Comparison of Troponin Elevation, Prior Myocardial Infarction, and Chest Pain in Acute Ischemic Heart Failure

Cassandra Freitas, MSc, Xuesong Wang, MSc, Yin Ge, MD, Heather J. Ross, MD, MHSc, Peter C. Austin, PhD, Peter S. Pang, MD, MS, Dennis T. Ko, MD, MSc, Michael E. Farkouh, MD, MSc, Therese A. Stukel, PhD, John J.V. McMurray, MBChB (Hons), MD, and Douglas S. Lee, MD, PhD

ABSTRACT

Background: Patients with heart failure (HF) with concomitant ischemic heart disease (IHD) have not been well characterized. We examined survival of patients with ischemic HF syndrome (IHFS), defined as presentation with acute HF and concomitant features suggestive of IHD.

Methods: Patients were included if they presented with acute HF to hospitals in Ontario, Canada. IHD was defined by any of the following criteria: angina/chest pain, prior myocardial infarction (MI), or troponin elevation that was above the upper limit of normal (mild) or suggestive of cardiac injury. Deaths were determined after hospital presentation.

Results: Of 5353 patients presenting with acute HF, 4088 (76.4%) exhibited features of IHFS. Patients with IHFS demonstrated a higher prevalence of more than 26 million people affected worldwide, a 20% lifetime risk of developing HF, and increasing mortality is also high, with up to 50% of those diagnosed with HF dying within 5 years. HF is also responsible for substantial healthcare costs, and a major contributor to the costs and morbidity of HF is acute HF decompensation, which often leads to hospital admission. Further, each decompensation leading to HF hospitalization is associated with an incremental risk of subsequent death.

Prior studies have highlighted that patients with HF with concomitant ischemic heart disease (IHD) are at heightened risk for adverse events. However, outcomes in this heterogeneous group of patients have not been fully characterized in the acute setting. Generally, the importance of IHD in patients with HF is assessed by comparing outcomes in those with an ischemic etiology or history of myocardial infarction...
rate of 30-day (hazard ratio [HR], 1.89; 95% confidence interval [CI], 1.33-2.68) and 1-year death (HR, 1.16; 95% CI, 1.00-1.35) compared with those with nonischemic HF. Troponin elevation demonstrated the strongest association with mortality. Mildly elevated troponin was associated with increased hazard over 30 days (HR, 1.77; 95% CI, 1.12-2.81) and 1-year (HR, 1.63; 95% CI, 1.38-1.93) mortality. Troponins indicative of cardiac injury were associated with increased hazard of death over 30 days (HR, 2.33; 95% CI, 1.63-3.33) and 1 year (HR, 1.40; 95% CI, 1.21-1.61). The association between elevated troponin and higher mortality at 30 days was similar in left ventricular ejection fraction subcategories of HF with reduced ejection fraction, HF with mildly reduced ejection fraction, or HF with preserved ejection fraction ($P$ interaction $= 0.588$). After multivariable adjustment, prior MI and angina were not associated with higher mortality risk.

**Conclusions:** In acute HF, elevated troponin, but not prior MI or angina, was associated with a higher risk of 30-day and 1-year mortality irrespective of left ventricular ejection fraction.

(MI). However, some patients may present with symptomatic myocardial ischemia, troponin elevation, or both, and outcomes in these subsets of patients are less well characterised, especially when they decompensate.

Although angina in patients with HF studied in an ambulatory clinical trial setting was associated with increased risk of cardiovascular events, the frequency and impact of angina in patients presenting with acute HF are unknown. In addition, there are conflicting reports about the relationship between troponin, a biomarker of myocardial injury, and outcomes in acute HF. Higher troponin was associated with higher risk in the Serelaxin, Recombinant Human Relaxin, for Treatment of Acute Heart Failure (RELAX-AHF) trial, whereas no such relationship was observed in Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF).

The relationship between IHD and outcomes may be modified by left ventricular ejection fraction (LVEF). In the Framingham Heart Study, coronary heart disease was a more common cause of death in those with HF with reduced ejection fraction (HFrEF), compared with those with HF with preserved ejection fraction (HFpEF). In the present study, we examined mortality and processes of care in patients with ischemic HF syndrome (IHFS), defined by the presence of anginal symptoms, prior MI, or troponin elevation compared with those without ischemic heart syndrome. We further examined these associations according to LVEF category: HFrEF, HF with mildly reduced ejection fraction (HfmrEF), and HFpEF.

