Do clinical pharmacy services improve outcomes for patients with heart failure (HF)?

A literature study

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Degree Thesis in Pharmacy 15 ECTS
Bachelor’s Level
Report passed: Spring 2015
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Abstract

Introduction: The total prevalence of heart failure (HF) is high and increasing further with aging of the population. HF remains a fatal disease; overall 50% of patients are deceased within 4 years. Forty per-cent of patients admitted to hospital with HF are deceased or readmitted within 1 year. HF is associated with significant health costs, mostly because of the cost of hospitalizations. The goals of the treatment for patients with HF are the life prolongation, the prevention of worsening, and reduction of symptoms for greater daily life activity. A complete heart failure management program is important. Addition of the clinical pharmacist to the HF management multidisciplinary care team or just sole pharmacist intervention may influence the patient outcomes.

Objective: The aim of this study was to make a narrative review of clinical pharmacy services for patients with HF. The study is focused on clinical pharmacy services provided by pharmacists working in hospitals worldwide. The study questions:

- What clinical pharmacy services are provided for patients with heart failure?
- What is the effectiveness of clinical pharmacy services on patients with heart failure?

Method: This is a literature study based on six randomized trials which were found through the search in electronic database PubMed between March 27th and April 16th 2015. Search items included pharmacy-related MeSH terms (pharmacist, pharmacy services, pharmaceutical services, clinical hospital pharmacy, pharmaceutical care, and pharmacy) and HF-related MeSH terms (heart failure, heart failure/drug therapy).

Results and Discussion: total of 6 studies were identified: 4 randomized controlled trials (RCT), 1 randomized, prospective, open clinical trial and 1 open randomized intervention study. Two studies were conducted in USA, the rest in the United Arab Emirates, Spain, Netherlands and UK. The interventions included medication reconciliation, therapy rationalization, discharge service, patient education and counseling, adherence aids, self-monitoring patient program and active telephone follow-up. The main outcomes evaluated were adherence, re-admissions and emergency visits, mortality rates, medication errors and ADEs, quality of life, satisfaction with pharmaceutical care and health costs. Most studies reported positive effect from clinical pharmacy services in HF patients’ outcomes compared with the control group though some of the results lack statistical significance. Discharge service, patient education and telephone follow-up were common features of more successful programs. Statistically significant improvement was demonstrated in many outcomes i.e. adherence to medication regime, re-admissions rate, satisfaction with pharmaceutical care and total health costs.

Conclusion: The interventions provided by clinical pharmacy services included medication reconciliation, therapy rationalization, discharge service, patient education and counseling, adherence aids, self-monitoring patient program and active telephone follow-up. Discharge service, patient education and telephone follow-up were common features of more successful programs.

The clinical pharmaceutical services may improve adherence, re-admissions and emergency visit rates, mortality rates, decrease medication errors, improve quality of life and satisfaction with pharmaceutical care for HF patients and decrease health costs. Low-intensity short-time pharmacist-led intervention is proved to be less effective than high-intensity intervention with long follow-up. More studies needed for evaluating of effectiveness of pharmacy services for HF patients.

Key words: heart failure, pharmacist, pharmaceutical care, pharmaceutical services
# Table of contents.

1. Introduction  
   1.1 Epidemiology ................................................................. s. 1  
   1.2 HF disease ................................................................. s. 1  
   1.3 Symptoms ................................................................. s. 1  
   1.4 Causes ................................................................. s. 1  
   1.5. Classification ................................................................. s. 1  
   1.6 Diagnostics ................................................................. s. 1  
   1.7 Treatment ................................................................. s. 2  
   1.8 Health care costs ................................................................. s. 3  
   1.9 HF and pharmaceutical care services ................................................................. s. 3  

2. Objective ................................................................. s. 3  

3. Method ................................................................. s. 4  

4. Results ................................................................. s. 5  
   4.1. Pharmaceutical Care of Patients with Heart Failure ......................... s. 6  
   4.2 Randomized Clinical Trial of a Postdischarge Pharmaceutical Care Program vs Regular Follow-up in Patients with Heart Failure ......................... s. 7  
   4.3 The PILL-CVD Study (The Pharmacist Intervention for Low Literacy in Cardiovascular Disease) ................................................................. s. 7  
   4.4 Pharmacist intervention to improve medication adherence in heart failure: a randomized trial ................................................................. s. 8  
   4.5 The Effect of a Clinical Pharmacist Discharge Service on Medication Discrepancies in Patients with Heart Failure ................................................................. s. 9  
   4.6. The Heart failure and Optimal Outcomes from Pharmacy Study (The HOOPS study) ................................................................. s. 10  

5. Discussion ................................................................. s. 12  

6. Conclusion ................................................................. s. 15  

Acknowledgments ................................................................. s. 15  

References ................................................................. s. 16  

Appendix A. Diary card for patient self-monitoring ................................................................. s. 19  

Appendix B. Example of a personalized medication schedule ................................................................. s. 20
List of abbreviations

ADEs – Adverse Drug Events

A preventable ADE is one in which absence of the error would have prevented the ADE.

An ameliorable ADE is one in which absence of the error would have decreased the severity and/or duration of the ADE.

A potential ADE is an error that could lead to an adverse event but has not yet caused harm (e.g., because the error was caught or because of patient variability in response to the error).

ACEI - angiotensin converting enzyme inhibitors

ACS - acute coronary syndrome

ARB – angiotensin receptor blocker

BMQ - Brief Medication Questionnaire—Regimen Screen

GP – general prescriber, primary care physician specializing in family medicine

HF - Heart failure

HOOPS - The Heart failure and Optimal Outcomes from Pharmacy Study

LVSD - left ventricular systolic dysfunction

MEMS - Medication Event Monitoring System (MEMS lids record the time and date of each opening and closing onto a digital chip.)

