Acute Heart Failure
Perspectives From a Randomized Trial and a Simultaneous Registry

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Background—Randomized controlled trials (RCT) are limited by their generalizability to the broader nontrial population. To provide a context for Acute Study of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, we designed a complementary registry to characterize clinical characteristics, practice patterns, and in-hospital outcomes of acute heart failure patients.

Methods and Results—Eligible patients for the registry included those with a principal diagnosis of acute heart failure (ICD-9-CM 402 and 428; ICD-10 ISO.x, 111.0, 113.0, 113.2) from 8 sites participating in ASCEND-HF (n=697 patients, 2007–2010). Baseline characteristics, treatments, and hospital outcomes from the registry were compared with ASCEND-HF RCT patients from 31 Canadian sites (n=465, 2007–2010). Patients in the registry were older, more likely to be female, and have chronic respiratory disease, less likely to have diabetes mellitus: they had a similar incidence of ischemic HF, atrial fibrillation, and similar B-type natriuretic peptide levels. Registry patients had higher systolic blood pressure (registry: median 132 mm Hg [interquartile range 115–151 mm Hg]; RCT: median 120 mm Hg [interquartile range 110–135 mm Hg]) and ejection fraction (registry: median 40% [interquartile range 27–58%]; RCT: median 29% [interquartile range 20–40 mm Hg]) than RCT patients. Registry patients presented more often via ambulance and had a similar total length of stay as RCT patients. In-hospital mortality was significantly higher in the registry compared with the RCT patients (9.3% versus 1.3%, P<0.001), and this remained after multivariable adjustment (odds ratio 6.6, 95% CI 2.6–16.8, P<0.001).

Conclusions—Patients enrolled in a large RCT of acute heart failure differed significantly based on clinical characteristics, treatments, and inpatient outcomes from contemporaneous patients participating in a registry. These results highlight the need for context of RCTs to evaluate generalizability of results and especially the need to improve clinical outcomes in acute heart failure.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00475852. (Circ Heart Fail. 2012;5:735-741.)

Key Words: acute heart failure ■ clinical trial ■ epidemiology

Although randomized controlled trials (RCT) form the standard for generating clinical evidence for the efficacy of novel treatments, the importance of clinical registries has become increasingly appreciated to understand the broader generalizability, effectiveness, and safety of such therapies. Findings from registries provide an authentic window on the epidemiology of disease and are generally more reflective of real-world clinical practice.1–3 As such, they characterize current management strategies and generate novel hypotheses. These factors are particularly germane to clinical syndromes, such as acute heart failure which are time-sensitive, and involve patients potentially difficult to recruit into RCTs.

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Because both registries and RCT are essential in clinical research to address questions regarding the potential population under study and evaluate the efficacy of interventions, it is important to compare these 2 populations according to their clinical characteristics, care processes, and clinical outcomes. However, registries are rarely developed in a contemporary fashion from the institutional sources of a clinical trial. For example, comparisons between registries and RCT (when collected at the same site) in studies of patients with acute myocardial infarction have demonstrated that registry...
populations have more high-risk baseline characteristics, are less frequently treated according to guidelines, and have increased mortality compared with RCT patients. Importantly however, no acute heart failure studies have yet directly compared the populations of associated registries and RCTs.

The recently completed Acute Study of Nesiritide in Decompensated Heart Failure (ASCEND-HF) RCT is the largest acute heart failure (AHF) trial to date (n=7141 patients) and provides key information on the management and outcomes of patients with AHF. To better understand the population from which this trial was recruited and the results of the ASCEND-HF trial, a corresponding AHF registry was compiled using non-RCT patients from 8 Canadian sites participating in this RCT. In this report, we describe the baseline patient risk profile, in-hospital and discharge management, and clinical outcomes of patients enrolled in the registry and the RCT.

Methods

Study Design

The registry was a multicenter, retrospective, observational cohort to study the management of patients with AHF treated in the emergency department and inpatient setting (if admitted) based on estimated monthly enrollment in the RCT and local disease prevalence. ASCEND-HF was a double-blind RCT that enrolled patients with AHF within 24 hours of first intravenous heart failure related treatment. The full inclusion and exclusion criteria have been published. Briefly, participants were required to have each of the following at time of randomization: dyspnea at rest or with minimal activity; ≥1 accompanying sign (respiratory rate ≥20 breaths/min or pulmonary congestion/edema with radiographs ≥1/3 base) and ≥1 objective measure of heart failure (evidence of congestion/edema on chest x-ray; BNP ≥1000 pg/mL or pulmonary capillary wedge pressure >20 mm Hg; or left ventricular ejection fraction <40% in the previous 12 months). A full description of patients enrolled in the registry is provided in Table 1.

