Pharmacist Care of Patients With Heart Failure

A Systematic Review of Randomized Trials

Sheri L. Koshman, BScPharm, PharmD, ACPR; Theresa L. Charrois, BSc(Pharm), MSc; Scot H. Simpson, BSP, PharmD, MSc; Finlay A. McAlister, MD, MSc, FRCPC; Ross T. Tsuyuki, BSc(Pharm), PharmD, MSc, FCSHP

Background: While the role of multidisciplinary teams in the treatment of patients with heart failure (HF) is well established, there is less evidence to characterize the role of individual team members. To clarify the role of pharmacists in the care of patients with HF, we performed a systematic review evaluating the effect of pharmacist care on patient outcomes in HF.

Methods: We searched PubMed, MEDLINE, EMBASE, International Pharmaceutical Abstracts, Web of Science, Scopus, Dissertation Abstracts, CINAHL, Pascal, and Cochrane Central Register of Controlled Trials for controlled studies from database inception to August 2007. We included randomized controlled trials that evaluated the impact of pharmacist care activities on patients with HF (in both inpatient and outpatient settings). Summary odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a random-effects model for rates of all-cause hospitalization, HF hospitalization, and mortality.

Results: A total of 12 randomized controlled trials (2060 patients) were identified. Extent of pharmacist involvement varied among studies, and each study intervention was categorized as pharmacist-directed care or pharmacist collaborative care using a priori definitions and feedback from primary study authors. Pharmacist care was associated with significant reductions in the rate of all-cause hospitalizations (11 studies [2026 patients]) (OR, 0.71; 95% CI, 0.54-0.94) and HF hospitalizations (11 studies [1977 patients]) (OR, 0.69; 95% CI, 0.51-0.94), and a nonsignificant reduction in mortality (12 studies [2060 patients]) (OR, 0.84; 95% CI, 0.61-1.15). Pharmacist collaborative care led to greater reductions in the rate of HF hospitalizations (OR, 0.42; 95% CI, 0.24-0.74) than pharmacist-directed care (OR, 0.89; 95% CI, 0.68-1.17).

Conclusions: Pharmacist care in the treatment of patients with HF greatly reduces the risk of all-cause and HF hospitalizations. Since hospitalizations associated with HF are a major public health problem, the incorporation of pharmacists into HF care teams should be strongly considered.

Arch Intern Med. 2008;168(7):687-694
randomized controlled trial. RCT indicates randomized controlled trials. Language restrictions were not applied. Search items included pharmacy-related terms (pharmacist, pharmaceutical care, pharmaceutical services, clinical pharmacy services, hospital pharmacy, community pharmacy, and pharmacy) and HF-related terms (heart failure, congestive heart failure, heart disease, cardiomyopathy, and ventricular dysfunction). Also, bibliographies of identified studies were hand searched.

STUDY SELECTION

Two of us (S.L.K. and T.L.C.) independently screened the citations from the literature search for eligibility. Studies were included if they tested (in randomized controlled trials) the impact of pharmacist care on patients with HF (compared with no pharmacist care) on the outcomes of all-cause hospitalizations, HF hospitalizations, and all-cause mortality. Secondary outcomes included health-related quality-of-life measures and medication adherence. We contacted all primary study authors and asked them to fill out a standardized questionnaire to better define the role that the pharmacist played in each multidisciplinary team and to verify outcome definitions and published results. Publications were excluded if they were not randomized, if they did not have adequate description of the pharmacist’s intervention and the author could not be contacted, or if they did not report the outcomes of interest. Disagreements were resolved by consensus. Based on information provided in the article or from corresponding author responses to our questionnaire, we classified pharmacist interventions using a priori-defined categories: pharmacist-directed care (pharmacist-initiated and managed intervention) or pharmacist collaborative care (member of a multidisciplinary team).

DATA EXTRACTION AND QUALITY ASSESSMENT

Data extraction was performed by 2 of us (S.L.K. and T.L.C.) independently using a standardized data collection form. Outcomes from individual studies were assigned according to the intention-to-treat principle. We documented all-cause hospitalizations and HF hospitalizations according to the definitions used by the authors of the individual studies. Hospitalization rates (all-cause or HF) were defined as the number of patients in each group who were hospitalized at least once for that diagnosis (only the first hospitalization was counted for patients with multiple hospitalizations). Randomized controlled trials were assessed for quality using the Jadad score and evaluated as to whether allocation concealment was adequately described. Disagreements were resolved by consensus. Based on information from the articles and corresponding authors, we determined that 7 studies compared pharmacist-directed interventions with usual care,10-16 and 5 studies compared pharmacist collaborative care with usual care.17-21 Details about study settings, patient demographics, intervention frequency, end point ascertainment, and usual care for each trial are provided in Table 1. The pharmacist-specific interventions in these studies typically involved education on both HF and evidence-based HF medications, including self-monitoring, medication management, and facilitation of compliance. Details on the specific educational interventions offered by the pharmacists (as reported by each of the primary study authors) are also provided in Table 1.