MLHFQ - Minnesota Living with Heart Failure Questionnaire

NHS – National Health Service (in Great Britain)

NYHA - The New York Heart Association Functional Classification provides a simple way of classifying the extent of heart failure

NCC MERP-index - The National Coordinating Council for Medication Error Reporting and Prevention an independent body composed of 27 national organizations in the United States

PILL-CVD - Pharmacist Intervention for Low Literacy in Cardiovascular Disease study

RCT - randomized controlled trial

SD - standard deviation

SMEs - Serious Medication Errors
1. Introduction

1.1 Epidemiology.
According to results of Zarrinkoub et al. study from 2013, the estimated prevalence of HF in Sweden is 2.2% (1).
The total prevalence and incidence of HF are high and increasing further with aging of the population, increasing risk factor spreading (hypertension, obesity, hyperlipidemii, diabetes etc.) and improved survival rates from other cardiovascular diseases. The mean age of patients with HF in developed countries is about 75 years (2). Worldwide more than 23 million people have HF (3). The European Society of Cardiology finds the prevalence of HF in developed countries between 1% and 2%, rising sharply to ≥10% among persons older than 70 years of age (2). In persons who are 55 years old, almost 1 in 3 will get HF during their remaining lifetime(4).
HF incidence is higher in men, but the total prevalence is similar in both sexes, since women survive longer after they have been diagnosed with heart failure which they tend to get in older age than men (after menopause) (4).

1.2 HF disease.
Heart failure remains a fatal disease; overall 50% of patients are deceased within 4 years. Forty per-cent of patients admitted to hospital with HF are deceased or readmitted within 1 year (2).
Heart failure is a condition where a heart for variety of reasons loses the ability to provide all organs and tissues of the body with necessary amount of blood (5). When the heart’s pumping function does not respond to body’s needs, the different compensation mechanisms begin to work. This is the basis of symptoms and signs of the heart failure. Therefore, the heart failure is a clinical syndrome and no aetiological diagnosis (6).

1.3 Symptoms.
Common symptoms of HF are tiredness, fatigue, breathlessness or shortness of breath (dyspnea), increased need to urinate at night, irregular or increased heart rate, going up in weight due to fluid accumulation in body tissues (edema) and swelling of the feet, ankles, legs or abdomen.

Severe HF, that can be life-threatening, can have symptoms such as sudden, severe shortness of breath, wheezing, cold sweats, fainting, skin that appears blue (from lack of oxygen in the lungs), severe palpitations and anxiety, a cough that develops from congested lungs, coughing up pink, foamy mucus, called a pulmonary edema (7, 8).

1.4 Causes.
All heart diseases can cause heart failure, as well as several other diseases and conditions not related to this organ, e.g. poisoning, anemia, lung disease, drug abuse and certain endocrine diseases (9, 10). Most common causes are ischemic heart disease, with or without underlying heart attack, is by far the most common cause of congestive heart failure (50-75% of all congestive heart failure), hypertension (about 10%), cardiac muscle diseases, (cardiomyopatier), valvular heart disorders, diabetes and high alcohol consumption (alcoholism) (9).

1.5 Classification.
Three main types of heart failure can be distinguished. 
Left ventricular heart failure (LVHF) is a result of an overload of the left ventricle or due to the reduction of myocardial contractility. The cause of the overload can be, for example, narrowing of the aorta. Reduced contractility occurs, for example, as a result of myocardial infarction, which leads to a decrease in the amount of blood ejected into the systemic circulation and the stagnation of blood in the pulmonary.
Right heart failure has the opposite process arising - the stagnation of blood in the systemic circulation, and reduce the amount of blood supplied to the pulmonary circulation. Right heart failure occurs as a result of overloading of the right ventricle, which can occur, for example, in pulmonary hypertension. Dystrophic form of the right heart failure is the final stage of the disease. Patient is suffering from edema, exhaustion, skin changes (becomes loose, thinner and appears shine) (11).

The third type is simultaneously LVHF and right heart failure which is quite common.

![Diagram of Normal Heart vs Heart Failure](image)

Figure 1. LVHF. (The picture modified by author from http://www.semashko.com)

Functional classification generally relies on the New York Heart Association functional NYHA Class I - NYHA Class IV (12). The severity of symptoms scoring can be used to value response to the treatment of HF. NYHA III and IV are associated with 30-50% mortality over 1-2 years. Therefore, it is of great importance to find the cause of the heart failure and to correct the treatment if possible (6).

1.6 Diagnostics.

HF Diagnostics is based on typical symptoms and signs of impaired heart function. In case of doubt about the diagnosis, a positive treatment response with pharmacological target in heart failure can be indicative. Echo-cardiography is required in most cases to determine the diagnosis and cause of heart failure, systolic or diastolic dysfunction. Investigation on primary care level includes complete ECG, Cardiac Chest x-ray, MRI and blood test for natriuretic peptides (BNP or NT-pro BNP). Natriuretic peptides are released from cells in the heart's atria and ventricle in response to rising filling pressure and extension (9).

1.7 Treatment.

The goals of the treatment for patients with HF are the life prolongation, the prevention of worsening and the reduction of symptoms for greater daily life activity. It is also important that other simultaneous disorders are identified and treated because they sometimes can affect myocardial elasticity. Examples of such diseases are chronic obstructive pulmonary disease (COPD), high blood pressure, diabetes, infections, anemia, thyroid disorders and alcohol abuse (11).

A complete heart failure management program is important. Patients with heart failure should be offered personalized physical training. A heart-healthy diet, avoiding or limiting alcohol and caffeine, smoking cessation if appropriate, tracking salt and fluid intake, vaccinations against flu and pneumonia are parts of lifestyle changes for better
HF control. To improve quality of life, stress management and adequate rest is recommended. Blood pressure monitoring, losing or maintaining weight can reduce the risk of hospital admission for worsening symptoms (13).

First line of medical therapy consists of Angiotensin-converting enzyme inhibitors (ACE-I) or Angiotensin receptor blockers (ARBs), Beta- blockers and Mineralocorticoid receptor antagonists (MRA). Strong evidence is shown by many studies that these medicines improve survival and patient well-being, reduce hospital re-admission. ESC guidelines for the diagnosis and treatment of acute and chronic HF 2012 highlight ACEI or ARB, a beta-blocker, and an MRA as a fundament in HF modifying. Even a new drug ivabradine inhibiting the If channel in the sinus node is recommended for the treatment of patients with HF NYHA class II-IV with systolic dysfunction and heart rate ≥ 75 beats per minute, in combination with standard therapy, including treatment with beta-blockers or when treatment with beta-blockers is contraindicated or not tolerated (2). Medication treatment is usually lifelong and often combines drugs with each other or with other medications such as diuretics.