**Methods**

**Patient cohort**

To select cases for detailed chart abstraction, we identified patients who (1) were aged $\geq$ 18 years; (2) presented to the emergency department (ED) with a primary diagnosis of HF as encoded in the National Ambulatory Care Reporting System; and (3) met the clinical Framingham criteria for HF. Patients were excluded if brain natriuretic peptide or NT-pro brain natriuretic peptide levels were not indicative of HF as published in the guidelines of the Canadian Cardiovascular Society (ie, < 100 pg/mL and < 300 pg/mL, respectively). We also excluded patients who (1) had HF as a secondary diagnosis developing after admission, (2) had an acute MI hospitalization within 14 days before presentation, (3) were considered for palliative treatment only or deemed “do not resuscitate” before ED arrival, or (4) visited for a nonacute condition that could have been managed in ambulatory care, as determined by a Canadian Triage Acuity Score of 5.

**Data sources**

We identified eligible patients who presented to the ED using National Ambulatory Care Reporting System and those subsequently hospitalized with a primary diagnosis of HF using the Canadian Institute for Health Information Discharge Abstract Database and the International Classification of Diseases and Related Health Problems 10th Revision Canada (ICD-10-CA) code I50. The Canadian Institute for...
Health Information Discharge Abstract Database and Same-Day Surgery Databases were used to identify cardiac procedures performed in hospital. The Registered Persons Database was used to identify deaths and the Ontario Registrar General Database provided information on cardiovascular vs noncardiovascular causes of death.

Sampling and data abstraction

We used stratified cluster sampling of patients admitted to hospitals in Ontario that had an ED on-site and a yearly volume of greater than 50 patients with acute HF per year. Patients who presented to teaching, medium-sized (51-150 annual HF ED visits), and large (>150 annual HF ED visits) community hospitals, from April 1, 2010, to March 31, 2013, were eligible. If a patient had multiple visits during this period, only the first visit was included. Highly trained, specialized nurse or physician abstractors collected data on approximately 140 patients from each of 13 teaching and 30 large hospitals and approximately 50 patients from each of 27 medium-sized hospitals. Data were collected from hospital medical records using electronic case report forms with automated range checks, double-data entry for key variables, and preloaded medical record numbers to minimize errors in administrative database linkage. To ensure greater representation of patients with IHFS, we oversampled patients who underwent cardiac catheterization (approximately one-third of our total cohort) within 14 days of hospital admission. Research ethics board approval was obtained from all hospitals before data abstraction. Information was retrieved on demographics, clinical characteristics (including cardiac and noncardiac conditions), medications, and laboratory tests, including biomarkers (eg, troponin, brain natriuretic peptide), electrocardiogram, evaluations of left ventricle function, and findings on invasive and noninvasive diagnostic tests. Information on revascularization procedures was also collected.

IHD subgroups

A patient with a primary admission diagnosis of HF was deemed, broadly, to have concomitant IHD syndrome if he/she fulfilled any of the following criteria before index ED presentation: (1) concurrent or prior diagnosis of MI based on the presence of ICD-10 codes I21-I23 or atherosclerotic/IHD (ICD-10 codes I20, I24-25) in any of the primary or secondary diagnosis codes in the previous 5 years; (2) troponin elevation (troponin I, T, or high-sensitivity) above the upper limit of normal (ULN) (including grey zone values of conventional troponin) or exceeding the ULN on peak sample drawn within the first 24 hours; or (3) angina within 48 hours before admission. All other patients were classified as having non-IHFS.

We further stratified troponin elevations as mildly elevated or cardiac injury based on the reference ranges provided by the clinical biochemistry laboratory at participating hospitals. The cardiac injury threshold was defined as the troponin value corresponding to an older definition of MI using creatine kinase-MB and was ascertained for each participating hospital. Mildly elevated troponin was deemed to be present if troponin was higher than the ULN but did not exceed the cardiac injury threshold. Both mildly elevated troponin and cardiac injury were included because prior prognostic studies included both together, and a clear threshold for defining ischemic from nonischemic etiologies has yet to be determined. To characterize the mildly elevated and cardiac injury groups, we examined the median ratios of peak troponin to the ULN within the initial 24 hours after emergency presentation. We also stratified our analysis by LVEF groupings where HFrEF was defined as LVEF < 50%, HFmrEF was defined as LVEF 40% to 49%, and HFrEF was defined as LVEF < 40%.

