Pharmacist intervention to prevent hospitalization and death in patients with heart failure: A prospective cluster randomized controlled trial

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On behalf of the Heart failure Optimal Outcomes from Pharmacy Study (HOOPS) investigators
Background and Introduction

- Disease-modifying drugs (e.g. ACE inhibitors and β-blockers) are under-used and under-dosed in patients with heart failure in primary care.

- “Collaborative medication review” - pharmacists evaluate patients’ medications and suggest changes which are enacted with the agreement of the patient and the family doctor.

- We hypothesised that pharmacist intervention to optimize medical treatment in patients with left ventricular systolic dysfunction would improve clinical outcomes.

- Comparative-effectiveness, cluster randomized, trial in primary care
Inclusion: Left ventricular systolic dysfunction (confirmed by cardiac imaging). Patients did not have to have symptoms or signs of heart failure.

Exclusions:

- Registration with heart failure-nurse service - provided to patients recently hospitalized with heart failure (excluded higher risk patients with more severe symptoms).

- Concurrent disease (other than heart failure) likely to reduce life-expectancy; severe cognitive impairment or psychiatric illness; dialysis, or a resident in a long-term care facility.
Pharmacist Intervention

- 27 pharmacists
- 30 minute, face-to-face consultation
- If changes were made (e.g. treatment initiation or dose modification), 3-4 additional consultations were arranged
- All study pharmacists attended a training day which covered signs and symptoms and evidence based medical treatment of left ventricular systolic dysfunction
Primary and Secondary Outcomes

• **Primary:** Death from any cause or hospital admission for worsening heart failure

• **Secondary:**
  • Death from any cause or hospital admission for pre-specified cardiovascular causes
  • Death from any cause or hospital admission for any cause
  • Total number of admissions (and patients admitted) for heart failure, cardiovascular causes and any cause
  • Days alive out of hospital
  • ER visits, hospital out-patient clinics, primary care visits,
  • Prescribing of disease modifying medicines
Statistical Assumptions

- Rate of primary endpoint in the usual care group 10% per year
- Relative risk reduction in the primary outcome of 26% with pharmacist intervention
- 2.6 years recruitment plus 2 further years of follow-up
- Needed 673 patients to experience primary outcome for 80% power to detect a difference between treatments.
- Sample size inflated by a factor of 1.55 to account for cluster-randomization design - needed 87 practices/1044 patients per group.
- Due to longer than anticipated recruitment >750 patients expected to experience primary outcome providing 80% power to detect a 19% relative risk reduction.
The primary analysis compared the main outcomes between the treatment groups using a Cox proportional hazards frailty model.

Treatment effect adjusted for:

- the stratification variables - level of socioeconomic deprivation (affluent, intermediate, deprived) and practice type (single-handed or group-practice)
- and age, creatinine, grade of left ventricular systolic dysfunction, atrial fibrillation, respiratory disease, total number of medications and diuretic use.
The UK National Health Service – Greater Glasgow & Clyde Health Board. 1.2 million people ~25% of Scottish population.

Whole population registered with one of 220 family medical centers (practices); all centers invited to participate.

174 of 220 centers consented (6620 patients with left ventricular systolic dysfunction).

4451 patients declined/did not reply; 2169 (33%) patients consented and enrolled between Oct 2004 and Sept 2007.

Randomization by center (cluster-randomization design) to avoid “contamination”.

Study Outline

Follow-up through NHS electronic records
Median follow-up 4.7 years (range 6 days – 6.2 yrs)

Cluster randomization

Usual care
(n=87 practices/1074 patients)

Pharmacist intervention
(n=87 practices/1090 patients)