ROLE OF THE PHARMACIST

Eleven of the 12 trial authors responded to our survey to define the exact role of the pharmacist in each multidisciplinary team. Seven trialists identified the pharmacist as the key driver of the intervention (pharmacist-directed care), with their responsibilities including medication and HF education, self-monitoring, recommendations to physicians, and adherence aids (Table 1).10-16 Four trialists identified the pharmacist as one of the members of the multidisciplinary team (pharmacist collaborative care).17,18,20,21 We received no response from 1 study author; however,
Table 1. Key Features of Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Study Population (Country)</th>
<th>Mean Age of Patients, y</th>
<th>Key Components of Pharmacist Intervention (Setting)</th>
<th>Usual Care Description</th>
<th>End Point Measurement (Intervention Frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varma et al, 1999</td>
<td>RCT (2)</td>
<td>83</td>
<td>Patients aged &gt;65 y with heart failure who were either hospitalized or attended an outpatient clinic; the majority were in NYHA class II (Northern Ireland)</td>
<td>76</td>
<td>Med recommendations, HF Med education, self-monitoring, liaison with GP or community pharmacist, written information (outpatient clinic)</td>
<td>No counseling, no education, no self-monitoring, no liaison with GP or community pharmacist</td>
<td>12 mo (every 3 mo)</td>
</tr>
<tr>
<td>Bouvy et al, 2003</td>
<td>RCT (3)</td>
<td>152</td>
<td>Patients with HF using loop diuretics; the majority were in NYHA class II/III (the Netherlands)</td>
<td>70</td>
<td>Med education, compliance assessment, liaison with GP (community pharmacy)</td>
<td>No structured interview, no follow-up</td>
<td>6 mo (every mo)</td>
</tr>
<tr>
<td>Tsyuky et al, 2004</td>
<td>RCT (3)</td>
<td>276</td>
<td>Patients hospitalized with HF; the majority were in NYHA class II (Canada)</td>
<td>72</td>
<td>Patient support program, including HF Med education, self-monitoring, Med organizer, Med recommendations, written information (outpatient clinic)</td>
<td>General heart disease pamphlet provided</td>
<td>6 mo (2 and 4 wk, then every mo)</td>
</tr>
<tr>
<td>Sadik et al, 2005</td>
<td>RCT (2)</td>
<td>208</td>
<td>Patients with HF; the majority were in NYHA class II (United Arab Emirates)</td>
<td>58</td>
<td>Med recommendations, HF Med education, self-monitoring, written information (outpatient clinic)</td>
<td>No counseling, no education, no self-monitoring</td>
<td>12 mo (every 3 mo)</td>
</tr>
<tr>
<td>Holland et al, 2007</td>
<td>RCT (3)</td>
<td>293</td>
<td>Patients admitted to the ED with HF as an ongoing condition; the majority were in NYHA class III (United Kingdom)</td>
<td>77</td>
<td>HF Med education, adherence aid, diary, Med recommendations (home visit)</td>
<td>No counseling, no education, no home visit</td>
<td>6 mo (2 and 6-8 wk)</td>
</tr>
<tr>
<td>López-Cabezas, 2006</td>
<td>RCT (2)</td>
<td>134</td>
<td>Patients hospitalized for HF; the majority were in NYHA class I-II (Spain)</td>
<td>76</td>
<td>HF diet and Med education (in hospital)</td>
<td>No counseling, no education</td>
<td>12 mo (2, 6, and 12 mo)</td>
</tr>
<tr>
<td>Murray et al, 2007</td>
<td>RCT (3)</td>
<td>314</td>
<td>Patients with HF from a single primary care group practice; the majority were in NYHA class II (United States)</td>
<td>62</td>
<td>Med history, Med education, assessment of Med compliance (outpatient clinic)</td>
<td>Regular pharmacy dispensing services, no education materials</td>
<td>12 mo (at prescription refills × 9 mo)</td>
</tr>
<tr>
<td>Stewart et al, 1998</td>
<td>RCT (1)</td>
<td>97</td>
<td>Patients discharged from hospital with HF and high-risk clinical features for readmission; the majority were in NYHA class II (Australia)</td>
<td>75</td>
<td>Med compliance assessment, Med organizer, Med education, referral to community pharmacist (home visit)</td>
<td>Preexisting postdischarge care, regular home support if needed</td>
<td>6 mo (1 wk)</td>
</tr>
<tr>
<td>Gattis et al, 1999</td>
<td>RCT (2)</td>
<td>181</td>
<td>Patients with HF being evaluated in a cardiology clinic; the majority were in NYHA class II (United States)</td>
<td>67</td>
<td>Med recommendations, education on Med (outpatient clinic)</td>
<td>No Med recommendation, followed by physician, physician assistant, or nurse practitioner</td>
<td>6 mo (2, 12, and 24 wk)</td>
</tr>
<tr>
<td>Rainville, 1999</td>
<td>RCT (1)</td>
<td>34</td>
<td>Patients aged &gt;50 y discharged from hospital with HF; the majority were in NYHA class III (United States)</td>
<td>70</td>
<td>Med recommendations, HF Med education, Med organizer, self-monitoring (in-hospital and telephone follow-up)</td>
<td>Nurse review of diet plan and Med, computerized Med sheets</td>
<td>12 mo (3, 7, 30, 90, and 365 d)</td>
</tr>
<tr>
<td>Gwardy-Sridhar et al, 2005</td>
<td>RCT (2)</td>
<td>134</td>
<td>Patients admitted to hospital with HF and an LVEF of ≲ 40%; the majority had an LVEF of &lt; 20% (Canada)</td>
<td>66</td>
<td>HF Med education, written and audio video information (in hospital)</td>
<td>Received written and audio video information, no pharmacist education</td>
<td>12 mo (2 d)</td>
</tr>
<tr>
<td>Triller and Hamilton, 2007</td>
<td>RCT (1)</td>
<td>154</td>
<td>Patients discharged from hospital with a primary or secondary diagnosis of HF and receiving home care (United States)</td>
<td>80</td>
<td>Med assessment, Med recommendations, Med education (home visit)</td>
<td>No description</td>
<td>6 mo (1, 2, and 3 wk)</td>
</tr>
</tbody>
</table>