Setting

Select sites participating in the ASCEND-HF trial were approached to participate in the registry based on feasibility and enrollment into the RCT. Overall, 8 sites (3 community and 5 tertiary care) across 5 Canadian provinces participated: Vancouver General Hospital (VGH), Vancouver, B.C., University of Alberta, Edmonton, Alberta (UA); St. Boniface Hospital (SB), Winnipeg, Manitoba; Ajax & Pickering Hospital (APH), Ajax, Ontario, Cornwall General Hospital (CGH); Toronto General Hospital (TGH), Toronto, Ontario; Montreal Heart Institute (MHI), Montreal, Quebec; and the Hospital Laval (HL), Laval, Quebec.

Registry Participants

Patients >18 years of age were included if they were seen in the emergency department, or directly admitted to the participating hospital and had the most responsible (principal) diagnosis of heart failure. The most responsible diagnosis was identified by ICD-10 codes (I50.x, I11.0, I13.0, I13.2). Patients were excluded if they were participating in a RCT of AHF therapy or had heart failure as an in-hospital complication of a surgical procedure. Each site was asked to collect data for multiple 1-month blocks of time on consecutive patients with AHF. The 1-month blocks were dispersed during May 2007 through December 2009 across sites to cover the 12-month calendar year and the enrollment period of ASCEND-HF. Each site was asked to provide data for <4 months, and a total of 57-month blocks were obtained. For this analysis, only patients admitted to hospital are included (n=697 patients). A full description of patients enrolled in the RCT have been described previously; 465 patients enrolled in Canada were included in the current study.

Variables, Data Sources, and Measurements

Registry data, including clinical history and exam findings, symptoms, and investigation results were abstracted from the chart by trained study personnel to standardized paper case-report forms. Only in-hospital data were available from all sites. Audit and feedback was provided to sites as part of quality assurance. Data were transferred to the Epidemiology Coordinating and Research Centre (Edmonton, Alberta, Canada) for data entry, and the database was then transferred to the Canadian Virtual Coordinating Centre for Global Collaborative Cardiovascular Research (VIGOUR) Center (Edmonton, Alberta, Canada) for statistical analysis. All data management, analyses, and interpretation of the results were done independent of the sponsor.

Statistical Analysis

Data for continuous variables are presented as medians with 25th and 75th percentiles (unless otherwise indicated), and categorical variables are presented as frequencies and percentages. The Wilcoxon rank-sum test was used to test differences among groups for continuous variables and χ² test for categorical variables.

The association between registry (versus RCT) and in-hospital mortality was examined and adjustments were made using a baseline, patient characteristic model predicting 30-day mortality, which was developed and validated in the overall ASCEND-HF trial. Covariates in the model included age, systolic blood pressure, blood urea nitrogen, sodium, the presence of dyspnea at rest, and site location. The risk-adjusted association is reported as an odds ratio with a corresponding 95% CI. All statistical tests were two sided, and the level of statistical significance was P<0.05. As this study is among the first of its kind in patients with heart failure and hypothesis generating in nature, we did not adjust the level of statistical significance for multiple comparisons. All analyses were performed using SAS (version 9.2, Cary, NC).

Results

Baseline Characteristics

There were 465 patients enrolled in the ASCEND-HF trial and 697 patients in the registry (Table 1). Patients enrolled in the RCT at sites participating or not participating in the registry were similar in age, sex, medical history, symptoms, physical exam findings, and investigation results (data not shown). Patients in the registry were significantly older, less likely to be male, more likely to have cerebrovascular disease, chronic respiratory disease, prior cancer, depression, and more likely to have an implantable cardiac defibrillator or pacemaker. The only comorbidities more common in the RCT patients were diabetes mellitus and hyperlipidemia.