Second-line drugs for HF treatment do not improve survival. Digitalis is used to complete the treatment if the beta-blockers are not sufficient. The drug has a narrow therapeutic window and high toxicity, therefore it is now used in only a small number of patients with atrial fibrillation and/or chronic hypotension. Most likely there is no protective effect of anticoagulants in patients with congestive heart failure. Patients with heart failure and atrial fibrillation should be treated with anticoagulants (2,11).

1.8 Health care costs.
HF is associated with significant health costs, estimated as 2-3% of the total cost of medical treatment in Sweden, mostly because of the cost of hospitalizations (14). Costs of HF treatment in the United Kingdom have been estimated to amount to 2% of the total budget of the National Health Service, and in the United States to more than $35 billion (15, 16).

1.9 HF and pharmaceutical care services.
Clinical pharmacists play different roles in the care of cardiovascular patients optimizing medication therapy, applying evidence-based medicine and promoting health, quality of life, and disease prevention (17). An addition of the clinical pharmacist to the HF management multidisciplinary care team or just sole pharmacist intervention influences the patient outcomes. Altowaijri et al. (18)2013 evaluated in one review effectiveness of clinical pharmacist intervention in secondary prevention of cardiovascular disease in a systematic review and concluded that pharmacist intervention resulted in greater improvements in many outcomes than using usual care only. Another systematic review of Koshman et al. (19)2008 demonstrated an improvement for many outcomes, including mortality and hospitalization, for patients with HF when a clinical pharmacist participated in the patient care. This study was undertaken in order to explore latest results in the field of pharmaceutical care on HF patients and understand how positive experience can be used in Sweden.

2. Objective
The aim of this study is to make a narrative review of clinical pharmacy services for patients with heart failure (HF). The study is focused on clinical pharmacy services provided by pharmacists working in hospitals worldwide.
The study questions:
  - What clinical pharmacy services are provided for patients with heart failure?
  - What is the effectiveness of clinical pharmacy services on patients with heart failure?
### 3. Method

The electronic database PubMed was searched between March 27th and April 16th 2015 in order to detect published studies assessing the effectiveness of clinical pharmacy services for patients with heart failure (HF). Search items included pharmacy-related MeSH terms (pharmacist, pharmacy services, pharmaceutical services, clinical hospital pharmacy, pharmaceutical care, and pharmacy) and HF-related MeSH terms (heart failure, heart failure/drug therapy). Selection criteria were clinical trials published in English during last 10 years. Table 1 shows selection process. References of found relevant studies were manually searched. Two of selected studies were described in two articles each one, first as Rationale and Design and then as the Results (19-20, 31-32), all four articles were selected for this study.

<table>
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<th>Date</th>
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<th>Limitations</th>
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<th>Selected items</th>
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<td>English 10 years Clinical Trial</td>
<td>19</td>
<td>24, 28, 29</td>
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<tr>
<td>150416</td>
<td>((Heart Failure) AND Pharmacists) AND Treatment Outcome</td>
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<td>6</td>
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<td>Clinical Trial English 10 years</td>
<td>7</td>
<td>25, 26</td>
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</table>

Articles were excluded if there was no pharmacist intervention on the study, if it was no full text available, if intervention consisted of home visits (this study is focused on the hospital pharmacists) and if a specific small topic was described (i.e. Chaga disease.)
One study had HF as exclusion criteria and therefore was excluded here also. Figure 2 shows exclusions stages.

Figure 2. Study Selection Process

The analysis was provided in seven main categories: adherence, re-admissions and emergency visits, mortality rates, medication errors, ADEs, quality of life, satisfaction with pharmaceutical care and health costs.

4. Results

Six studies were found, two of these were conducted in USA, the rest in the United Arab Emirates, Spain, Netherlands and UK. The interventions provided by clinical pharmacy services included medication reconciliation, therapy rationalization, discharge service, patient education and counseling, adherence aids, self-monitoring patient program and active telephone follow-up. Discharge service, patient education and telephone follow-up was a common feature of more successful programs.

The main outcomes evaluated were adherence, re-admissions and emergency visits, the number of deaths, medication errors and ADEs, quality of life, satisfaction with pharmaceutical care and health costs.

The collected data from the studies with total of seven different outcomes measured (see table 2) was compared. Improvement was demonstrated in many outcomes i.e. adherence to medication regime, re-admissions rate, satisfaction with pharmaceutical care and total health costs (see table 2).
### Table 2. Comparative outcomes in the studies.

<table>
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<tr>
<td>Re-admissions and emergency visits</td>
<td>20, 24, 28, 32</td>
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<tr>
<td>The number of deaths</td>
<td>24, 32</td>
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<tr>
<td>Medication errors</td>
<td>26, 28, 29</td>
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<tr>
<td>ADEs</td>
<td>26,28, 29</td>
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<tr>
<td>Quality of life</td>
<td>20, 24, 28</td>
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<tr>
<td>Satisfaction with pharmaceutical care</td>
<td>24, 28</td>
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<tr>
<td>Costs</td>
<td>20, 24, 28</td>
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#### 4.1. Pharmaceutical Care of Patients with Heart Failure

Study of Sadik et. al. (20) was conducted in the United Arab Emirates during one year with follow-up visits every 3 months. Intervention group consisted of 109 patients and 112 patients in the control group with mild to moderate HF, mean age 58 years. In this study, the research pharmacist observed groups of drugs prescribed to all patients randomized to the intervention. The purpose of observation was to rationalize the dosage regimen or therapy in collaboration with physicians according to the treatment algorithm used in a previous pharmaceutical care study in the UK (21). Patients from intervention group also received education on heart failure, knowledge about their prescribed medication and how to cope with HF symptoms from the research pharmacist. Every patient was given a copy of a printed brochure specially designed for this type of education and meant to be used at home. A monitoring diary card was given to all intervention group patients with instructions on a self-monitoring program (Appendix A).

