Risk-Treatment Mismatch in the Pharmacotherapy of Heart Failure

Douglas S. Lee, MD, PhD
Jack V. Tu, MD, PhD
David N. Juurlink, MD, PhD
David A. Alter, MD, PhD
Dennis T. Ko, MD
Peter C. Austin, PhD
Alice Chong, BSc
Therese A. Stukel, PhD
Daniel Levy, MD
Andreas Laupacis, MD, MSc

HEART FAILURE AFFECTS MORE than 5 million people in Canada and the United States and is associated with a high mortality rate.1,2 Medications shown to reduce the mortality and morbidity of this condition include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and β-adrenergic receptor antagonists.3-5 These drug classes have been studied extensively and recommended strongly by disease management guidelines.6,7 Given the proven mortality benefits of these drugs, it is important to ensure that patients at the highest risk of death receive these therapies.8-12

Intuitively, it might be expected that higher propensity to receive treatment would occur in those individuals at highest risk. However, prior studies suggest that the opposite may occur in practice.13-18 For example, among elderly patients with acute coronary syndromes, rates of treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors were lower among patients with higher probability of death,19 despite the proven benefits of such treatment.20,21 Discordant patterns of treatment rates and risk of death may significantly impact disease outcomes of other conditions associated with mortality burden. Heart failure is associated with substantial mortality, and failure to treat higher-risk patients with life-sustaining therapies could adversely affect outcomes. Prior studies have not evaluated whether the propensity to treatment is directly or inversely associated with risk of death in patients with heart failure.

Context Patients with heart failure have a wide spectrum of mortality risks. To maximize the benefit of available pharmacotherapies, patients with high mortality risk should receive high rates of drug therapy.

Objective To examine patterns of drug therapy and underlying mortality risk in patients with heart failure.

Design, Setting, and Patients In the Enhanced Feedback for Effective Cardiac Treatment (EFFECt) population-based cohort (1999-2001) of 9942 patients with heart failure hospitalized in Ontario, Canada, we evaluated 1418 patients with documented left ventricular ejection fraction of 40% or less and aged 79 years or younger with low-, average-, and high-predicted risk of death within a year; all patients survived to hospital discharge. Administration of angiotensin-converting enzyme (ACE) inhibitors, ACE inhibitors or angiotensin II receptor blockers (ARBs), and β-adrenergic receptor antagonists was evaluated according to predicted risk of death.

Main Outcome Measure Heart failure drug administration rates at time of discharge and 90 days after hospital discharge.

Results At hospital discharge, prescription rates for patients in the low-, average-, and high-risk groups were 81%, 73%, 60%, respectively, for ACE inhibitors; 86%, 80%, 65%, respectively, for ACE inhibitors or ARBs; and 40%, 33%, 24%, respectively, for β-adrenergic receptor antagonists (all P < .001 for trend). Within 90 days following hospital discharge, the rates were 83%, 76%, and 61% for ACE inhibitors; 89%, 83%, and 67% for ACE inhibitors or ARBs; and 43%, 36%, and 28% for β-adrenergic receptor antagonists for the 3 risk groups, respectively (all P < .001 for trend). The pattern of lower rates of drug administration in those patients at increasing risk was maintained up to 1 year postdischarge (P < .001). After accounting for varying survival time and potential contraindications to therapy, low-risk patients were more likely to receive ACE inhibitors or ARBs (adjusted hazard ratio [HR], 1.61; 95% confidence interval [CI], 1.49-1.74) and ACE inhibitors or ARBs (adjusted HR, 1.80; 95% CI, 1.60-2.01) compared with high-risk patients (both P < .001).

Conclusions Patients with heart failure at greatest risk of death are least likely to receive ACE inhibitors, ACE inhibitors or ARBs, and β-adrenergic receptor antagonists. Understanding the reasons underlying this mismatch may facilitate improvements in care and outcomes for patients with heart failure.