Statistical analyses

We compared baseline characteristics between the overall ischemic and nonischemic groups using the Kruskal–Wallis test for continuous variables and chi-square test for categorical variables. Multivariable Cox proportional hazards regression models were used to compare the hazard of death between those with ischemic HF and the subcomponent groups of the IHFS (ie, prior MI, angina, troponin elevation) for outcomes over 30 days and 1 year. The multivariable models were adjusted for age, sex, and type of HF (classified as HFrEF, HFmrEF, HFrEF, or unknown ejection fraction if left ventricular function was not measured during the index admission or in the prior 6 months). Multivariable models were also adjusted for components of the Emergency Heart Failure Mortality Risk Grade and other prognostic factors, including diabetes, hypertension, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, hepatic cirrhosis, prior percutaneous coronary intervention or coronary artery bypass graft surgery, respiratory rate, haemoglobin levels, sodium concentration, left bundle branch block or paced rhythm on 12-lead electrocardiogram, atrial fibrillation/flutter, and QRS duration. To account for clustering of patients within hospitals, robust standard errors were obtained when using the Cox model. Cumulative incidence curves for mortality were compared using Gray’s test. Statistical significance was determined as a 2-tailed P value < 0.05. Analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Patient characteristics

Initially, 6846 patients were evaluated (flow diagram in Fig. 1). After exclusions, there were 4088 patients with IHFS, of whom 65.8% had troponin above the ULN (troponin positive), 45.0% had angina, and 52.7% had a prior MI (Fig. 2). Baseline characteristics are shown in Table 1. Patients with HF with IHFS were more likely to be male, were more often transported via emergency medical services, and had more comorbid diabetes, hypertension, cerebrovascular disease, and peripheral artery disease. Nonischemic patients more often had atrial fibrillation or flutter. Echocardiographic findings demonstrated that patients in the ischemic group more often had a lower LVEF (ie, had HFrEF or HFmrEF) compared with the nonischemic group. Cohort characteristics stratified by angina, prior MI, and troponin elevation are shown in Supplemental Tables S1-S3. The ratios of peak troponin to ULN are shown for troponin I, high-sensitivity troponin I, troponin T, and high-sensitivity troponin T in
Figure 3. These ratios were further stratified into 3 levels: normal, mildly elevated, and cardiac injury. Interquartile ranges of these ratios are shown in Supplemental Table S4. Those with mildly elevated troponin had values that were approximately 2-fold higher, whereas cardiac injury was 3 to 4 times higher than the ULN independent of the type of troponin test used.

Thirty-day mortality

The 30-day mortality was 6.9% in patients with ischemic HF and 3.9% in patients with nonischemic HF. After adjusting for age and sex, the hazard ratio (HR) for death over 30 days in ischemic HF was 1.92 (95% confidence interval [CI], 1.46-2.55) compared with nonischemic HF (P < 0.001). The HR was similar after multivariable adjustment: 1.89 (95% CI, 1.33-2.68; P < 0.001). When troponin elevation, angina, and prior MI were entered into the multivariable model in place of any ischemia, only troponin was independently associated with a higher rate of mortality over 30 days. The adjusted HR was 2.19 (95% CI, 1.55-3.10; P < 0.001) for elevated vs normal troponin and 0.87 (95% CI, 0.67-1.12; P = 0.269) for angina, and the HR was 0.92 (95% CI, 0.74-1.14; P = 0.433) for prior MI vs no prior MI.

There was no significant interaction for 30-day mortality between LVEF categories (ie, HFrEF, HFmrEF, and HFpEF) and troponin elevation at 1-year follow-up (P = 0.037). The HR for elevated troponin (vs not elevated) was 1.50 (95% CI, 1.20-1.86; P < 0.001) for HFrEF, 1.22 (95% CI, 0.89-1.68; P = 0.225) for HFmrEF, and 1.31 (95% CI, 1.03-1.67; P = 0.028) for HFpEF. Figure 4A-C illustrates the adjusted cumulative incidence curves for the HFrEF, HFmrEF, and HFpEF categories.
groups, respectively, stratified by troponin positivity. The incidence of death was higher in those with troponin elevation (troponin positive) compared with those with normal troponin levels (troponin negative). Differences in mortality rates over 1 year were significant in the HFrEF ($P < 0.001$) and HFpEF ($P = 0.034$) groups. However, there was no significant interaction between LVEF category and chest pain (interaction $P$ value = 0.849) or prior MI (interaction $P$ value = 0.090).

**Effect of the degree of troponin elevation as a multilevel variable**

In those with IHFS, we found that crude 30-day mortality increased as troponin levels increased from mildly elevated to values indicative of cardiac injury (Table 2, $P$ trend < 0.001). Mortality rates were significantly higher among patients with troponins that were mildly elevated or indicative of cardiac injury compared with normal levels, even after multivariable adjustment (Table 2). At 30 days, the multivariable-adjusted HR for mildly elevated troponin was 1.77 (95% CI, 1.12-2.81) and for cardiac injury range was 2.33 (95% CI, 1.63-3.33) compared with those with normal levels (Table 2). At 1 year, the multivariable-adjusted HR, for mildly elevated troponin was 1.63 (95% CI, 1.38-1.93) and 1.40 (95% CI, 1.21-1.61) when troponins were indicative of cardiac injury.