RCT patients were more likely to report dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, and weight gain because of fluid retention. Registry patients had a higher systolic blood pressure and a lower respiratory rate, and were less likely to have pulmonary congestion, an elevated jugular venous pressure, or peripheral edema on examination.

B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide was similar in both groups. Poor renal function (elevated creatinine, elevated blood urea nitrogen, and lower creatinine clearance) was more common in the registry patients. Ejection fraction was lower in RCT patients (median 29 versus 40%, P<0.001).

Process of Care

Process of care measures for the trial and registry patients are reported in Table 2. Registry patients were more...
likely to have presented via ambulance (52% versus 27%, \( P<0.001 \)), received medication in the ambulance (53% versus 34%, \( P<0.001 \)), and to have received a family medicine (13.2% versus 1.9%) or internal medicine consultation (58.4% versus 12.3%) compared with trial patients. The time from triage to first physician evaluation was also longer for registry patients than for trial patients (51 versus 43 minutes).
Table 2. Process of Care Indicators According to RCT and Registry Enrollment

<table>
<thead>
<tr>
<th>Indicator</th>
<th>RCT</th>
<th>Registry</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrival and triage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrived by ambulance</td>
<td>27</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Self-present</td>
<td>73</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Medications given in ambulance</td>
<td>34</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Time from triage to first MD, min, median (IQR)</td>
<td>43 (8–102)</td>
<td>51 (25–109)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Consultations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family medicine</td>
<td>2</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Internal medicine</td>
<td>12</td>
<td>58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiology</td>
<td>56</td>
<td>56</td>
<td>0.88</td>
</tr>
<tr>
<td>Intravenous medications given in ER or hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>90</td>
<td>86</td>
<td>0.03</td>
</tr>
<tr>
<td>Dobutamine/milrinone/dopamine</td>
<td>7</td>
<td>9</td>
<td>0.31</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>10</td>
<td>12</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Variables are % unless otherwise specified. RCT indicates randomized controlled trials; IQR, interquartile range; ER, emergency room.

Medications
Registry patients were less likely to receive in-hospital intravenous diuretics than RCT patients (Table 2). However, there were no differences in inotropic or vasodilator use between registry or RCT patients. There were substantial differences in oral baseline and discharge medications between the registry and RCT patients (Table 3). At baseline, registry patients were less likely to be on an angiotensin-converting enzyme (ACE)-inhibitor and statins; there were no statistically significant differences in percentage of patients on any of the other medications at baseline. However, at discharge, registry patients were less likely than RCT patients to be on ACE-inhibitors, β-blockers, aldosterone antagonists, digoxin, aspirin, or statins. For example, among registry patients, 55% and 68% were discharged on an ACE-inhibitor or a β-blocker, compared with 76% and 80%, respectively, for RCT patients (P<0.001 for both comparisons).

Clinical Outcomes
Registry patients had a shorter median total length of stay (8 versus 9 days, P=0.003), although the number of intensive care days were similar (4 days, P=0.69; Table 4). In patients who survived hospitalization (RCT n=459; registry n=632), the total length of stay remained shorter for registry patients (7 versus 9 days, P<0.001). In terms of in-hospital medical events, registry patients were more likely to experience worsening heart failure (10.3% versus 3.4%) and require mechanical ventilation (intubation, continuous, or bilevel positive airway pressure ventilation; 13.2% versus 6.9%; P=0.001). The overall in-hospital mortality for the registry patients was significantly higher than for the RCT patients (9.3% versus 1.3%, P<0.001). After adjusting for key patient characteristics, registry patients still had a nearly 7-fold increased risk of in-hospital death (odds ratio 6.57; 95% CI 2.57–16.77; P<0.001).

Discussion
This is the first study in acute heart failure to compare RCT patients directly with registry patients. Our study demonstrates that differences exist between these 2 patient populations in terms of baseline characteristics, processes of care, and inpatient outcomes. First, despite the pragmatic design of ASCEND-HF, the 2 patient populations varied significantly in age, sex, and baseline comorbidities. It is important to recognize that clinical trials select patients by inclusion criteria (and select out by exclusion criteria), whereas population health studies or registry data have broader generalizability, but may lack precision. Hence, evaluation of novel therapies outside of the typical clinical trial environment should be undertaken to expand the scope of where and how novel therapies are assessed. One such current example is the Thrombus Aspiration in Myocardial Infarction trial (www.clinicaltrials.gov NCT01093404), where randomization into a clinical trial via a registry streamlines recruitment of a broadly inclusive population. Second, although patients in the current RCT and registry sample had a similar number of days in a critical care unit and use of intravenous inotropes or vasodilators, interestingly the registry patients had a higher ejection fraction and systolic blood pressure—features generally associated with lower risk for clinical events. However, the most striking observation is the observed in-hospital mortality: 9.3% for registry patients compared with only 1.3% in RCT patients. Even after adjustment for patient characteristics, registry patients had a 7-fold higher risk of mortality compared with RCT patients.