Author Affiliations: Institute for Clinical Evaluative Sciences (Drs Lee, Tu, Juurlink, Alter, Ko, Austin, Stukel, and Laupacis, and Ms Chong), Department of Health Policy, Management, and Evaluation, University of Toronto (Drs Tu, Juurlink, Alter, Ko, Austin, Stukel, and Laupacis), Sunnybrook and Women’s College Health Sciences Centre, University of Toronto (Drs Tu, Juurlink, Alter, Ko, and Laupacis), Toronto, Ontario; and the Framingham Heart Study of the National Heart, Lung, and Blood Institute, National Institutes of Health, Framingham, Mass (Drs Lee and Levy).

Corresponding Author: Andreas Laupacis, MD, MSc, Institute for Clinical Evaluative Sciences, Room C-106, 2075 Bayview Ave, Toronto, Ontario, Canada M4N 3M5 (alaupacis@ices.on.ca).
A requisite for study of the patterns of risk and treatment rates is the availability of an objective method for identifying risk. Recently, our group developed and validated the Enhanced Feedback for Effective Cardiac Treatment (EFFEKT) heart failure mortality risk-stratification method, which stratifies patients with heart failure according to their probability of death.22 In this study, we examined the use of drug therapies for heart failure in relation to predicted 1-year mortality rates. We hypothesized that patients at greatest risk of death would be the least likely to receive beneficial drug therapies.

**METHODS**

**Study Sample**

The patients included in our study were those hospitalized for heart failure as part of the EFFEKT study. The EFFEKT study included 103 acute-care hospitals in Ontario, Canada, providing care to patients with heart failure from April 1999 to March 2001; details of the study have been described previously.22 Patients with a primary diagnosis of heart failure, according to the International Classification of Diseases, Ninth Revision, in the Canadian Institute for Health Information discharge abstract database and who met the Framingham heart failure criteria23 were identified for detailed chart abstraction of presentation clinical variables, comorbidities, laboratory measurements, and left ventricular ejection fraction (LVEF). Ethics approval was obtained from all participating institutions before the study, and individual-level informed consent was deemed not required.

We initially examined all patients with heart failure aged 79 years or younger who had an LVEF of 40% or less by echocardiography, radionuclide ventriculogram, or left ventricular angiography, and subsequently expanded the analysis to include elderly patients older than 79 years. Because the primary outcomes of the study were drug prescription rates at discharge or 90 days after hospital discharge, we excluded patients who died during hospital admission. In additional analyses, we examined a healthier subset of patients with heart failure without life-limiting noncardiac comorbidities (cancer, cerebrovascular disease, dementia, and hepatic cirrhosis). In these individuals, we anticipated that prescribing patterns would not be affected by perceived lack of adherence and competing risks of noncardiac death. Deaths in hospital were identified using both the Canadian Institute for Health Information and the registered persons vital statistics database.

**Hospital and Physician Data**

Hospitals were categorized as teaching, community, or small (≤50 inpatient beds), according to the classification of the Joint Policy and Planning Committee, which links the Ontario Hospital Association and the Ministry of Health.24 Patients were assigned to an attending physician, identified as the physician who submitted the most attending fee codes to the Ontario Health Insurance Plan billing database. Physician specialty, categorized as cardiologist, noncardiology internist, or general or family practitioner, and physician age were determined from an Ontario Ministry of Health health care organization database.25

**Prescription Rates by Risk Classification**

Rates were determined for drugs prescribed at discharge in the medical record and prescriptions filled within 90 days after hospital discharge. The former were determined by abstracting the medical record and the latter by linking hospital data with the Ontario Drug Benefit formulary database, which contains detailed prescription records for all ambulatory patients aged 65 years or older. We examined all medications classified as ACE inhibitors, ARBs, and β-adrenoceptor antagonists. We also examined rates of drug administration up to 1 year after hospital discharge.