Abbreviations: ED, emergency department; GP, general practitioner; HF, heart failure; LVEF, left ventricular ejection fraction; Med, medication; NYHA, New York Heart Association; RCT, randomized controlled trial.
it was clear from the article that the pharmacist worked in conjunction with a clinical nurse specialist and was therefore identified as providing collaborative care.19

**METHODOLOGICAL QUALITY OF INCLUDED STUDIES**

The studies were of variable methodological quality. Because of the nature of the interventions, none of the studies was double-blind. Only 6 of the 12 RCTs adequately described allocation concealment.12,14-17,20 Jadad scores are listed in Table 1.

---

**Figure 2.** Forest plot of total mortality. CI indicates confidence interval; OR, odds ratio (random-effects model).

**Figure 3.** Forest plot of all-cause hospitalization rate. CI indicates confidence interval; OR, odds ratio (random-effects model).
PRIMARY OUTCOMES

Mortality

All 12 RCTs (2060 patients) reported all-cause mortality (Figure 2). One study\(^\text{15}\) showed a significant difference in all-cause mortality between intervention and control. The pooled estimate of the 12 RCTs showed a nonsignificant reduction in mortality for pharmacist care compared with control (OR, 0.84; 95% CI, 0.51-0.94) (Figure 4). There was also some heterogeneity in these results (I\(^2\), 40%).

SECONDARY END POINTS

Health-related quality-of-life data are presented in Table 2. Health-related quality of life was measured in 7 studies; 6 studies used disease-specific measures,\(^{10,11,13,14,16,20}\) and 5 studies used generic measures.\(^{11,13,15,20}\) The way in which data were reported and the small number of studies using health-related quality of life precluded pooling of data. Adherence was measured as an outcome in 7 studies (Table 3).\(^{10,13,15,16,20}\) Methods for measuring adherence varied substantially among studies. Of the 3 studies that collected adherence data using community pharmacy refill records,\(^{10,12,20}\) only 1 found significant differences (favoring the intervention) between study groups.\(^{10}\) However, this study had adherence data available for only 28% of the total study population. Of the 3 studies that reported adherence using patient self-report,\(^{10,13,16}\) 1 reported significant differences (favoring intervention).\(^{13}\) Two studies used an electronic monitoring system to measure adherence, and both studies demonstrated that patients in the control group had lower adherence.\(^{11,16}\)

SENSITIVITY ANALYSES

Indirect Comparison of Pharmacist-Directed Care and Collaborative Care

The indirect comparisons of pharmacist-directed interventions and collaborative pharmacist care showed no significant difference between the 2 types of intervention in their effects on mortality or rate of all-cause hospitalizations (P = .40 and P = .40, respectively). In terms of HF hospitalization rates, the effects of these interventions were significantly different, with pharmacist collaborative care being associated with a greater risk reduction (P = .02).