When troponin was evaluated as a 3-level variable (normal, mildly elevated, and cardiac injury), there was a significant

---

**Table 1. Cohort characteristics**

| Variable, median (IQR) or n (%) | IHFS (N = 4088) | Nonischemic (N = 1265) | $P$ value |
|---------------------------------|-----------------|------------------------|-----------|
| **Demographic**                 |                 |                        |           |
| Age, y                          | 76 (66-83)      | 77 (67-85)             | 0.004     |
| Men                             | 2354 (57.6%)    | 568 (44.9%)            | < 0.001   |
| **IHFS features**               |                 |                        |           |
| Troponin positive               | 2688 (65.8%)    | 0 (0%)                 | < 0.001   |
| Acute angina/chest pain         | 1840 (45.0%)    | 0 (0%)                 | < 0.001   |
| Prior MI                        | 2153 (52.7%)    | 0 (0%)                 | < 0.001   |
| **Presenting features**         |                 |                        |           |
| Transport by EMS                | 1999 (48.9%)    | 522 (41.3%)            | < 0.001   |
| Systolic BP, mm Hg              | 141 (122-161)   | 140 (123-158)          | 0.189     |
| Heart rate, beats/min           | 90 (74-110)     | 90 (74-109)            | 0.523     |
| Oxygen saturation, %            | 0.96 (0.92-0.98)| 0.95 (0.92-0.98)       | 0.096     |
| **Comorbid conditions**         |                 |                        |           |
| Diabetes                        | 1799 (44.0%)    | 493 (39.0%)            | 0.002     |
| Hypertension                    | 3166 (77.4%)    | 928 (73.4%)            | 0.003     |
| Cerebrovascular disease         | 658 (16.1%)     | 167 (13.2%)            | 0.013     |
| Peripheral artery disease       | 478 (11.7%)     | 86 (6.8%)              | < 0.001   |
| Chronic pulmonary disease       | 875 (21.4%)     | 304 (24.0%)            | 0.049     |
| Dementia                        | 210 (5.1%)      | 94 (7.4%)              | 0.002     |
| Active cancer                   | 604 (14.8%)     | 204 (16.1%)            | 0.241     |
| **Laboratory features**         |                 |                        |           |
| Hemoglobin concentration, g/L   | 123 (108-139)   | 120 (106-135)          | < 0.001   |
| White blood count, $\times 10^9$ cells/L | 9.0 (7.1-11.6) | 8.4 (6.6-10.7)        | < 0.001   |
| Sodium concentration, mmol/L    | 138 (135-141)   | 138 (135-141)          | 0.231     |
| Potassium concentration, mmol/L | 4.2 (3.9-4.6)   | 4.2 (3.9-4.6)          | 0.914     |
| Creatinine concentration, $\mu$mol/L | 106 (82-140) | 94 (74-129)            | < 0.001   |
| BNP, pg/mL                      | 466 (231-714)   | 432 (247-612)          | 0.743     |
| **ECG features**                |                 |                        |           |
| Atrial fibrillation or flutter  | 1093 (26.7%)    | 517 (40.9%)            | < 0.001   |
| QRS duration, ms                | 104 (90-136)    | 96 (84-122)            | < 0.001   |
| **Echocardiogram, n (%)**       |                 |                        |           |
| HFrEF                           | 1605 (39.3%)    | 259 (20.5%)            | < 0.001   |
| HFmrEF                          | 634 (15.5%)     | 121 (9.6%)             |           |
| HFpEF                           | 1132 (27.7%)    | 548 (43.3%)            |           |
| LVEF unknown                    | 717 (17.5%)     | 337 (26.6%)            |           |

*BNP, brain natriuretic peptide; BP, blood pressure; EMS, emergency medical services; HF, heart failure; IQR, interquartile range; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IHFS, ischemic HF syndrome; LVEF, left ventricular ejection fraction; MI, myocardial infarction.*