All patients were classified according to their baseline predicted risk of 1-year mortality using the validated EFFEKT heart failure risk prediction score. The risk scoring method uses age, vital signs at presentation, comorbidities, and laboratory test result values to calculate an aggregate risk score.22 Based on the 1-year mortality score, patients were categorized into 3 groups [low risk [score, ≤90], average risk [score, 91-120], or high risk [score, ≥121]). From prior model validation, the corresponding 1-year mortality rate ranges for low-, average-, and high-risk groups were 17.7% or less (upper 95% confidence interval [CI]); 26.3% to 34.0% (95% CI); and at least 49.4% (lower 95% CI); the model’s performance characteristics have been previously reported.22 We compared observed 1-year mortality rates in each category of predicted risk by querying the registered persons vital statistics database.26 Rates of drug administration at discharge, at 90 days, and up to 1 year following hospital discharge were examined according to predicted baseline risk of death.

Sensitivity analyses were conducted to further explore the risk-treatment association in selected clinical subsets relevant to prescription of ACE inhibitors, ARBs, and β-adrenoceptor antagonists. For example, we anticipated that increased serum creatinine concentration (≥2.0 mg/dL [≥176.8 µmol/L]) might influence prescription of ACE inhibitors or ARBs; therefore, treatment rates were reexamined in patients with creatinine thresholds varying from less than 2.0 mg/dL (<176.8 µmol/L) to less than 1.6 mg/dL (<141.4 µmol/L). Similarly, because of the blood pressure lowering effects of these drugs, we examined patients without hypotension, defined by systolic blood pressure threshold of at least 115 mm Hg, as used previously.27 For β-adrenoceptor antagonist administration rates, we examined those patients without tachycardia (heart rate ≥60/min) or tachycardia-related complications during the hospital stay, and those without chronic obstructive pulmonary disease or asthma. We also examined treatment patterns according to risk for all patients with heart failure irrespective of LVEF.
Statistical Analysis

Trends in rates of discharge drug prescription according to risk category were evaluated using the Mantel-Haenszel χ² test for trend and, when small cell sizes were present, statistical significance was assessed using permutation tests. The primary results are reported as unadjusted drug administration rates stratified by risk category. The effect of patient age and sex, risk category, attending physician specialty and age, and hospital type on the likelihood of ACE inhibitor or ARB and β-adrenoreceptor antagonist prescription was assessed using logistic regression. The logistic regression model was estimated using generalized estimating equation methods to account for the clustering of patients within physicians, adjusting for hospital type, and patient characteristics; standard errors increased negligibly.

Time to first outpatient discharge prescription was analyzed using Cox proportional hazards regression analysis with risk stratum as the predictor variable, using the high-risk group as the referent category, censoring patients at death. The Cox proportional hazards regression analysis was restricted to those patients aged 65 years or older, in whom Ontario Drug Benefit outpatient prescription records were available. Kaplan-Meier survival curves were constructed for time to drug prescription event stratified by risk category and compared using the log-rank statistic. Statistical analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC); P<.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 9942 patients were hospitalized for heart failure and met clinical criteria for inclusion. Overall, 8641 patients (86.9%) survived hospitalization and, of these, 5218 (60.4%) were aged 79 years or younger. Among this group, 2681 patients had left ventricular function documented, of whom 1418 with LVEF of 40% or less constituted the study cohort. Of the 1418 patients, 784 (55.3%) were categorized as low risk, 473 (33.4%) as average risk, and 161 (11.4%) as high risk. A total of 1020 patients were aged between 65 and 79 years for postdischarge outpatient drug prescription analysis. Baseline characteristics of patients, hospital type, and health care practitioner specialty by risk category are shown in Table 1. The attending physician was identifiable for 98.7% of low- and average-risk patients and for 98.8% of high-risk patients. The median number (interquartile range) of cardiovascular prescription drugs was similar across risk categories (4 [3-6] in low-risk, 5 [3-6] in average-risk, and 4 [3-6] in high-risk groups).