Traditional management without research pharmacist education, pharmacist-physicians cooperation and self-monitoring etc. was given to control group patients. After three months from the beginning of the study, both intervention and control groups of patients were assessed in MLHFQ (Minnesota Living with Heart Failure Questionnaire) (22) and the SF36 quality of life questionnaires (23), compliance with given drug treatment and non-drug advices. Patients’ self-reported compliance with prescribed medications was the ground for assessment. If patients missed doses or took extra doses of their medication, without medical advice to do so, it was judged as noncompliance.

The content of MLHFQ represents degree of affecting physical, emotional, social and mental aspects of quality of life. In MLHFQ intervention group patients scored higher vs. control group patients demonstrating that their HF disease was not a barrier for them to live as they wanted.

SF36 questionnaire consists of eight sections: Physical functioning, Physical and Emotional Roles, Bodily pain, General health, Vitality, Social functioning, and Mental health. Each of the intervention group patients, and in general, reached significantly higher scores in all sections, bodily pain, vitality, physical and emotional roles, social functioning and mental health excluding general health and physical functioning compared with control group patients.

Intervention group patients demonstrated significantly higher self-reported compliance with the prescribed medication vs. control patients (85 vs. 35). Fewer hospital admissions occurred for the intervention group patients compared the control group patients. Nevertheless the intervention group patients had more acute visits to compared to the control group patients.

The total costs for hospital admissions and emergency visit were significantly higher for the control group patients compared to the intervention patients over the 12-month study period.
4.2 Randomized Clinical Trial of a Postdischarge Pharmaceutical Care Program vs. Regular Follow-up in Patients with Heart Failure

López et al. (24) included 70 patients in the intervention group and 64 patients in the control group, mean age 75 years and follow-up time one year. The intervention group patients were involved in the active information program performed by a research team pharmacist. Two different issues of the program activities were focused on:

- Information on the heart failure: main characteristics of HF (pathogenesis and symptoms: explanation with a simple language tailored to the patient’s social and cultural background, and supported by verbal, visual and written educational material.
- Telephone reinforcement: all intervention group patients got a phone number and the name of the pharmacist, to turn to with any questions or doubts concerning their treatment or the disease. A research pharmacist made telephone calls to all the patients’ home each month during the first half year of follow-up, and later, once in two months to strengthen the intervention and to help with any problems or doubts that could have arisen.

Compliance was higher among the intervention group patients than among the patients in the control group: 88.2% vs. 60.5% at 2 months, 91.1 vs. 69.0% at 6 months and 85.0 vs. 73.9% at the end of the follow-up time. The results were statistically significant at 2 months (p= 0.002) and 6 months (p= 0.015) but not at 12 months.

Re-admissions occurred rarer with the patients in the intervention group than with the control group patients: a decrease of 54% was reached at 2 months, of 42.4% at 6 months follow up and of 32% at 12 months. The results were statistically significant at 2 months (p = 0.041) and 6 months (p = 0.028), not statistically significant at 12 months.

Quality of life was assessed as approximately equal for both study groups without significant differences relating to the measurement during the follow-up.

Satisfaction with the care and the information received was greater in the intervention group patients (p = 0.026 at second visit), at 6 months and at the end of the follow-up time the result was not statistically significant.

The number of deaths was significantly lower in the intervention group. At one year follow-up the percentage of deaths in the intervention group was 12.9% compared with 29.7% in the control group (p < 0.05).

The financial analysis showed that the costs incurred from larger use of health resources in the control group are greater than the costs assumed from the educational intervention, with a significant difference in favor of the intervention group.

4.3 The PILL-CVD Study (The Pharmacist Intervention for Low Literacy in Cardiovascular Disease)

Schnipper et al (25) undertook a study in USA with 430 patients in the intervention group vs. 432 patients in the control group, mean age 60 years and follow-up time 30 days. Pharmacist intervention consisted of four components: 1) pharmacist-assisted medication review, 2) patient-centered counseling by a pharmacist, 3) providing low-literacy compliance aids and 4) personal telephone follow-up after discharge.

- Medication reconciliations were delivered by study pharmacists at enrollment time, in-hospital transfers and on discharge. The patient’s health literacy and cognitional ability was a ground for pharmacist counseling.
- Intervention was typically provided during 2 sessions on the day of admission and the discharge day. At the first consultation the data about the patient’s initial understanding of medications and prescription labels was gathered together with limitations to adherence and social support status. Collected information was used at the second meeting mainly at discharge day and concentrated on the medication regime after discharge and previously recognized patient’s needs. The pharmacist highlighted changes between the
pre-admission and discharge regime, ways to achieve compliance and minimize possible side effects. “Teach-back” technic was used to ensure understanding (27).
- The intervention group of patients was dispensed low-literacy adherence aids consisting of a pillbox and illustrated daily medication schedule (Appendix B).
- The intervention group patients visited within one to four days after discharge an unblinded research coordinator who determined medication-related cases through a structured interview. All identified problems were redirected to pharmacists who resolved them together with the hospital personnel and responsible primary care physicians.

Control group patients received usual consulting at the hospital at the discharge from the nurse and treating physicians following to every hospital’s protocol for carrying medication consulting within 24 hours of admission, at transfers of care, and discharge. Patients in the usual care group were not regularly supplied with a pillbox, illustrated medication schedule, or telephone follow-up.

PILL-CDV study reported primary and secondary outcomes when follow-up period was over. One or more clinically important medication errors occurred for 432 (50.8%) out of all 851 study patients during the first month after hospital discharge. A total of 777 errors were identified, of which 585 (75.2%) were categorized as significant in severity, 178 (22.9%) were serious, 14 (1.8%) were life-threatening, and 0 were fatal.

Intervention and usual care groups showed analog average amount of clinically important medication errors respectively 0.87 per patient vs. 0.95 per patient. Classification of medication errors is shown on Figure 5.

