (9.9 months)    | Yes                 |
| RELAX-AHF^7             | 1,161        | –          | 9% (6 months)       | Yes                 |
| **Registries**         |              |            |                    |                     |
| Lee et al (Canada)^29   | 4,031        | 8.7%       | 10.6% (30 days), 31% (1 year) | No      |
| ADHERE (USA)^21         | 187,565      | 3.8%       | –                  | No                  |
| OPTIMIZE-HF (USA)^22    | 41,267       | 3.8%       | 8.0% (60–90 days)   | No                  |
| Tavazzi et al (Italy)^23| 2,807        | 7.3%       | 12.8% (6 months)    | No                  |
| EHFS II (EU)^24         | 3,580        | 6.7%       | –                  | No                  |
| Damasceno et al (sub-Saharan Africa)^25 | 1,006 | 4.2% | 18.0% (6 months) | No |
| ATTEND (Japan)^26       | 4,837        | 6.3%       | –                  | No                  |

**Table**

MOD, mode of death.

**Adjudication of MOD**

The majority of deaths in AHF occur out of the hospital, and a significant challenge in analyzing MOD is ensuring accuracy and consistency in the categorization of deaths. The Second Follow-Up Serial Infusions of Nesiritide (FUSION II) trial investigated the use of outpatient nesiritide infusion in advanced HF patients with renal dysfunction. Although not AHF per se, these data on outpatients with advanced HF may provide insights into the reliability of investigator reported vs. adjudicated cases of death in a similar population. After the trial, the rate of concordance between events reported by the clinical events committee and international site investigators using case report forms was analyzed. Of 911 enrolled patients, there were 151 deaths at 24 weeks (16.5% mortality rate). A cardiac cause of death was agreed upon 74% of the time ($\kappa=0.40$, McNemar $P=0.001$), and non-cardiac cause of death was agreed upon 87% of the time ($\kappa=0.40$, McNemar $P=0.001$). Although these results suggest reasonably good consistency between investigator reported and centrally adjudicated MOD in HF patients, they provide a rationale for the use of adjudication where feasible to ensure the greatest degree of consistency and accuracy.
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ment of renal function to either intravenous serelaxin or placebo and found that post-discharge mortality at 180 days from randomization was improved in patients randomized to serelaxin. A clinical events committee blinded to treatment allocations adjudicated all deaths through 180 days post-discharge. Subsequent analysis revealed an overall 9.3% death rate (placebo group: 11.3%, serelaxin group: 7.3%), with 82% of these deaths being CV and 18% non-CV. Within the CV deaths, 35% were attributed to HF and 23% to SCD. Other CV deaths, including those from acute coronary syndrome, stroke, procedural complications, and unknown, accounted for the remaining 24% of deaths.

Serelaxin significantly reduced CV death (hazard ratio (HR): 0.63, 95% confidence interval (CI): 0.41–0.96, P=0.028) and all-cause death (HR: 0.63; 95% CI: 0.43 to 0.93, P=0.020), with no difference in non-CV deaths (Figure 2). Of the CV deaths, both SCD (HR: 0.46, 95% CI: 0.20–1.07, P=0.065) and other CV deaths (HR: 0.294, 95% CI: 0.118–0.733, P=0.0052), particularly deaths from stroke (1 death in serelaxin-treated group vs. 8 deaths in placebo-treated group), showed the greatest reduction with serelaxin treatment. Of note, serelaxin did not appear to have a significant effect on HF deaths (HR: 1.16, 95% CI: 0.61–2.21, P=0.65).

Relationship of MOD to HF Characteristics

EF
Hospitalizations for AHF patients with HFpEF have significantly increased over the past decade. HFpEF is associated

Figure 2. Mode-Specific Kaplan-Meier curves over time to 180 days in the serelaxin and placebo groups in the RELAX-AHF study analysis. CI, confidence interval; HF, heart failure. (Adapted with permission from Felker GM, et al.)

Failure (RELAX-AHF) trials have offered valuable insights into MOD in AHF.