Rates of Drug Use According to Risk of Death

Rates of drug prescription at hospital discharge for all patients aged 79 years or younger with an LVEF of 40% or less are shown in Table 2, according to mortality risk category. Observed 1-year mortality rates were associated with predicted risk of death. With increasing mortality risk, discharge prescription rates of ACE inhibitors, ACE inhibitors or ARBs, and β-adrenoreceptor antagonists decreased. Similar patterns were observed for prescription rates at 90 days posthospital discharge in patients aged 65 to 79 years with an LVEF of 40% or less. In patients with heart failure aged 79 years or younger with an LVEF of 40% or less and without major comorbidities, higher mortality risk remained associated with lower rates of ACE inhibitor, ACE inhibitor or ARB, and β-adrenoreceptor antagonist prescriptions at discharge and within 90 days postdischarge. The risk-treatment mismatch remained for all heart failure drugs when patients older than 79 years with an LVEF of 40%

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of Study Sample According to Predicted Risk of Death Within 1 Year (N=1418)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
</tr>
<tr>
<td>Female, No. (%)</td>
</tr>
<tr>
<td>Presentation variables, mean (SD), mm Hg</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
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<tr>
<td>Serum creatinine concentration, mg/dL</td>
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<tr>
<td>Hemoglobin concentration, &lt;10 g/dL</td>
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<tr>
<td>Comorbid conditions, No. (%)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
</tr>
<tr>
<td>Dementia</td>
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<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>Cancer</td>
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<tr>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td>Type of hospital, No. (%)</td>
</tr>
<tr>
<td>Attending physician, No. (%)</td>
</tr>
<tr>
<td>Risk score for 1-year mortality, mean (SD)</td>
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</tbody>
</table>

Abbreviation: COPD, chronic obstructive pulmonary disease.
SI conversion: To convert serum creatinine to µmol/L, multiply by 88.4.
Sensitivity Analyses

Prescription rates for ACE inhibitors or ARBs at hospital discharge and 90-day outpatient administration of β-adrenoreceptor antagonists are shown in Table 4 for those patients without reduced blood pressure, bradycardia, increased creatinine concentration (ACE inhibitors or ARBs), or chronic obstructive pulmonary disease or asthma (β-blockers). A risk-treatment mismatch was present in a broad range of possible heart failure patient samples. Analyses repeated for ACE inhibitor prescriptions alone paralleled that for either ACE inhibitors or ARBs, and when patients with intolerance to these drugs were excluded, similar results were observed. Inclusion of patients who died in hospital (and their treatments at the time of death) increased the observed 1-y mortality rate, % by 1% for low risk, 2% for average risk, and 5% for high risk.

Table 2. Drug Prescription Rates for Patients Aged ≤79 Years With Left Ventricular Ejection Fraction of ≤40% *

<table>
<thead>
<tr>
<th>Drug prescription</th>
<th>No. (%) of Patients At Hospital Discharge (All Patients ≤79 y)</th>
<th>90 Days Postdischarge (Patients Aged 65-79 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Risk</td>
<td>Average Risk</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>635 (81)</td>
<td>346 (73)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>677 (86)</td>
<td>380 (80)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>314 (40)</td>
<td>154 (33)</td>
</tr>
<tr>
<td>No ACE inhibitor, ARB, or β-blocker</td>
<td>76 (10)</td>
<td>73 (15)</td>
</tr>
</tbody>
</table>

Observed 1-y mortality rate, %

13.9 26.4 47.2
13.8 25.9 50.6

Table 3. Drug Prescription Rates for All Patients With Left Ventricular Ejection Fraction of ≤40% *

<table>
<thead>
<tr>
<th>Drug prescription</th>
<th>No. (%) of Patients At Hospital Discharge (All Patients)</th>
<th>90 Days Postdischarge (Patients Aged ≥65 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Risk</td>
<td>Average Risk</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>696 (81)</td>
<td>571 (73)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>733 (86)</td>
<td>620 (80)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>338 (40)</td>
<td>250 (32)</td>
</tr>
<tr>
<td>No ACE inhibitor, ARB, or β-blocker</td>
<td>81 (10)</td>
<td>116 (15)</td>
</tr>
</tbody>
</table>

Observed 1-y mortality rate, %

14.0 26.5 46.0
13.9 26.7 51.4

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

*For all drug classes, P < .001 for trend.
†Cancer, cerebrovascular disease, dementia, or cirrhotic liver disease.

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death) into the analysis also yielded similar results. P values obtained from permutation tests were similar to the corresponding Mantel-Haenszel \( \chi^2 \) statistic for all analyses.