![Figure 5. Medication Errors Classification. (modified by author from reference 25)](image)

Intervention group and control group demonstrated similar level of preventable or ameliorable ADEs number per patient (0.43) vs. (0.40) respectively. Intervention had no significant treatment effect on ADEs. Potential ADEs happened more rarely between intervention patients (0.44 per patient) than between control patients (0.55 per patient).

**4.4 Pharmacist intervention to improve medication adherence in heart failure: a randomized trial**

Murray et. al. study (28) was carried out on the base of Indiana University Medical Group in Indianapolis, USA with 122 patients in intervention group, 192 patients in the control group and one year follow up time. Mean age was 50 years old.
A pharmacist delivered the intervention by using a protocol specially formed for this purpose. On the baseline interview the history of all patient's prescription, over-the-counter drugs and dietary supplements were collected and patient's medication knowledge and skills were assessed. The pharmacist filled patient's prescriptions approximately for two months period. The patients received customized verbal and written information about the medications. Patients with low health literacy received written instructions with easy-to-follow schedule as a reminder when to take their medications.

A study database was used by the pharmacist to monitor patients' medication usage, health care appointments, body weight and other appropriate data. If needed, patient information was supplied to the general prescriber (GP) or clinic nurses. Usual care group patients knew about the aim of the study, and their involvement was approved by their primary care physicians.

Medication adherence was measured with help of Medication Event Monitoring System (MEMS) V prescription container lids produced by AARDEX Ltd., Zug, Switzerland by electronic monitoring. MEMS lids were dispensed with all prescribed cardiovascular medications. The time and date of each opening and closing was recorded onto a digital chip. Data from the lids was used to confirm intake and scheduling adherence.

Total intake adherence was 78.8% vs. 67.9% in the intervention and control group, respectively (difference 10.9 percentage points [95% CI, 5.0 to 16.7 percentage points]) during the 9-month intervention. These beneficial effects dissolved in the 3-month post intervention follow-up period, in which taking adherence was 70.6%, and 66.7% respectively (difference, 3.9 percentage points [CI, −5.9 to 6.5 percentage points])

Total scheduling adherence was 53.1% vs. 47.2% in the intervention and control groups respectively (difference, 5.9 percentage points [CI, 0.4 to 11.5 percentage points]) during the intervention period. This effect also dissipated during the 3-month post intervention period (difference, 0.3 percentage point [CI, −5.9 to 6.5 percentage points]). Self-reported adherence in both groups was approximately the same.

The combined end point of hospital admission or emergency department visit due to HF exacerbation was 19.4% lower for the intervention group (incidence risk ratio, 0.82 [CI, 0.70 to 0.95].

Quality of life raised in both groups according to questionnaires. The intervention group showed improvement in the disease-specific quality of life from baseline to 6 months and 12 months by 0.28 and 0.39, respectively, the control group by 0.21 and 0.24, respectively ($P = 0.52$ at 6 months; $P = 0.21$ at 12 months). The total improvement in patient satisfaction with pharmacy service was greater in the intervention group than the control group (1.0 vs. 0.7; $P = 0.022$) from baseline to 12 months.

Total Direct Costs. The intervention saved $2960 per patient (CI, −$7603 to $1338) because of less acute visits and hospitalizations. Patients had big variability in costs in both groups what made comparisons between groups not statistically significant. It was no statistical difference in adverse drug events and medication errors between groups. 91 of 192 patients in the control group (47.4%) had an adverse event or medication error vs. 42 of 112 patients (37.5%) in the intervention group.

### 4.5 The Effect of a Clinical Pharmacist Discharge Service on Medication Discrepancies in Patients with Heart Failure

Eggink et al. (29) evaluated discharge service in an academic teaching hospital in Tilburg, the Netherlands for 41 patients in the intervention group and 44 patients in the control group, mean age 73 years, follow-up time 6 weeks. The intervention consisted initially of recognizing potential errors in the prescribed discharge medication by a clinical pharmacist. Discussions with the cardiologist resulted in the final treatment sheet. Then during hospital discharge the clinical pharmacist provided the intervention group patients with verbal and printed information about their
medications, effects, possible side effects and changes in drug therapy. A discharge medication list containing supplementary information about dose adjustments and suspended medication was prepared by the clinical pharmacist. When approved by the physician, the list was faxed to the community pharmacy and given as written information to the patients for a delivery to the GP. Control group patients received usual care from a nurse at the discharge from the hospital, which included verbal and printed information about their medications. After 6 weeks the pharmacist checked patient’s medication for prescription errors and for discrepancies. The findings were discussed with the cardiologist or HF nurse and the patient. A discrepancy was defined as a difference in real medication use compared to mediation prescribed for a patient at the discharge. Classification of discrepancies included: reintroduction of suspended drugs, disruption of prescribed discharge drugs, use of lower or higher doses, wrong time of taking drugs and more or less frequent use than prescribed.

An error happening during medication prescribing process was defined as a prescription error. It could be dosage form errors, dosing errors, drug–drug interactions, contra-indications, and double-medication. The clinical pharmacist determined prescription errors and collected them after the cardiologist consent. The NCC MERP-index (30) was used to estimate clinical relevance of the discrepancies or prescription errors. This index uses an algorithm for categorization of medication errors (class A–I). In summary, class A: no error, class B, C and D: error, but no harm, class E, F, G and H: error and harm, class I: error and death. Class E or more (i.e. errors resulting in harm) discrepancies and prescription faults assumed as clinically relevant. At least one discrepancy or prescription error was detected for 68% of patients in the control group compared with 39% in the intervention group (RR 0.57 (95% CI 0.37–0.88). The control group had 14.6% medications with a discrepancy or prescription error and in the intervention group it was 6.1% (RR 0.42 (95% CI 0.27–0.66).