---

**Figure 3.** Median ratios of peak troponin to upper limit of normal (ULN) according to classification as normal, mildly elevated, or cardiac injury, stratified by type of troponin test. Inj, cardiac injury; mild, mildly elevated; N, normal.
interaction with LVEF category (HFrEF, HFmrEF, and HFpEF) for the outcome of 30-day mortality ($P_{\text{interaction}} = 0.036$). There was also a significant interaction between LVEF category and 3-level troponin for 1-year mortality ($P_{\text{interaction}} = 0.028$). Multivariable-adjusted HRs stratified by HFrEF, HFmrEF, or HFpEF status are shown in Table 3 for those with troponins that were mildly elevated or indicative of cardiac injury. There was a significantly higher risk of 30-day mortality in those with mildly elevated troponin with HFpEF (HR, 3.25; 95% CI, 1.59-6.67; $P = 0.001$) and higher 1-year mortality in those with HFmrEF (HR, 1.80; 95% CI, 1.19-2.73; $P = 0.006$). Troponins that were mildly elevated or indicative of cardiac injury were associated with higher risks of death at both 30-day and 1-year time points in those with HFrEF (Table 3).

**Discussion**

The objective of our study was to evaluate prognosis in acutely decompensated patients with IHFS. As a working definition, IHFS was characterized inclusively as the presence of anginal symptoms, history of MI, and biomarkers. We found that those with IHFS had higher short-term and 1-year mortality, and this risk persisted after adjustment for other important predictors of outcome in a multivariable model. However, the excess risk among those with ischemia was confined to the subset of individuals with at least mildly elevated troponin. Troponin was predictive of mortality, irrespective of LVEF category. Angina and prior MI were not associated with increased risk of mortality in the setting of acute HF when entered into a multivariable model including troponin.

There is currently no prognosis-based definition of what constitutes ischemic etiology in HF, although patients with a history of MI or significant coronary stenoses are typically assigned this etiology. Several previous studies have examined the prognostic value of chest pain and history of coronary artery disease in stable HF, but have not studied those presenting with an acute hospitalization. In the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study, Badar et al. examined patients with HFrEF randomized to rosuvastatin or placebo. A current or
Table 2. Associations between troponins that were mildly elevated or indicative of cardiac injury with 30-day and 1-year mortality

| Outcome/LVEF category | No troponin elevation (N = 2665) | Mildly elevated (N = 618) | Cardiac injury (N = 2070) | P value |
|-----------------------|----------------------------------|--------------------------|--------------------------|---------|
| Death                 | n (%)                            | n (%)                    | n (%)                    |         |
| No. of 30-d deaths    | 113 (4.2%)                       | 43 (7.0%)                | 175 (8.5%)               | < 0.001 |
| No. of 1-y deaths     | 588 (22.1%)                      | 185 (29.9%)              | 558 (27.0%)              | < 0.001 |

Death 30 d

| Age, sex | Reference | Adjusted HR (95% CI) | P value vs No troponin elevation | Adjusted HR (95% CI) | P value vs No troponin elevation |
|----------|-----------|----------------------|---------------------------------|----------------------|---------------------------------|
| HFpEF    | 1.65 (1.13-2.42) | 0.010                     | 2.11 (1.54-2.89)               | < 0.001              |
| HFmrEF   | 1.69 (1.15-2.49) | 0.008                     | 2.21 (1.62-3.02)               | < 0.001              |
| HFrEF    | 1.77 (1.12-2.81) | 0.015                     | 2.33 (1.63-3.33)               | < 0.001              |

Death 1 y

| Age, sex | Reference | Adjusted HR (95% CI) | P value | Adjusted HR (95% CI) | P value |
|----------|-----------|----------------------|---------|----------------------|---------|
| HFpEF    | 1.44 (1.21-1.70) | < 0.001              | 1.31 (1.14-1.51)               | < 0.001  |
| HFmrEF   | 1.45 (1.22-1.72) | < 0.001              | 1.34 (1.17-1.54)               | < 0.001  |
| HFrEF    | 1.63 (1.38-1.93) | < 0.001              | 1.40 (1.21-1.61)               | < 0.001  |

CI, confidence interval; HR, hazard ratio; HFpEF, left ventricular ejection fraction; MI, myocardial infarction.