**Multivariable Analysis**

Age was not associated with prescription of ACE inhibitors or ARBs at discharge (P = .64) or within 90 days postdischarge (P = .11). Although increasing age decreased the likelihood of receiving \( \beta \)-adrenoreceptor antagonists at discharge (odds ratio [OR], 0.98; 95% CI, 0.97-0.99; P = .002, per year of age), it was not associated with 90-day postdischarge administration (OR, 1.00; 95% CI, 0.97-0.99; P = .80, per year of age). Patient sex did not influence drug administration at either time point and there were no significant interactions between age and sex.

Adjusting for patient age, sex, and their interactions, and physician and hospital characteristics, ORs for ACE inhibitor or ARB prescriptions were 2.28 (95% CI, 1.58-3.17; P < .001) for ACE inhibitors or ARBs within 90 days were 2.42 (95% CI, 1.58-3.71; P < .001) for average-risk and 4.47 (95% CI, 2.79-7.18; P < .001) for low-risk groups. Similarly, \( \beta \)-adrenoreceptor antagonists were more likely to be prescribed at discharge in low-risk patients, with adjusted ORs of 1.55 (95% CI, 1.03-2.33; P = .04) in average-risk and 1.84 (95% CI, 1.12-2.79; P = .004) in low-risk individuals. Within 90 days, the adjusted ORs for \( \beta \)-adrenoreceptor antagonists were 1.44 (95% CI, 0.96-2.17; P = .08) and 1.88 (95% CI, 1.25-2.84; P = .003) for average- and low-risk groups, respectively, relative to the high-risk group.

Although there was no effect of hospital type on ACE inhibitor or ARB prescription, patients who were admitted to large community hospitals were less likely to receive \( \beta \)-adrenoreceptor antagonists than teaching hospitals (OR, 0.69; 95% CI, 0.52-0.91; P = .009 at discharge, and OR, 0.70; 95% CI, 0.50-0.97; P = .03 within 90 days). Small community hospitals exhibited a similar directional trend for \( \beta \)-adrenoreceptor antagonist prescription (OR, 0.55; 95% CI, 0.25-1.21; P = .14 at discharge, and OR, 0.49; 95% CI, 0.19-1.28; P = .14 within 90 days). There was no effect of physician specialty or physician age on heart failure drug prescriptions.

### Table 4. Sensitivity Analysis

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Rates of Heart Failure Drug Administration, No. of Patients/Total (%)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB†</td>
<td>LVEF ≤40%, Excluding Limiting Comorbidities, No Age Restriction*</td>
<td>Low Risk</td>
</tr>
<tr>
<td>Systolic BP ≥115 mm Hg</td>
<td>589/682 (86)</td>
<td>319/407 (78)</td>
</tr>
<tr>
<td>Serum creatinine &lt;2.0 mg/dL</td>
<td>638/734 (87)</td>
<td>345/432 (80)</td>
</tr>
<tr>
<td>Serum creatinine &lt;1.6 mg/dL</td>
<td>621/712 (87)</td>
<td>293/365 (80)</td>
</tr>
<tr>
<td>( \beta )-Blocker‡</td>
<td>LVEF ≤40%, Excluding Limiting Comorbidities, Age ≤79 y*</td>
<td>Low Risk</td>
</tr>
<tr>
<td>Systolic BP ≥115 mm Hg</td>
<td>179/419 (43)</td>
<td>142/400 (36)</td>
</tr>
<tr>
<td>Heart rate ≥60/min</td>
<td>187/428 (44)</td>
<td>162/454 (36)</td>
</tr>
<tr>
<td>Bradycardia absent during hospital stay</td>
<td>145/337 (43)</td>
<td>123/340 (36)</td>
</tr>
<tr>
<td>COPD or asthma absent</td>
<td>185/403 (46)</td>
<td>145/361 (40)</td>
</tr>
</tbody>
</table>

**Heart Failure Hospital Survivors Irrespective of LVEF and Comorbidity Status, No Age Restriction**

| ACE inhibitor or ARB† | 2307/2868 (80) | 2237/3129 (71) | 898/1424 (63) | <.001 |
| \( \beta \)-Blocker‡ | 720/2004 (36) | 909/3093 (29) | 337/1497 (23) | <.001 |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction.