4.6. The Heart failure and Optimal Outcomes from Pharmacy Study (The HOOPS study)

Lowrie et al. (31) performed 2011 a study in UK with 1090 patients in the intervention group and 1074 patients in a usual care group. Mean age of patients was 71 years; the trial had median follow-up time 4.7 years. Each patient in the intervention group got a 30-min appointment with a pharmacist. During the consultation the pharmacist reviewed the patients’ medical treatment according to the local Heart Failure Liaison Nurse Service guidelines for management of heart failure due to left ventricular systolic dysfunction (LVSD). No disease symptom information was collected by the study pharmacists and no patients’ examination was performed as this was not a part of their professional training.

GP in the control group with usual care practices obtained no instructions from pharmacists and no patient-pharmacist appointments were arranged.

The primary outcome was the combination of death from any reason or readmission for HF, analyzed as time to first event. The primary endpoint happened in 35.8% (390 patients) in the intervention group and 35.4% (380 patients) in the control group. Lower adjusted hazard ratio (HR) 0.97, 95% CI 0.83–1.14, P = 0.72) for the primary endpoint was counted in the intervention group compared to the control group. Death from any reason or hospitalization for a cardiovascular event was registered in 44.7% (487 patients) of the intervention group compared with 44.2% (475 patients) in the usual care group (HR 0.97, 95% CI 0.84–1.12, P = 0.70). Approximately the same percentage of patients in the intervention group (30.9%) and in the usual care group patients (30.8%) died (HR 0.96, 95% CI 0.80–1.16, P = 0.68).
The studies are summarized in the Table 3.

Table 3. Six studies of pharmaceutical intervention on HF patients.

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Design, follow-up time</th>
<th>Intervention group size, Services</th>
<th>Control group size, Services</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Sadik et. al. (20) 2005 United Arab Emirates (UAE)</td>
<td>Randomized, controlled, longitudinal, prospective clinical trial 12 months</td>
<td>109 patients therapy rationalization or simplification of dosage if appropriate. Patient education, a self-monitoring patient program</td>
<td>112 patients traditional management</td>
<td>improved adherence, a lower rate of hospitalization, better quality of life, less health costs</td>
</tr>
<tr>
<td>López Cabezas et. al. (24) 2006 Spain</td>
<td>Randomized, prospective, open clinical trial 12 months</td>
<td>70 patients patient education, active telephone follow-up</td>
<td>64 patients usual care</td>
<td>improved adherence, less re-admissions, equal quality of life, greater satisfaction with pharmacist care, lower number of deaths, less costs.</td>
</tr>
<tr>
<td>Schnipper et. al. (25) 2010 USA</td>
<td>Randomized controlled trial 30 days</td>
<td>430 patients medication reconciliation, patient counseling, low-literacy adherence aids, and individualized telephone follow-up after discharge</td>
<td>432 patients usual care</td>
<td>no difference in SMEs and ADEs after hospital discharge between groups, equal adherence</td>
</tr>
<tr>
<td>Kripalani et al (26) 2012 – results of Schnipper J. L et. al study</td>
<td>Randomized controlled trial with concealed allocation and blinded outcome assessors 12 months</td>
<td>122 patients patient education, collaboration with primary care physicians</td>
<td>192 patients standard pharmacutical service</td>
<td>improved measured, though equal self-reported adherence lower admission rate, the same rate of SMEs and ADEs, improved quality of life, patient satisfaction with pharmacy services, and total direct costs</td>
</tr>
<tr>
<td>Murray et. al. (28) 2007 USA</td>
<td>Open randomized intervention study 6 weeks</td>
<td>41 patients discharge service provided with the clinical pharmacist review of discharge medication, communicating prescribing errors with the cardiologist, patient education</td>
<td>44 patients discharge service provided with regular care by doctors and nurses</td>
<td>the same adherence, less discrepancies and prescription errors in medication</td>
</tr>
<tr>
<td>Eggink et al. (29) 2010 Netherlands</td>
<td>A prospective randomized controlled trial median follow-up time 4.7 years</td>
<td>1090 patients medication reconciliation</td>
<td>1074 patients usual care</td>
<td>the same number of deaths or hospital admissions for HF worsening</td>
</tr>
<tr>
<td>Lowrie et al. (32) 2011/2012 UK</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4 Discussion

The aim of this literature study was to find out what clinical pharmacy services are provided for patients with HF and what is the effectiveness of clinical pharmacy services on HF patients. The six studies used different component combinations in pharmaceutical intervention and measured different kind of outcomes that makes comparison complicated. The analysis was provided in seven main categories: adherence, re-admissions and emergency visits, mortality rates, medication errors, ADEs, quality of life, satisfaction with pharmaceutical care and health costs. The reviewed studies reported different outcomes from clinical pharmacy services for HF patients. Improvements in many outcomes (adherence to medication regime, re-admissions rate, satisfaction with pharmaceutical care and total health costs) were mostly achieved (20, 24, 28, 29). Some studies results lack statistical significance (26, 28, 29, 32) and mainly show the way for further improvement. Diverse definitions, data collection routines, and continuation of follow-up period make studies comparison problematic.

Adherence. Of six studies chosen for this literature review five studies evaluated adherence as one of the main outcomes (20, 24, 26, 28, 29). Three studies (20, 24, 28) showed improved adherence, in two studies results were not statistically significant. In the Eggink et. al. (29) study both intervention and control groups’ similarity regarding the percentage of patients who were potentially non-adherent was nearly predictable because of short 6 weeks follow-up period (29). Earlier research of Murray et al (36) and Haynes et. al. (37) presented a fact that a combination of interventions lasting 3 weeks and longer is needed to reach improvement in medication adherence. Earlier research assess the rate of non-adherence 25% to 50% (33). Non-compliance has been named as a major cause of unnecessary hospitalization of patients with HF (34). It has been shown in one study that 27% of patients hospitalized for HF were re-hospitalized within 90 days (35), with most of these hospitalizations resulting from medication or dietary non-compliance. Improved patient counseling and education are essential for greater improving outcomes, including patient compliance (35).

Re-admissions and emergency visits. The single most common reason of hospitalization in people aged 65 years and over is HF. Four studies (17, 18, 21, 23 (24) assessed re-admissions and emergency visits. The mean age of the patients participating in studies were 50 years to 75 years. Sadik et. al. demonstrated a reduction of hospital admissions in the intervention group patients compared to the control group. Authors consider it was a result of the pharmacist interventions, better adherence with the prescribed medications and lifestyle advices. (20).