The accompanying registry and the ASCEND-HF trial highlight several novel early process of care features. ASCEND-HF enrolled patients early in their course of care for AHF with a median of 15.5 hours from time of first medical hospital-based contact. Importantly, we also collected data regarding ambulance use in AHF. Ambulance use for patients with AHF has not been previously described in a chor and community where detailed clinical data are known: we observed that 52% of AHF used an ambulance within the registry compared with
Table 4. Clinical Outcomes According to RCT and Registry Enrollment

<table>
<thead>
<tr>
<th>Medical events during hospitalization, %</th>
<th>RCT</th>
<th>Registry</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening heart failure</td>
<td>3.4</td>
<td>10.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>6.9</td>
<td>13.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Ventricular fibrillation/tachycardia</td>
<td>1.5</td>
<td>2.6</td>
<td>0.22</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>1.3</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>5.0</td>
<td>4.2</td>
<td>0.53</td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>0.4</td>
<td>1.0</td>
<td>0.33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Length of stay</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay, total days, median (IQR)</td>
<td>9 (6–14)</td>
<td>8 (4–16)</td>
</tr>
<tr>
<td>No. of days in ER, days, median (IQR)</td>
<td>1 (1–1)</td>
<td>1 (1–1)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.04 (0.84)</td>
<td>1.29 (0.77)</td>
</tr>
<tr>
<td>Length of stay, CCU/ICU days, median (IQR)</td>
<td>4 (2–7)</td>
<td>4 (2–7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unadjusted mortality, %</th>
<th>RCT</th>
<th>Registry</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted mortality, %</td>
<td>1.3</td>
<td>9.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Adjusted mortality, odds ratio (95%CI)*

| Mechanical ventilation includes tracheal intubation, continuous or bilevel positive airway pressure. RCT indicates randomized controlled trials; IQR, interquartile range; CCU, cardiac care unit; ICU, intensive care unit. |

*Adjusted for age, systolic blood pressure, blood urea nitrogen, and sodium.

27% of patients in the trial. These differences may relate to the older age, sex differences, or other characteristics of patients in the registry which may influence ambulance use. As is the case in acute myocardial infarction they likely reflect a higher risk profile.7 Ambulance-based initial emergency care remains important as in many jurisdictions, working diagnoses and medications are given in the prehospital setting and triage decisions are made based on risk-assessment in the ambulance. In turn, this can determine how quickly patients are treated upon arrival to an emergency department. For example, we identified that the median value for arrival from emergency department to first treatment of patients with AHF remained under 1 hour for both groups. Whether or not ambulance arrival indirectly affects initial triage in a system with universally accepted triage scoring is unknown.

The rate of use of continuous positive airway pressure, bilevel positive airway pressure, and mechanical intubation in the registry patients was higher than expected and has not been previously described in a community-based AHF cohort. It is unclear whether this was related to the severity of the initial presentation, a terminal event, or a complication occurring during care. Continuous positive airway pressure and bilevel positive airway pressure have limited evidence supporting their routine use in clinical practice given the large RCT that did not demonstrate any differences in mortality or intubation rates by day 7.10 The real-world application of noninvasive ventilation requires further interrogation via registry data to establish whether clinicians are over- or under-applying these therapies, and in whom they are applying this therapy.