†Conversion: To convert serum creatinine to \( \mu \)g/dL, multiply by 88.4.

‡Limiting comorbidities include cancer, cerebrovascular disease, dementia, or cirrhotic liver disease.

*Rates of ACE inhibitors or ARBs prescribed at discharge.

†Rates of \( \beta \)-blockers at 90 days postdischarge.

### Time to First Outpatient Prescription

Kaplan-Meier plots for time from discharge to first outpatient drug prescription demonstrated significant differences (all log-rank P < .001) among risk strata (FIGURE). In the Cox proportional hazards regression analysis relative to patients at high baseline risk, patients at low risk (hazard ratio [HR], 1.61; 95% CI, 1.49-1.74) and average risk (HR, 1.38; 95% CI, 1.28-1.48) were significantly more likely to receive ACE inhibitors or ARBs (both P < .001). Similarly, those patients at low risk (HR, 1.80; 95% CI, 1.60-2.01) and average risk (HR, 1.30; 95% CI, 1.17-1.46) were more likely to receive \( \beta \)-adrenoreceptor antagonists after hospital discharge compared with those at high risk (both P < .001).

### Comment

Although the benefits of ACE inhibitors, ARBs, and \( \beta \)-adrenoreceptor antagonists in patients with heart failure are well established,\(^3\) these drugs were underused in those patients at highest risk of death. In all clinical subgroups examined, an inverse associa-
tion was found between probability of death (ie, higher a priori risk) and rates of treatment with these pharmacotherapies. Even after eliminating perceived contraindications and life-limiting comorbidities that could potentially confound the risk-treatment relationship, the mismatch remained. Thus, among hospital survivors without increased serum creatinine, there were lower rates of ACE inhibitor or ARB administration in those at higher mortality risk. In addition, among patients without obstructive pulmonary disease, a paradoxical relationship between β-adrenoreceptor antagonist treatment rates and risk was observed. Indeed, the inverse relationship persisted in subsets of patients without major comorbidities and the wider population-based sample of all patients with heart failure admitted to the hospital. The inverse relationship between risk and treatment propensity was also not explained by patient age or sex.

Several studies have found that there are equivalent or greater benefits of heart failure therapy in patients at higher risk of death. Greater absolute benefits of ACE inhibitors were found in patients with heart failure and characteristics associated with higher risk, including hyponatremia, low LVEF, and impaired functional capacity. Additionally, ACE inhibitors have been demonstrated to be beneficial in elderly patients and those with perceived contraindications to therapy. The Metoprolol Controlled Release/Extended Release Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF) study found greater absolute reductions in sudden death, death from worsening heart failure, and all-cause mortality in older patients who were treated with metoprolol. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II) investigators found preserved benefits of bisoprolol in the spectrum of higher-risk individuals defined by a composite of age, New York Heart Association classification, LVEF, systolic blood pressure, and heart rate. In the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial, low pretreatment systolic blood pressure signified both a higher risk of death and greater absolute treatment benefits with carvedilol. Given the preserved or larger relative benefits and higher baseline probability of death in high-risk patients, these studies collectively suggest that patients at higher risk of death should not have life-sustaining treatments withheld.

We found that high mortality risk was associated with lower rates of ACE inhibitor, ARB, and β-adrenoreceptor antagonist administration. Other studies have reported similar findings in patients with acute coronary syndromes and myocardial infarction, with lower rates of therapeutic intervention in elderly patients. Our findings add to current knowledge regarding risk-treatment patterns by demonstrating that a mismatch between rates of treatment and mortality risk exist in patients with heart failure even when the patient cohort is limited to potential real-world counterparts of patients eligible for randomized controlled trials. Because drug administration was inversely associated with risk, the potential benefit of heart failure pharmacotherapy will not be realized if current patterns continue. Greater quality improvement efforts aimed at increasing use of heart failure drugs in higher-risk individuals may be needed.