The number of deaths. López et al. and Lowrie et al. (24, 32) showed completely opposite result in the number of deaths. The reduction of mortality shown in the López et al. study is difficult to associate with the educational intervention, a larger population sample, and a multivariate analysis adjusted for baseline would have probably required (24). As known, it is very difficult to show reduced mortality in a study (regardless of studying intervention). Usually a very large study with a big sample is required and a very effective intervention must occur in order to prove reduced number of deaths. To make a pharmaceutical service able to demonstrate improvement in this outcome is very complicated considering many different factors it depends of, moreover, in as few as 1000 patients.

Medication errors. Schnipper et al., Murray et. al and Eggink et. al. (26, 28, 29) evaluated medication errors, only the last one could demonstrate statistically significant improvement. These results show clearly that improving of medication safety during patients’ way from hospital to home is a complicated issue. Patients have
difficulties to understand changes in their medication regime, GP and community pharmacists not always get information about those changes. ADEs. Both Schnipper et al. and Murray et al. (26, 28) reported no statistically significant difference in the number of ADEs. The main goal of PILL-CVD study was to reduce SMEs after hospital discharge using a pharmacist-based intervention. This randomized controlled trial showed that clinically important medication errors affected 50.8% of patients during the first 30 days after hospital discharge hence were very common. Summarily, the pharmacist intervention at the study hospitals did not have clinically significant effect on reducing of clinically important medication errors or ADEs. Visible decreasing of potential ADEs was not statistically significant either. These results underline the difficulty of improving medication safety during the patient’s way from hospital to home (25, 26).

The Schnipper et al. study (26) was conducted at two academic hospitals that had reserves to support medication reviews with health information technology already at baseline. Therefore additional benefit from the PILL-CVD intervention was problematic to demonstrate. Probably hospitals with diverse characteristics, such as less electronic medical record support for medication reconciliation or fewer pharmacist resources, may get benefit over usual care from this type of intervention.

Another factor limiting generalizability is that the study population at baseline was well educated “(median 14 years of education), cognitively unharmed (88%), and had a relatively low prevalence of inadequate health literacy (10%)”, compared to a 26% prevalence in the medical literature (32). The PILL-CVD intervention was created to help the patients with small health literacy or cognitive impairment and possibly may be more effective in such populations.

The intervention was mentioned to be given to all patients but not all of them received the full intervention, although most part did (25).

Intervention program in Murray et al. study was managed from a pharmacy by a pharmacist who dispensed medications and provided other help and support (28). Despite pharmacists’ contact with GP improvement in ADE was not statistically significant.

Quality of life. This outcome was shown to be improved in Sadik et al. study (20), both Murray et al. and López et al. (24, 28) reported not statistically significant result in this outcome. According to the MLHF questionnaire scores analysis the intervention group patients’ quality of life was not affect their by HF disease as much as in the control group patients. SF 36 scores demonstrated also that the quality of life increased over time in the intervention group, in the same time life quality in control group remained at a relatively stable level. HF disease with related symptoms affects the patients’ ability to perform normal daily activities in large extent, in such way affecting their health-related quality of life (38). Sadik et. al. (20) consequently demonstrated that pharmaceutical care interventions can have a positive influence on HF patients’ capacities to manage daily activities (20). As a limitation can be mentioned the difficulty in administering the EuroQol questionnaire and the satisfaction survey as both contained some abstract elements difficult to interpret by people older than 75 years and with low cultural level. It could be more relevant to use questionnaires specifically designed to estimate quality of life in HF, like the Chronic Heart Failure Questionnaire or the MLHF Questionnaire, yet these questionnaires had not been validated in Spanish at the study period (24).

Satisfaction with pharmaceutical care. Both López ed. al. and Murray et. al. studies(24, 28) reported greater satisfaction with pharmaceutical care in the intervention group. It is always beneficial to include this outcome in pharmacist
intervention assessment because it gives valuable information about pharmacist intervention influence and shows fields that require development.

Costs. In two studies (20, 24) health costs were counted as decreased by pharmacist intervention, one study (28) didn't reach statistical significance in costs assessment. Hospitalization is known as the main cause of the costs generated by the management of HF. The expenses depend on many factors, such as the country of study, the hospital level, or how global calculation was conducted that make it problematic to compare studies by these criteria (24). Differences in the studies results can be found in different age of study populations, ethnical, educational and cultural level of patients, their cognitive state, not least pharmacists’ training level and personality.

Sadik et. al. (20) reported all outcomes improvement though the results were delivered selective and not in per-cent form as in other studies that carries the risk of bias. Probably success of this study is related to younger study population mean age 58,6 years and mild to moderate HF (NYHA Class 1, 29,5%; Class 2, 50,5%). In the United Arab Emirates (UAE), the country in which the present study was performed, clinical pharmacy services are at an early stage of development so the intervention therefore probably had a big impact on patients that did not get help from clinical pharmaceutical care before.

López et al. (24) also reported all outcomes improvement except the quality of life outcome that could not reach clinical significance. The study population was oldest of all represented in comparable here studies with mean age 75 years. Study success may be can be found in education provided to caregivers.