Table 3. Multivariable-adjusted HRs in those with troponins that were mildly elevated or indicative of cardiac injury by LVEF category: HFpEF, HFmrEF, and HFrEF

| Outcome/LVEF category | No troponin elevation | Mildly elevated | Cardiac injury | P value |
|-----------------------|----------------------|-----------------|----------------|---------|
| No. of 30-d deaths    | n (%)                | n (%)           | n (%)          |         |
| HFpEF                 | 29 (4.0%)            | 10 (4.3%)       | 77 (8.4%)      | < 0.001 |
| HFmrEF                | 11 (3.5%)            | SC              | 20 (5.9%)      | 0.159   |
| HFrEF                 | 28 (2.8%)            | 17 (9.8%)       | 22 (4.3%)      | < 0.001 |
| No. of 1-y deaths     | n (%)                | n (%)           | n (%)          |         |
| HFpEF                 | 133 (18.5%)          | 60 (25.8%)      | 221 (24.2%)    | 0.009   |
| HFmrEF                | 74 (23.3%)           | 33 (34.0%)      | 84 (24.6%)     | 0.099   |
| HFrEF                 | 205 (20.6%)          | 45 (26.0%)      | 126 (24.5%)    | 0.112   |

Death 30 d

| Multivariable | Reference | Adjusted HR (95% CI) | P value | Adjusted HR (95% CI) | P value |
|---------------|-----------|----------------------|---------|----------------------|---------|
| HFpEF         | 1.32 (0.75-2.33) | 0.336                     | 2.28 (1.42-3.67)               | < 0.001 |
| HFmrEF        | 0.96 (0.11-8.48) | 0.970                     | 1.72 (0.67-4.43)               | 0.257   |
| HFrEF         | 3.25 (1.39-6.67) | 0.001                     | 1.69 (0.78-3.70)               | 0.186   |

Death 1 y

| Multivariable | Reference | Adjusted HR (95% CI) | P value | Adjusted HR (95% CI) | P value |
|---------------|-----------|----------------------|---------|----------------------|---------|
| HFpEF         | 1.73 (1.23-2.44) | 0.002                     | 1.44 (1.16-1.79)               | 0.001   |
| HFmrEF        | 1.80 (1.19-2.73) | 0.006                     | 1.07 (0.77-1.50)               | 0.677   |
| HFrEF         | 1.32 (0.91-1.92) | 0.149                     | 1.31 (0.99-1.72)               | 0.055   |

Multivariable adjusted: adjusted for age, sex, arrival by emergency medical services, triage systolic blood pressure, triage heart rate, respiratory rate, triage oxygen saturation, diabetes, hypertension, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, hepatic cirrhosis, prior percutaneous coronary intervention or coronary artery bypass graft, haemoglobin, sodium concentration, potassium concentration, creatinine concentration, active cancer, metolazone, left bundle branch block or paced rhythm on 12-lead electrocardiogram, atrial fibrillation/flutter, and QRS duration.

Table 2. Acute Ischemic HF and Mortality

Table 3. Value of Endothelin Receptor Inhibition With Tizosentan in Acute Heart Failure Studies (VERITAS) trial found that...
troponin only marginally improved model discrimination for 90-day mortality.18 Our study was novel because, unlike in other studies, we demonstrated that the prognostic value of troponin elevation was maintained across the range of LVEF categories.16,25 An earlier study did report an association between peak troponin in hospital and prognosis, but unlike in our study in which troponins were only captured at initial emergency presentation, elevation of this biomarker could have occurred at any time during the hospital stay.26 Thus, troponin elevation in this prior study could have occurred after initial presentation and could have been a consequence of acute hemodynamic stress.26 The prevalence of IHFS was higher in our study than in some population-based studies,27,28 but was consistent with another prior study.29 This may have resulted from our intentionally broad inclusion of mildly elevated troponin as part of an IHFS.

The mechanisms by which troponin elevation could confer worsened prognosis include myocyte ischemia or injury, defect in cell membrane integrity, inflammation, and apoptosis.30 These could be exacerbated by activation of the renin-angiotensin-aldosterone system, adrenergic activity, inflammatory cytokines, and mechanical or oxidative stress.30 It is still not defined to what extent demand—supply mismatch related to volume overload and decompensated HF or nonischemic mechanisms may contribute to the worsened prognosis of troponin elevation.30 In our study, angina was associated with lower risk of death at 1 year, and this could have resulted because those with IHFS who have manifest symptoms may enable the detection of ischemia. This hypothesis is supported by the CORONA, CHARM, and I-PRESERVE trials mentioned previously because angina was associated with increased risk of ischemic events, but not mortality. Alternatively, the beneficial effects of anginal symptoms may be mediated by ischemic preconditioning, including via protein kinase C signaling pathways and downstream effects on Akt, P13 kinase, and ERK.31 Even brief episodes of angina can promote ischemic preconditioning32 and could have been responsible for the effects we observed. It should also be noted that although a significant impact of troponin elevation was not observed in those with elevated troponin and HFmrEF, this was the smallest LVEF subgroup with only 35% power to detect a multivariable HR of 1.72.33,34 In contrast, there was 99% power to detect this effect size in the overall HF cohort of 5353 patients.