We demonstrated that even among patients with reduced LVEF without potential contraindications to ACE inhibitors or β-adrenoreceptor antagonists, the paradoxical association between mortality risk and utilization rates was still evident. However, prior studies have found that the beneficial effects of β-adrenoreceptor antagonists extend to the broader sample of patients with nonasthmatic chronic obstructive lung disease. Although ACE inhibi-
tors have been studied in heart failure trials among patients with serum creatinine levels as high as 3.4 mg/dL. \( \leq 300.6 \mumol/L \), we found that the risk-treatment mismatch persisted despite restricting the analysis to lower thresholds \( <1.6 \text{ mg/dL} \) \( <141.4 \mumol/L \) than those used in randomized controlled trials. The partial attenuation of the gradient in treatment rates that occurred when those patients with increased serum creatinine were excluded suggested that, although important, renal dysfunction did not fully explain the risk-treatment mismatch. Accounting for differences in hospital type, physician characteristics, and patient age and sex, and in clustered multivariable regression analyses also did not abrogate the risk-treatment mismatch.

A potential explanation for the inverse relationship between risk and treatment rates could be under appreciation of the benefits of therapy, particularly in patients with chronic disease who are at risk of death from noncardiac causes. Additionally, clinicians may be distracted from heart failure care in patients with multiple comorbid conditions. However, despite excluding patients with several potential life-limiting comorbidities, the treatment mismatch remained. The possible need for multiple prescription medications could also be a consideration in withholding therapy. However, we found that the median number of cardiovascular prescription drugs at discharge was similar across risk categories. Alternatively, there may be uncertainty about risks vs benefits in treating patients who are underrepresented in randomized controlled trials, or perceived potential for harm associated with treatment particularly in high-risk patients. All of the above could also affect the clinician's discussion with patients regarding their preferences when making informed treatment-related decisions.

Our findings are relevant to clinicians since pharmacologic therapy is the cornerstone of heart failure management. Additionally, this study has implications for performance measurement and quality improvement efforts, where drug utilization rates are commonly reported as an aggregate statistic. Given our findings, heart failure outcome improvement may be accelerated by greater utilization in those patients at higher risk of death. In our study of patients with heart failure with an LVEF of 40% or less, only 11% of low-risk patients did not receive ACE inhibitors or ARBs within 90 days post-discharge, whereas 33% of high-risk patients did not receive therapy. For \( \beta \)-adrenoreceptor antagonists, 72% of high-risk patients remained untreated up to 90 days after hospital discharge. The mismatched pattern of drug administration persisted up to 1 year after hospital discharge, even after accounting for variable survival times. The implications of our study likely extend to other regions, since reported rates of heart failure drug prescription are comparable between Ontario and other jurisdictions. Additionally, the potential reasons for the risk-treatment mismatch would also not be limited by geographic boundaries, and thus common underlying reasons for this paradox may exist.

Some limitations of our study merit emphasis. Although we accounted for several important contraindications, other relative contraindications, such as cough or hypoglycemia, were not assessed. However, given the literature demonstrating benefits of drug therapy even in those patients with perceived contraindications, exclusion of patients from the analysis based on less important relative contraindications was considered unjustified. Furthermore, repeat analysis excluding patients who had a documented history of drug intolerance did not alter the results. Our study was limited to patients with heart failure in the acute care hospital setting and, although our findings cannot be directly extrapolated to patients initially identified as outpatients, we hypothesize that similar results would be observed in the latter case based on the consistent pattern of discharge prescriptions and postdischarge drug administration. Although our study was able to identify patterns of association between treatment and risk, the underlying reasons were beyond the scope of this study and are potential areas for future research.

In conclusion, the predicted and observed risks of death in patients with heart failure were inversely associated with discharge and postdischarge administration of potentially life-saving drug therapies. This finding is particularly important because patients at highest risk of death have great need for effective treatment. Clinical use of quantitative multifactorial risk profiles or algorithms that convey information regarding probability of poor outcomes could be applied to better identify such patients. Further study is needed to quantify the adverse consequences attributable to the mismatch between risk and treatment rates and may also identify potential solutions to correct this undesirable phenomenon.
REFERENCES