The studies reviewing here used different types of services such as medication reconciliation, patient counseling, patient and patient’s caregiver education, low-literacy adherence aids, discharge service and individualized telephone follow-up after discharge. The study results comes in consent with the conclusions of metaanalysis by Phillips et al. (39) that the personal contact with the patients is much more effective than the telephone follow-up and interventions on discharge or shortly after it are the most beneficial, it can be considered that the interview on discharge is mainly responsible for the positive outcomes of the active information program. With the search method used in this literature review, it was not possible to find information how pharmaceutical clinical services work with HF patients in Sweden. If only it is not done yet to present moment, it will be beneficial to use positive experience with including the clinical pharmacist in a multidisciplinary team. Because pharmacotherapy is central to the management of heart failure, almost all management programs are focused on appropriate use of medications and adherence (28). Routinely medication reconciliations at admission, hospital transitions and discharge can help to optimize drug treatment, to decrease SME and ADEs. The PILL- study showed that clinically important medication errors usual take place during the 30 days after a cardiac hospitalization (26). Thus it may be favorable for HF patients to get help from a clinical pharmacist in this period with control of possible SME and discrepancies. Clinical pharmacists can collect the history of all patient’s prescription, over-the-counter drugs and dietary supplements and a way can be found to make this history available for GP, nurse and community pharmacist at any time. Pharmacists can provide information about HF, drug therapy, special diet and physical activity advantages, education in self-monitoring of patients, intensive patient and their caregivers education. The pharmacists are experts in pharmacological knowledge and resolving of medication problems that should be used more widely for patients benefit. Managing of co-morbidities as lung diseases and diabetes, help with lifestyle changes such as smoke cessation can also be a field for clinical pharmaceutical services.
Method limitations. This literature study is limited to a small number of articles. Not many articles were found that matched the pharmacist intervention on HF patients and it may be due to the fact that the health scientific research interest is focused on cardiovascular diseases in general. Some articles could not be obtained in full text. Wider results probably could be achieved without search being limited to 10 years and English language. Advantage of search being limited to 10 years is in delivering latest research results in challenging healthcare system.

In the future new and larger studies might include: Comparative studies between interventions with short (at discharge) and a much longer duration with intensive follow-up; studies including a large population to assess the effect of interventions on patients’ mortality rate. It might be possible to conduct a study with large population and intensive clinical pharmacy services across long follow-up time to decrease the number of deaths with help of clinical pharmacy services. An assessment of costs and cost-effectiveness of pharmaceutical interventions is also important.

6. Conclusion

The interventions provided by clinical pharmacy services included medication reconciliation, therapy rationalization, discharge service, patient education and counseling, adherence aids, self-monitoring patient program and active telephone follow-up. Discharge service, patient education and telephone follow-up were common features of more successful programs. The clinical pharmaceutical services may improve adherence, re-admissions and emergency visit rates, mortality rates, decrease medication errors, improve quality of life and satisfaction with pharmaceutical care for HF patients and decrease health costs. Low-intensity short-time pharmacist-led intervention is proved to be less effective than high-intensity intervention with long follow-up. More studies needed for evaluating of effectiveness of pharmacy services for HF patients.

Acknowledgments

I was very fortunate that Helena Holmgren agreed to be my mentor in this study. I am grateful to you also for guidance over the past two years and I hope you should be willing to lead me further to next stage.

I would like to express my gratitude to my chef in the VitusApotek Valdres in Norway Knut Bjørgo who makes possible for me to combine job and study, who supports and inspires me at work. Thanks to all my fantastic colleagues for their understanding and friendship.

I would also like to thank my older daughter Svetlana and her husband Jesper for motivation and cheering, for real interest to my success and failures.

My sincere thanks to my partner daughter Dana for her assistance with text editing and her help in my fight with English grammar.

I wish to express my deep appreciation and gratitude to my beloved Jan who helps me to fulfill my childhood dreams about university and science. Without your love and patience I would not be able to complete many of my projects.
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17. The Definition of Clinical Pharmacy American College of Clinical Pharmacy (Pharmacotherapy 2008;28(6):816–817


Appendix A

Diary card for patient self-monitoring, covering a period of 1 month (first 8 days only shown)
(modified by author from reference 20).

<table>
<thead>
<tr>
<th>Start date</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Physical Activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without limitation</td>
<td>0</td>
<td>Marked limitation</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slight limitation</td>
<td>1</td>
<td>Unable to carry on any</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2. Tiredness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>Marked amount</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slight amount</td>
<td>1</td>
<td>Severe fatigue</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3. Shortness of Breath When Sitting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>Marked amount</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slight amount</td>
<td>1</td>
<td>Severe breathlessness</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4. Ankle Swelling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>Marked amount</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slight amount</td>
<td>1</td>
<td>Severely swollen</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5. Body Weight</strong> in Kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6. How many times did you get last night to urinate?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0,1,2,3 etc.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>7. Drugs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of doses taken during the past 24 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix B

Example of a personalized medication schedule (modified by author from reference 25).

<table>
<thead>
<tr>
<th>Medication name and dose</th>
<th>What it’s for</th>
<th>Morning/ Breakfast</th>
<th>Afternoon/ Lunch</th>
<th>Evening/ Dinner</th>
<th>Night/ Bedtime</th>
<th>Common Side Effects</th>
<th>Special instruktions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin 81 mg</strong></td>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Upset stomach, rush, bleeding</td>
<td>Take with food if you get upset stomach</td>
</tr>
<tr>
<td>Take 1 a day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metoprolol 50 mg</strong></td>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Feel tired or depressed, feel dizzy, rush, trouble breathing, problem with sex</td>
<td></td>
</tr>
<tr>
<td>Take 2 in the morning and 1 in the evening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Atorvastatin 40 mg</strong></td>
<td>Cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>May make your muscles hurt or feel weak. Urine may turn dark, skin and eyes may turn yellow. Let doctor know if it happens.</td>
<td>Doctor will check blood results to make sure they’re ok. Do not drink grapefruit juice.</td>
</tr>
<tr>
<td>Take 1 at night</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Medication to take only when you need it**

<table>
<thead>
<tr>
<th>Medication name and dose</th>
<th>What it’s for</th>
<th>Morning/ Breakfast</th>
<th>Afternoon/ Lunch</th>
<th>Evening/ Dinner</th>
<th>Night/ Bedtime</th>
<th>Common Side Effects</th>
<th>Special instruktions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxycodone (OxyCONTIN, Oxyfast, Roxicodone) 5 mg</strong></td>
<td>Painkiller</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>May make you sleepy</td>
<td>Avoid driving. Do not take alcohol.</td>
</tr>
<tr>
<td>Take 1 tablet every 6 hour when you need it</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Medication to stop taking**

<table>
<thead>
<tr>
<th>Medication name and dose</th>
<th>Common Side Effects</th>
<th>Special instruktions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol 100 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin 20 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>