Assessing Influence of Single Studies on Primary End Points

Using the method defined by Tobias,\(^7\) we looked at each primary end point to determine whether re-
removal of any 1 study would dramatically affect the results. The pooled OR did not change more than 8% after removal of each study for the end points of HF hospitalizations and all-cause hospitalizations. For mortality, the removal of the study by López Cabezas et al15 increased the OR by 15%; however, the result was still nonsignificant (P = .75).

Study Quality

The results for the sensitivity analyses based on study quality are presented in Table 4. Only 4 studies (n = 1035) had Jadad scores that were higher than 3.11,12,14,16 The studies with Jadad scores that were lower than 2 had consistently more positive results than studies with Jadad scores that were higher than 3. In terms of allocation concealment, the results were similar when studies with adequate allocation concealment were compared with those with inadequate allocation concealment for the outcomes of all-cause hospitalizations and mortality.

There are several plausible explanations for our findings of reductions in HF hospitalizations and all-cause hospitalizations but no change in mortality. Given that the majority of events examined were hospitalizations and our sample size was relatively small, it is unlikely that we would be able to show a decrease in mortality as a result of low statistical power. Also, the duration of follow-up in these studies ranged from 2 days to 12 months, with the majority of follow-ups lasting only 6 months or less, likely too short to see an impact on mortality.

Given the significant heterogeneity in many of the primary outcomes, we sought to determine the potential sources. First, we analyzed the data in predefined categories (pharmacist-directed care or pharmacist collaborative care). When these categories were compared, we found no difference in the type of intervention and outcomes for mortality and all-cause hospitalizations. For HF hospitalizations, pharmacist collaborative care did appear to be more beneficial than pharmacist-directed care. This finding is not surprising given that medication management and patient education would complement care given by nurses, physicians, and other health care professionals. Second, we compared the data using the method described by Tobias10 to examine the influence of single studies on each outcome. No particular study influenced the pooled OR when taken out of the analysis. Finally, we evaluated results by study quality and, not surprisingly, found that lower-quality studies reported greater beneficial effects with the tested interventions. The Jadad score is well recognized for randomized controlled trials; however, it may not be the best for practice research, where blinding is not possible. In the absence of alternative quality scores, this sensitivity analysis should be interpreted as hypothesis generating only.

There are a number of limitations that warrant discussion. There were notable differences in pharmacist activities between studies, making it difficult to define precisely which intervention provides the best outcomes (even after contact with

### Table 2. Summary of Reported Health-Related Quality-of-Life (HRQL) Measures in Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>HRQL Measure Used</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouvy et al,11 2003</td>
<td>MLHF</td>
<td>Both groups improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>intervention worsened and control improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no change in favor of control</td>
</tr>
<tr>
<td>Gwadyr-Sridhar et al,12 2005</td>
<td>MLHF</td>
<td>Both groups improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>significant difference between groups in favor of intervention</td>
</tr>
<tr>
<td></td>
<td>SF-36</td>
<td>no significant difference between groups</td>
</tr>
<tr>
<td>Sadik et al,13 2005</td>
<td>MLHF</td>
<td>Significant difference between groups in favor of intervention</td>
</tr>
<tr>
<td></td>
<td>SF-36</td>
<td>Significant difference between groups in favor of intervention in 6 of 8 domains</td>
</tr>
<tr>
<td>Varma et al,10 1999</td>
<td>MLHF</td>
<td>Both groups improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no significant difference between groups</td>
</tr>
<tr>
<td>López Cabezas,15 2006</td>
<td>EQ-5D</td>
<td>Intervention improved and control worsened</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no significant difference between groups</td>
</tr>
<tr>
<td>Holland et al,14 2007</td>
<td>MLHF</td>
<td>Intervention worsened and control improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no significant difference between groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>intervention had no change and control worsened</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no significant difference between groups</td>
</tr>
<tr>
<td>Murray et al,16 2007</td>
<td>Chronic HF questionnaire</td>
<td>Both groups improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no significant difference between groups</td>
</tr>
</tbody>
</table>

Abbreviations: COOP/WONCA, Dartmouth Primary Care Cooperative Research Network/World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians; EQ-5D, EuroQol-5 Dimensions form; HF, heart failure; MLHF, Minnesota Living With Heart Failure questionnaire; SF-36, 36-Item Short-Form Health Survey.