Our findings highlight the value of troponin as an important predictor of mortality in acute HF, with the risk of death beginning to increase with mildly elevated troponin. Although mortality risk was slightly higher at 30 days in those with MI-range troponin, the risks were comparable to mildly elevated troponin at 1 year, suggesting the possibility that higher intensity of acute medical care in the former group could have attenuated outcome differences. The heightened risk observed irrespective of LVEF advocates for troponin testing upon presentation to the ED.18 Ischemia testing could be considered even among those with mildly elevated troponin, but before doing so, further research is warranted to elucidate the mechanisms for troponin’s role in IHFS.

Study strengths and limitations

This study has several strengths, including a large sample of “real-world” patients with acute HF, characterised in detail and linked to multiple administrative databases. Our study was limited by the absence of a standard definition of IHFS. Thus, our study was designed with a pragmatic definition of IHFS broadly defined by the trio of troponin elevation, anginal symptoms, and prior MI. Additionally, it is conceivable that there is overlap between those with HF and an associated increase in troponin vs those with acute MI with complicating HF. Although similar clinically, there may be pathophysiologic differences between these 2 conditions. Although it has been debated whether HFmrEF is a separate entity,35 practice guidelines differentiate it separately from HFpEF or HFrEF,36 and prior work has shown that a 10% decrement in LVEF is associated with significantly increased risk of HF hospitalization, cardiovascular hospitalization, and mortality.37

Conclusions

Our study demonstrated the importance of IHFS in acute decompensated HF irrespective of underlying HFrEF, HFmrEF, or HFpEF status. Even a mildly elevated troponin was associated with 30-day and 1-year mortality. Troponin testing may serve as a useful tool to guide medical decision-making in acute HF care.

Funding Sources

ICES is supported in part by a grant from the Ontario Ministry of Health and Long-Term Care. The opinions, results, and conclusions are those of the authors, and no endorsement by the Ministry of Health and Long-Term Care or by ICES is intended or should be inferred. Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions, and statements expressed herein are those of the authors and not necessarily those of CIHI. This study was supported by a Grant in Aid from the Heart and Stroke Foundation and a Foundation Grant from the Canadian Institutes of Health Research (Grant FDN 148446). Dr Lee is supported by a mid-career investigator award from the Heart and Stroke Foundation and the Ted Rogers Chair in Heart Function Outcomes, a joint Hospital-University Chair of the University Health Network, and the University of Toronto. Dr Austin is supported by a Mid-Career investigator award from the Heart and Stroke Foundation. Dr Ko is supported by a mid-career award from the Heart and Stroke Foundation.

Disclosures

The authors have no conflicts of interest to disclose.
References

1. Ketchum ES, Levy WC. Establishing prognosis in heart failure: a multimarker approach. Prog Cardiovasc Dis 2011;54:85-96.

2. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 2014;63:1123-33.

3. Braga JR, Leong-Poi H, Rac VE, et al. Trends in the use of cardiac imaging for patients with heart failure in Canada. JAMA Netw Open 2019;2:e198766.

4. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. JAMA 2004;292:344-50.

5. Lee DS, Austin PC, Stukel TA, et al. Dose-dependent” impact of recurrent cardiac events on mortality in patients with heart failure. Am J Med 2009;112:162-9 e161.

6. Chun S, Tu JV, Wijeyasurya HC, et al. Lifetime analysis of hospitalizations and survival of patients newly admitted with heart failure. Circ Heart Fail 2012;5:414-21.

7. Badar AA, Perez-Moreno AC, Jhund PS, et al. Relationship between angina pectoris and outcomes in patients with heart failure and reduced ejection fraction: an analysis of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA). Eur Heart J 2014;35:3426-33.

8. Pang PS, Teeflink JR, Voors AA, et al. Use of high-sensitivity troponin T to identify patients with acute heart failure at lower risk for adverse outcomes: an exploratory analysis from the RELAX-AHF Trial. JACC Heart Fail 2016;4:591-9.

9. Felker GM, Hasselblad V, Tang WH, et al. Troponin I in acute decompensated heart failure: insights from the ASCEND-HF study. Eur J Heart Fail 2012;14:1247-64.

10. Lee DS, Gona P, Albano I, et al. A systematic assessment of causes of death after heart failure onset in the community: impact of age at death, time period, and left ventricular systolic dysfunction. Circ Heart Fail 2011;4:36:43.

11. Lee DS, Pencina MJ, Benjamin EJ, et al. Association of parental heart failure with risk of heart failure in offspring. N Engl J Med 2006;355:138-47.