EVEREST This study evaluated the use of the oral vaso-pressin V2 receptor blocker, tolvaptan, in an international, randomized, placebo-controlled double-blinded study of 4,133 patients with HFrEF hospitalized for AHF. Over a median of 9.9 months follow-up, there were 1,080 deaths, with no difference in the Kaplan-Meier estimated 1-year death rate (25.5%) between tolvaptan and placebo. The death rate from cardiovascular (CV) causes (86.8%) was similar to that seen in RELAX-AHF, but a relatively higher proportion of the EVEREST patients died of HF (47.2%) in the follow-up period. Sudden cardiac death (SCD) was the second most common MOD (30.0%) (Figure 1). The observed difference in HF deaths between the 2 AHF populations may be related to a sicker patient population in the EVEREST trial. All patients in EVEREST needed to have chronic HF with EF <40%. In contrast, both prior HF history and EF were not inclusion criteria in RELAX-AHF, with 45% of study patients having EF >40%. Finally, serelaxin and tolvaptan target patient populations with different hemodynamics: RELAX-AHF required systolic blood pressure (SBP) >125 mmHg, whereas EVEREST excluded patients for SBP <90 mmHg only. SBP at the time of admission is a major prognostic variable for patients admitted for AHF.
with certain comorbidities (hypertension, obesity, aging) and hemodynamic patterns that contribute to a clinical phenotype different from that of HFrEF. In-hospital mortality rates of patients with HFrEF seem similar to those of the patients with HfPEF (2.4–2.9% vs. 2.8–6.5%). However, post-discharge mortality rates tend to be lower (90-day mortality: 9.6% vs. 13.2%; 1-year mortality: 19.6% vs. 24.4%). In the individual patient data meta-analysis of the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC), including data from 41,972 patients with HF, patients with HfPEF had lower mortality than those with HFrEF with a linear increase in risk of death with EF values below 40%. The mortality of patients with HfPEF remains, however, significantly higher than in the general population, with annual mortality rates of 10–20% in most of the population-based studies and registries and the main causes are still SCD and HF. In the large Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) and Irbesartan in Heart Failure With Preserved Ejection Fraction Study (1-Preserve) trials, SCD and HF were the causes of 28% and 26%, and 21% and 14% of the deaths, respectively.

The major difference between the causes of death in patients with preserved and reduced EF is the larger prevalence of non-CV causes in the HfPEF patients. The proportion of CV causes of death was greater than 80% in the RELAX-AHF and EVEREST trials, with 74% and all of the patients with HFrEF, respectively. However, this proportion drops to approximately 70% in randomized controlled trials, and 50–60% in epidemiological studies and registries. Advanced age, N-terminal-pro-B-type natriuretic plasma (NT-proBNP) values, diabetes, extreme values of body mass index, and, in some studies, sex, have been identified as independent predictors of mortality in HfPEF patients.

**History of Prior HF**

Mortality and MOD in AHF may also be influenced by a history of prior HF. Patients with new-onset HF generally are older, more likely to be female and have a history of hypertension than patients with worsening chronic HF. Their in-hospital mortality may be similar or higher but their post-discharge mortality is lower, compared with that of the patients with decompensated chronic HF. However, the causes of death do not seem to be different between these 2 subgroups.

**Mechanisms of Death in AHF**

HF is a complex clinical syndrome, and multiple factors and underlying mechanisms may contribute to mortality in individual patients. In addition to the underlying severity of HF itself, multiple other factors contribute to post-discharge outcomes in this population, including comorbidities (cardiac and non-cardiac), the severity of and persistence of hemodynamic congestion, and the degree of end-organ damage that occurs during the AHF episode. In addition to these mechanisms, there are other mechanisms related to the hospitalization itself that may worsen outcomes. These include sleep deprivation, circadian rhythm disruption, poor nutrition, pain and discomfort, impaired cognitive functioning, and deconditioning, which may contribute to poor outcomes, especially in frail patients.

**Comorbidities**

Comorbidities (CV and non-CV) play a major role. CV comorbidities that may precipitate re-hospitalization include myocardial ischemia, arrhythmias (particularly atrial fibrillation), and uncontrolled hypertension. They are all tightly related to the clinical course of HF and may be potentially treated by targeted therapy at the time of the first hospitalization. Additionally, these cardiac comorbidities may contribute to progression of HF and increase the risk of subsequent mortality.

As a notable example, in the Assessment of Treatment with Lisinopril And Survival (ATLAS) study, acute coronary thrombosis on autopsy was a surprisingly common finding in patients initially classified as SCD, suggesting that other cardiac comorbidities (eg, ischemic heart disease) may play an important role in some deaths classified as being from HF progression or arrhythmia.

The non-CV comorbidities may also potentially contribute to event rates. In an analysis of the causes of re-hospitalizations in hospitals in the USA, the proportion of patients readmitted for the same condition was 35.2% after a first HF hospitalization. Thus, although to a lower extent than with other causes of hospitalization, the majority of readmissions after a first HF hospitalization may not be caused by HF itself. Non-CV causes of mortality are also common in clinical trials of AHF, as discussed earlier for the EVEREST and RELAX-AHF studies.

Patients enrolled in controlled trials generally have a lower prevalence of comorbidities compared with those in the “real world.” The effect of non-CV causes of hospitalizations and death is therefore larger in observational studies. In the European Heart Failure Pilot Survey, diabetes, chronic kidney disease and anemia were independently associated with a higher risk of mortality and/or HF hospitalization. Elevated blood glucose levels on admission and iron deficiency have been also shown to be independent prognostic factors in patients hospitalized for HF. In an analysis of the Cardiovascular Health Study of the risk factors for all-cause hospitalizations among elderly patients with a new diagnosis of HF, the only 2 CV variables related to outcomes were EF and New York Heart Association class, whereas many non-CV factors, namely diabetes mellitus, chronic kidney disease, weak grip strength, slow gait speed and depression, had prognostic value. Many other non-CV factors related to the patient’s characteristics may affect early re-hospitalizations. These include lack of adherence to treatment, dietary indiscretion, drug and alcohol abuse, family and social support, and access to care.