This systematic review confirms the benefits of pharmacist care in reducing hospitalization in patients with HF. Interventions that include some element of pharmacist care reduced the rates of both all-cause hospitalization and HF hospitalization by almost one-third. Because HF is one of the leading causes of hospitalization,22 we recommend the addition of a pharmacist to the HF team. Other studies have confirmed that a substantial proportion of HF exacerbations can be attributed to medication misadventures, highlighting the potential importance of pharmacists on the HF team.23 These results are consistent with an earlier systematic review of multidisciplinary care in HF3 but extends this earlier work by including data from 8 trials that were not included in the earlier review and by focusing specifically on the impact of the pharmacist within the setting of the multidisciplinary team (as defined by the primary authors of each of these trials).
included both hospitalized patients and ambulatory patients, making it difficult to elucidate which patient population would most likely benefit. It is also likely that there were different cointerventions across the studies that could not be accounted for.

In addition to contributing to the current body of literature supporting the beneficial effects of multidisciplinary teams in the treatment of patients with HF, our findings further describe the beneficial role of the pharmacist in the treatment of patients with HF. Because HF results in more than 1,000,000 hospitalizations each year in the United States, a 30% reduction would have a substantial impact.24 From our results, we can infer that including a pharmacist in the care of patients with HF, particularly within a multidisciplinary team, is beneficial and should be strongly considered by health policy makers.

Table 3. Summary of Adherence and Compliance Measures in Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Method of Measuring Adherence</th>
<th>Results</th>
</tr>
</thead>
</table>
| Bouvy et al,11 2003 | Medication event monitoring system (based on loop diuretic) | Intervention: 140/7656 d without use of diuretic  
Usual care: 337/6196 d without use of diuretic  
RR: 0.33 (95% CI, 0.24-0.38) |
| Gwadry-Sridhar et al,20 2005 | Pharmacy refill records (cumulative medication acquisition) | Noncompliance in intervention compared with control, RR (95% CI):  
ACE-I/ARB: 0.78 (0.33-1.89)  
β-Blocker: 0.89 (0.28-2.82)  
Diuretic: 1.02 (0.49-2.12) |
| Sadik et al,13 2005 | Self-reported | No. of patients who reported compliance with prescribed medications was significantly higher in control than in intervention (P < .05) |
| Tsuyuki et al,12 2004 | Pharmacy refill records (based on ACE-I) | Intervention: 83.5% adherence  
Usual care: 86.2% adherence (P=.70) |
| Varma et al,10 1999 | Pharmacy refill records | Intervention: 10 patients were compliant; 3 were noncompliant  
Usual care: 3 patients were compliant; 7 patients were noncompliant (P=.04) |
| López Cabezas,15 2006 | Tablet counts | Reliable (95%-100% of prescribed doses) at 12 mo  
Control: 73.9%  
Intervention: 85%  
Difference: NS |
| Murray et al,24 2007 | Medication event monitoring system | Intervention: 78.8% of doses taken  
Control: 67.9% of doses taken  
Difference: 10.9% (95% CI, 5.0%-16.7%)  
Postintervention period:  
Intervention: 70.6% of doses taken  
Control: 66.7% of doses taken  
Difference: 3.9% (95% CI, -2.8% to 10.7%) |
| Self-reported | No difference between groups |

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; NS, nonsignificant; RR, relative risk

Table 4. Sensitivity Analysis Based on Study Quality

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Based on Jadad Score</th>
<th>Based on Allocation</th>
</tr>
</thead>
</table>
| Mortality | Score <2: 0.65 (0.43-0.96)  
Score ≥3: 1.13 (0.78-1.66)  
Concealment: Inadequate: 0.87 (0.63-1.22)  
Adequate: 0.82 (0.52-1.29) |
| All-cause hospitalizations | Score <2: 0.55 (0.40-0.75)  
Score ≥3: 0.99 (0.76-1.29)  
Concealment: Inadequate: 0.58 (0.33-1.03)  
Adequate: 0.82 (0.63-1.07) |
| Heart failure hospitalizations | Score <2: 0.52 (0.37-0.72)  
Score ≥3: 1.05 (0.76-1.45)  
Concealment: Inadequate: 0.59 (0.40-0.86)  
Adequate: 0.80 (0.60-1.06) |

the primary study authors). There were also differences in terms of patient population and settings, which
REFERENCES