2164 patients with left ventricular systolic dysfunction

Data Collection:
Baseline characteristics
Drug therapy

Drug therapy
1 year

Drug therapy
2 years

770 primary events
Results

- Baseline characteristics and treatment
- Effect of pharmacist intervention on prescribing
- Effect of pharmacist intervention on clinical outcomes
### Baseline Characteristics (1)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pharmacist intervention (n=1092)</th>
<th>Usual care (n=1077)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>Age ≥ 70 years (%)</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Female (%)</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>Systolic/diastolic BP (mmHg)</td>
<td>127/72</td>
<td>128/72</td>
</tr>
<tr>
<td>Degree of left ventricular systolic function (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>43</td>
<td>39</td>
</tr>
<tr>
<td>Moderate</td>
<td>41</td>
<td>44</td>
</tr>
<tr>
<td>Severe</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Principal cause of left ventricular systolic function (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>80</td>
<td>76</td>
</tr>
<tr>
<td>Non ischemic/unknown</td>
<td>18/2</td>
<td>21/3</td>
</tr>
</tbody>
</table>
### Baseline Characteristics (2)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pharmacist intervention (n=1092)</th>
<th>Usual care (n=1077)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adm for heart failure in past yr.</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50</td>
<td>46</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>66</td>
<td>62</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Stroke</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td><strong>7</strong></td>
<td><strong>8</strong></td>
</tr>
<tr>
<td>Smoker</td>
<td>24</td>
<td>25</td>
</tr>
</tbody>
</table>
Baseline Cardiovascular Medication

<table>
<thead>
<tr>
<th>Patients taking drug (%)</th>
<th>Pharmacist intervention (n=1092)</th>
<th>Usual care (n=1077)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or/and ARB</td>
<td>87</td>
<td>85</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>75</td>
<td>71</td>
</tr>
<tr>
<td>≥100% recommended dose*</td>
<td>60</td>
<td>62</td>
</tr>
<tr>
<td>ARB</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>≥100% recommended dose*</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>≥100% recommended dose*</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Digitalis glycoside</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Diuretic</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>Antithrombotic</td>
<td>91</td>
<td>90</td>
</tr>
<tr>
<td>Lipid lowering agent</td>
<td>79</td>
<td>78</td>
</tr>
</tbody>
</table>

*Of patients taking drug
Results

• Baseline characteristics and treatment

• Effect of pharmacist intervention on prescribing

• Effect of pharmacist intervention on clinical outcomes
Changes in ACE inhibitor or ARB Prescribing (end of first year follow up)

- Started or increased dose
  - Pharmacist intervention: 35%
  - Usual care: 10%
  - $P < 0.001$

- Increased dose to $\geq 100\%$ of target*
  - Pharmacist intervention: 20%
  - Usual care: 10%
  - $P < 0.001$

* Of patients prescribed at baseline
Changes in Beta-blocker Prescribing (end of first year of follow up)

- **Started or increased dose**
  - Pharmacist intervention: 18%
  - Usual care: 10%
  - P < 0.001

- **Increased dose to ≥100% of target**
  - Pharmacist intervention: 7%
  - Usual care: 5%
  - P = 0.05

*Of patients prescribed at baseline*
Results

• Baseline characteristics and treatment
• Effect of pharmacist intervention on prescribing
• Effect of pharmacist intervention on clinical outcomes
Death from Any Cause or Hospitalization for Heart Failure (%)

Number at risk:
- Pharmacist Intervention: 1092, 1026, 950, 860, 673, 470
- Usual Care: 1077, 996, 922, 835, 692, 393
Components of the Primary Composite Outcome

Heart Failure Hospitalization

- Pharmacist Intervention
- Usual Care

Number at risk:
- Pharmacist Intervention: 1092, 1026, 950, 860, 673, 470
- Usual Care: 1077, 996, 922, 835, 692, 393

All-cause Mortality

- Pharmacist Intervention
- Usual Care

Number at risk:
- Pharmacist Intervention: 1092, 1040, 976, 901, 716, 505
- Usual Care: 1077, 1018, 957, 880, 737, 423
All-cause Death or Cardiovascular Hospitalization

Number at risk:
Pharmacist Intervention 1092 982 877 775 602 411
Usual Care 1077 947 851 755 606 339
A low-intensity, pharmacist-led, collaborative intervention in primary care resulted in:

- modest improvements in prescribing of disease-modifying medications
- but did not improve clinical outcomes in a population that was relatively well treated at baseline.
Discussion

• High baseline use of ACE inhibitors/ARBs a surprise – UK Government “pay for performance” scheme for family physicians?

• Consequently, less scope to initiate or increase doses of ACE inhibitors/ARBs.

• More scope to improve β-blocker prescribing but pharmacists failed to initiate these drugs (and limited success in increasing dose). Why?

• Low frequency of heart failure hospitalization and high proportion of non-cardiovascular deaths reduced likelihood of showing treatment effect.