**Congestion**

Vascular congestion is an important cause of HF hospitalizations. Most HF hospitalizations are heralded by a gain in body weight and when this does not occur, because of prevailing fluid redistribution, other markers of congestion such as pulmonary artery pressure or BNP levels are increased. Congestion also has a major role in post-discharge deaths and re-hospitalizations. Lack of or slower resolution of signs and symptoms of congestion during the first days of hospitalization for HF is associated with more adverse outcomes. In its most extreme form, lack of decongestion manifests as worsening in-hospital HF, and this event is an independent predictor of increased mortality. Measurement of BNP levels may identify persistent congestion even in the presence of a seeming resolution of clinical signs, and lack of decrease in BNP levels during hospitalization is associated with a poor prognosis. In the RELAX-AHF study, both worsening HF during the hospital stay and a lack of decrease in NT-proBNP levels during hospitalization were associated with increased 180-day all-cause mortality.

Assessment of the signs of congestion, such as pulmonary rales, jugular venous pressure, peripheral edema, and weight gain, is also important at the time of discharge or early after...
discharge.\textsuperscript{51,62} Similarly, during the hospitalization, better prognostic assessment can be obtained by other measurements such as pulmonary artery pressure monitoring or, more simply, by BNP or NT-proBNP levels.\textsuperscript{55,63–66}

Organ Damage
There are reasons to hypothesize that congestion is not the only determinant of the increase in CV events after discharge. Studies have shown that measurements related to congestion, such as weight gain, or poor diuretic response, are associated with re-hospitalizations and short-term outcomes but not with long-term mortality.\textsuperscript{51,67} Second, the risk of death after a HF hospitalization remains increased also in the long-term up to at least 12–18 months after the event,\textsuperscript{55,57,58} and this is consistent with persistent organ damage associated with the hospitalization, similar to what occurs after acute myocardial infarction, rather than to a mechanism, such as congestion, more likely to cause symptoms. Third, in addition to BNP levels, other markers related to organ damage and/or function are independently related to outcomes, namely mortality, after a HF hospitalization.\textsuperscript{59}

The RELAX-AHF trial was particularly important in this respect because biomarker measurements were repeated at baseline and during hospitalization and, different from other cases,\textsuperscript{60} the study drug was not associated with untoward effects on outcomes. Changes in markers of myocardial damage (serum troponins), renal function (cystatin-C) and liver function (transaminases) were shown to have an independent relation with 180-day mortality and this persisted after adjustment for their baseline values.\textsuperscript{60}

Multiple mechanisms may cause myocardial damage during acute HF.\textsuperscript{60} Consistently, an increase in plasma troponin levels is very common in patients hospitalized for HF and serum troponin levels are independent predictors of subsequent outcomes. In addition to baseline values, a rise in serum troponin levels during the hospitalization, an index of event-related myocardial necrosis, is also a powerful predictor of outcome.\textsuperscript{70,71}

The relationship between chronic renal dysfunction and/or worsening renal function and poor outcomes in patients with HF is well established.\textsuperscript{72,73} However, there are important exceptions to this because an increase in serum creatinine may have neutral, or even favorable, significance when it occurs after intensive diuretic treatment or after the initiation of renin–angiotensin inhibitor therapy.\textsuperscript{73,76} Taking into account these exceptions, worsening renal function as well as hepatic dysfunction during an episode of AHF are independently associated with poorer outcomes.\textsuperscript{60,73,77}

Application of Insights Gained From MOD Data
Greater understanding of the specific causes and mechanisms of death in AHF may have a favorable effect on AHF drug development. It is possible that a more nuanced approach to AHF risk assessment (and more specific patient selection) is required to show benefit of drugs.\textsuperscript{78} The evolving role of pharmacogenomics in HF also shows promise for the future.\textsuperscript{79} With an understanding of gene-dose interactions and the recognition of higher risk gene polymorphisms, the ability to match MOD risk with genotype data could lead to drug regimens and dose optimization. Furthermore, given the large epidemiologic burden of HF, efficacious resource utilization is of clear value. As an example, patients at high risk for specific MOD (eg, HF rather than sudden death or non-CV death) may be better candidates for intensive interventions aimed at detecting and treatment early congestion, such as a post-discharge care team, telemonitoring, and ambulatory invasive hemodynamic monitoring.

Conclusions
AHF is a major public health problem with substantial post-discharge morbidity, including a significant risk of death. Most deaths in the months after AHF hospitalization appear to be from HF and sudden death, but comorbidities, persistent congestion, and end-organ damage sustained during the AHF episode may be important contributors. More study is needed to better characterize the risks associated with mode-specific causes of death in AHF.\textsuperscript{77}

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