Other therapy, including oral heart failure medication use, varied between registry and RCT patients but is unlikely to account for the short-term, in-hospital mortality difference. The sites and time frame of the RCT and registry allow for direct rather than indirect comparisons and thus a closer reflection of the generalizability to clinical practice. For example, a significantly lower percentage of registry patients were discharged on an ACE-inhibitor or a β-blocker. Although it is possible that registry patients had fewer indications (eg, fewer patients with preserved systolic function) or more contraindications or prior intolerance, we did not collect more detailed information in the registry. It is plausible that by emphasizing a high standard of care in the RCT by providing an accompanying standard of care manual to RCT sites that we altered the natural history of the management of patients enrolled in the RCT.11 Notably, patients in the RCT had significant increases in the rate of ACE-inhibitor, β-blocker, and aldosterone antagonist prescriptions from baseline to discharge. Conversely, this likely had less effect on registry patients as they were not directly cared for by the clinical research team and unmeasured confounders, such as severity of noncardiac comorbid conditions or patient preferences may have played a significant role in these lower utilization rates.

Once admitted for AHF, patients in this registry had a slightly shorter length of stay than those in a RCT, yet the number of days in a critical care bed were similar. The shorter length of stay among registry patients remained, even after censoring those patients who died in hospital. We and others have previously described the use of critical care beds in the last 6 months of life (a mean of 2 days during the 6 months).12,13 Total, as well as critical care days, are a major driver for total costs of care for AHF; and AHF remains one of the most common causes for both admission and re-admission.14 Unless improvements are made in systems of care using evidence-based care pathways, algorithms or in- and out-patient clinical services, it will continue to be in this unenviable leading position.

Prior heart failure registries and quality of care initiatives (such as Get With The Guidelines or Acute Decompensated
Heart Failure National Registry [ADHERE]) suggest that registry populations are indeed highly generalizable to broader populations (ie, via Medicare data). However, only a few RCTs have used this opportunity to better understand the applicability and generalizability of the investigative product or population under study. The Valsartan in Acute Myocardial Infarction (VALIANT) registry is one example of a large-scale postmyocardial infarction heart failure registry that has generated a wealth of understanding of the clinical state of high-risk acute cardiovascular disease. Additionally, Bahit et al found that individuals in a thrombolysis in myocardial infarction registry had higher baseline Killip classes, were less likely to be treated with aspirin, β-blockers, and ACE-inhibitors, and had a higher mortality rate of 8.5% compared with 5.0% in the acute myocardial infarction trial population.

Limitations and Strengths
There are some limitations to our study. The registry data were collected via a retrospective chart review, whereas by design, the RCT data were collected prospectively. However, given that sites and site personnel generating the data were the same, it seems unlikely that there were systematic differences in the quality of the data collected at a site level. Additionally, variables were chosen to be similar between the registry and RCT to allow direct comparisons between the 2 different cohorts. We also did not capture if a patient was being considered for hospice or palliative care, although this remains uncommon in Canada and limited predominantly to cancer patients. Finally, in-hospital outcomes were collected in the registry, whereas RCT data collection extended beyond hospital discharge. Given the higher in-hospital mortality of the registry patients, it is unlikely that this difference would narrow significantly in the first 30 days; moreover, it could well further widen.

Even within our RCT and registry comparison, there may be bias inherent in obtaining consent, or patient or site ability or willingness to participate in research that may in part explain some of the differences observed. For example, patients with a lower socioeconomic status are less likely to participate in research, and the under-representation of elderly and female patients (both prominent in our registry but not the RCT) has been highlighted before.

Conclusions
Patients enrolled in a clinical trial of AHF therapy are at lower risk for clinical events and vary substantially from patients enrolled in a concurrent registry. This difference in mortality and other clinical outcomes persisted, even after adjusting patient for prognostically relevant characteristics. Additional commitment from patients, hospital systems, investigative sites, and physicians to participate in RCT of novel therapies or strategies is required to advance AHF research. Future phase III trials should collect and report data on patients both within and outside of the trial to place the results in an appropriate context.

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References


**CLINICAL PERSPECTIVE**

Randomized controlled trials play a key role in determining the efficacy of a new treatments or management strategies, but often lack generalizability to the broader population. We designed and implemented a registry with rich clinical detail at the same time and trial sites as a large randomized controlled trial, and found that registry patients were older, more likely to be female and have a higher ejection fraction than trial patients. Other important differences also existed highlighting the selection that exists even in a large pragmatic randomized clinical trial. Importantly, the in-hospital mortality was 6-fold higher even after adjustment for key differences and high-risk features. Placing new therapies in context of the target population is a key step for clinical research initiatives.
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