12. Ezekowitz JA, O’Meara E, McDonald MA, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can J Cardiol 2017;33:1342-3.

13. Bullard MJ, Unger B, Spence J, Grafstein E; CTAS National Working Group. Revisions to the Canadian Emergency Department Triage and Acuity Scale (CTAS) adult guidelines. CJEM 2008;10:136-51.

14. Van Spall HG, Arzema C, Schull MJ, et al. Prediction of emergent heart failure death by semi-quantitative triage risk stratification. PLoS One 2011;6:e23065.

15. Brush JE Jr, Kaul S, Krumholz HM. Troponin testing for clinicians. J Am Coll Cardiol 2016;68:2365-75.

16. Braga JR, Tu JV, Austin PC, et al. Outcomes and care of patients with acute heart failure syndromes and cardiac troponin elevation. Circ Heart Fail 2013;6:193-202.

17. Lee DS, Stirit A, Austin PC, et al. Prediction of heart failure mortality in emergent care: a cohort study. Ann Intern Med 2012;156:767-75.

18. Lee DS, Lee JS, Schull MJ, et al. Prospective validation of the emergency heart failure mortality risk grade for acute heart failure. Circulation 2019;139:1146-56.

19. Felker GM, Shaw LK, O’Connor CM. A standardized definition of ischemic cardiomyopathy for use in clinical research. J Am Coll Cardiol 2002;39:210-8.

20. Braga JR, Austin PC, Ross HJ, Tu JV, Lee DS. Importance of non-obstructive coronary artery disease in the prognosis of patients with heart failure. JACC Heart Fail 2019;7:493-501.

21. Badar AA, Perez-Moreno AC, Hawkins NM, et al. Clinical characteristics and outcomes of patients with angina and heart failure in the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) Programme. Eur J Heart Fail 2015;17:196-204.

22. Badar AA, Perez-Moreno AC, Hawkins NM, et al. Clinical characteristics and outcomes of patients with coronary artery disease and angina: analysis of the Irbesartan in Patients With Heart Failure and Preserved Systolic Function Trial. Circ Heart Fail 2015;8:717-24.

23. Raslan IR, Brown P, Westerhout CM, et al. Characterization of hemodynamically stable acute heart failure patients requiring a critical care unit admission: derivation, validation, and refinement of a risk score. Am J Heart 2017;188:127-35.

24. Cleland JGF, Teeflink JR, Davison BA, et al. Measurement of troponin and natriuretic peptides shortly after admission in patients with heart failure—does it add useful prognostic information? An analysis of the Value of Endothelin Receptor Inhibition with Tezosentan in Acute heart failure Studies (VERTITAS). Eur J Heart Fail 2017;19:739-47.

25. Peacock WFt, De Marco T, Fonarow GC, et al. Cardiac troponin and outcome in acute heart failure. N Engl J Med 2008;358:2117-26.

26. Pandey A, Golvala H, Sheng S, et al. Factors associated with and prognostic implications of cardiac troponin elevation in decompensated heart failure with preserved ejection fraction: findings from the American Heart Association Get With The Guidelines-Heart Failure Program. JAMA Cardiol 2017;2:136-45.

27. Fox KF, Cowie MR, Wood DA, et al. Coronary artery disease as the cause of incident heart failure in the population. Eur Heart J 2001;22:228-36.

28. Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for heart failure: a population-based case-control study. Am J Med 2009;122:1023-8.

29. Gheorghida M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. Circulation 1998;97:282-9.

30. Horwich TB, Patel J, MacLellan WR, Fonarow GC. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. Circulation 2003;108:833-8.

31. Yang X, Cohen MV, Downey JM. Mechanism of cardioprotection by early ischemic preconditioning. Cardiovasc Drugs Ther 2010;24:225-34.

32. Tomai F, Crea F, Chiariello L, Gioffre PA. Ischemic preconditioning in humans: models, mediators, and clinical relevance. Circulation 1999;100:559-63.

33. Hsieh FY, Lavori PW. Sample-size calculations for the Cox proportional hazards regression model with nonbinary covariates. Control Clin Trials 2000;21:552-60.
34. Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. Biometrics 1983;39:499-503.

35. Butler J, Anker SD, Packer M. Redefining heart failure with a reduced ejection fraction. JAMA 2019 Sep 13 [Epub ahead of print].

36. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.

37. Angaran P, Dorian P, Ha ACT, et al. Association of left ventricular ejection fraction with mortality and hospitalizations [Epub ahead of print]. J Am Soc Echocardiogr https://doi.org/10.1016/j.echo.2019.12.016.

**Supplementary Material**

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2020.02.007.