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REVIEW ARTICLE / DERLEME MAKALE

PHARMACIST INTERVENTIONS TO IMPROVE CLINICAL OUTCOMES IN HEART FAILURE

KALP YETERSİZLİĞİNDE KLİNİK SONUÇLARI İYİLEŞTİRMEYE YÖNELİK ECZACI MÜDAHALELERİ

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ABSTRACT

Objective: *Heart failure (HF) is associated with poor outcomes, such as high mortality and hospitalization rates, and impaired quality of life (QoL). Pharmacist participations in a multidisciplinary care team have demonstrated to be beneficial in HF, which includes optimization of guideline-directed medical therapy (GDMT) and medication adjustment, optimizing the transition of care (ToC) and medication reconciliation, and providing patient education. The aim of this literature review is to investigate the impact of pharmacist interventions on HF, with the intention to improve clinical outcomes.*
Result and Discussion: *Randomized controlled trials evaluating the efficacy of pharmacist intervention in HF patients were reviewed, and 8 randomized controlled trials were included. The pharmacist interventions that were investigated in these studies were medication review, patient counseling, and patient education. The included studies demonstrated that pharmacist interventions may reduce prescribing errors, medication discrepancies, and drug-drug interactions (DDIs). Studies demonstrated that patient counseling and education provided by the pharmacist may improve QoL and patient knowledge in HF. The rest of the outcomes lacked significance. In order to develop this issue further, large-scale randomized controlled trials and large-scale meta-analyses should be conducted involving pharmacist interventions in HF.*
Keywords: *Clinical pharmacist, heart failure, pharmaceutical care, pharmacist intervention*

ÖZ

Amaç: *Kalp yetersizliği (KY), yüksek mortalite ve hastaneye yatış oranları ve bozulmuş yaşam kalitesi gibi kötü sonuçlarla ilişkilendirilmiştir. Kılavuza yönelik tıbbi tedavi optimizasyonu ve ilaç düzenlemesi, bakım geçişi ve ilaç uzlaşısı, ve hasta eğitiminin sağlanmasını içeren multidisipliner bir bakım ekibinin içinde eczacı katkılarının KY'de faydalı olduğu gösterilmiştir. Bu literatür taramasının amacı, klinik sonuçları iyileştirmek amacıyla eczacı müdahalelerinin KY üzerindeki etkisini araştırmaktır.*
Sonuç ve Tartışma: *Kalp yetersizliği hastalarında eczacı müdahalelerinin etkinliğini değerlendiren randomize kontrollü çalışmalar taranmış ve 8 randomize kontrollü çalışma*

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derlenmiştir. Bu çalışmalarda araştırılan eczacı müdahaleleri ilaç incelemesi, hasta danışmanlığı ve hasta eğitimidir. Derlenen çalışmalar, eczacı müdahalelerinin reçeteleme hatalarını, ilaç uyuşmazlıklarını ve ilaç-ilaç etkileşimlerini azaltabileceğini göstermiştir. Çalışmalar, eczacı tarafından sağlanan hasta danışmanlığı ve eğitiminin KY'de yaşam kalitesini ve hastanın bilgisini arttırabileceğini göstermiştir. Diğer sonuçlarda anlamlı bir fark görülmemiştir. Bu konunun daha da geliştirilmesi için kalp yetersizliğinde eczacı müdahalelerini içeren geniş ölçekli randomize kontrollü çalışmalar ve meta-analizler yapılmalıdır.
Anahtar Kelimeler: *Eczacı müdahaleleri, farmasötik bakım, kalp yetersizliği, klinik eczacı*

INTRODUCTION

According to the European Society of Cardiology (ESC), heart failure (HF) is defined as a clinical syndrome of the heart that is characterized by a series of cardinal symptoms, such as dyspnea (shortness of breath), fatigue, and swelling at the ankles, which is caused by a functional or/and structural anomaly that leads to an insufficient cardiac output at rest or/and during exercise [1]. In addition, the American Heart Association/American College of Cardiology (AHA/ACC) defines HF as a complex syndrome with accompanying symptoms and signs that result from abnormalities of ejection or filling of blood to the ventricules of the heart [2]. It is difficult to define a specific reason for the development of HF, since multiple factors and comorbidities often exist, and contribute to the disease pathogenesis. The risk factors accompanying HF may include cardiovascular risk factors, such as coronary heart disease, hypertension, obesity, diabetes mellitus, and smoking; inflammation, and socioeconomic levels, which contribute to left or right ventricular dysfunction [3].

HF has characteristic symptoms, which include dyspnea and fatigue, with the presence of cardiac dysfunction. Some HF patients also show physical signs caused by fluid retention, which is an outcome of decreased cardiac output that results in activation of sympathetic nervous system with renin-angiotensin-aldosterone system (RAAS). Activation of the RAAS causes water and sodium retention, leading to fluid accumulation. The typical symptoms that fluid buildup may cause include dyspnea, orthopnea, edema, abdominal discomfort and distension, and hepatic congestion, while symptoms caused by reduction in cardiac output include fatigue and weakness [4].

It is predicted that the total population with HF worldwide is 64.3 million, and with more than half is estimated to have a preserved left ventricular ejection fraction (LVEF). The estimated prevalence of HF in developed countries is equal to 1% to 2% of their adult population[3]. HF is seen primarily in older people, especially individuals aged over 60 years [5]. Furthermore, for individuals aged >60 years, HF is the most common cardiovascular reason for hospitalization [6].

The prognosis and the outcomes of HF have improved over the past three decades. However, the outcomes of HF still remain poor today [3]. According to a 2018 study, 5-year mortality between 1990 and 2009 was 67% in HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). HFrEF and HFpEF subtypes showed similar mortality rates [7]. Additionally, a 2017 study reported a median survival of 2.1 years between 2005 and 2009, and 5-year mortality rates for HFrEF and HFpEF were 75.3% and 75.7%, respectively [8] .

Hospitalizations in HF is an important indicator for the prognosis of the disease, and the average incidence of hospitalization after HF diagnosis is once a year. Moreover, HF holds the highest 30-day readmission rate with 20-25% among other diseases. Nearly half of HF patients will be hospitalized within one year after the initial diagnosis, and 20% of them will be rehospitalized within the same year [3]. It is suggested that after hospitalization, long-term survival for HF patients may be poor [8]. Patients with HF often experience physical discomfort and emotional distress that significantly impairs their quality of life (QoL) as the disease progresses [9]. In addition to the worsening physical deterioration due to the progressive nature of the disease, patients with advanced HF often undergo social impairment and psychological problems like depression and anxiety [10].

Because HF is a heterogeneous syndrome, patients often have numerous comorbidities that may conclude in complex treatment regimens, medication nonadherences, and harmful drug-drug interactions [11]. After hospital discharge, it is also very crucial to optimize the transition of care (ToC) from the hospital setting to home, provide patient counseling and education, ensure that appropriate

medications are administered according to current guidelines, and ensure patient adherence to the therapy. However, each and every element may be challenging to accomplish, resulting in failure in treatment and disease management. Pharmacist may take proactive role in HF by using cognitive pharmacy services, such as medication review and patient counseling [12].

Medication review may be defined as the evaluation of patient's medications to optimize their therapy plan with the aim of improving health related outcomes. Within this practice, pharmacists review patient's prescription to address contradictions or changed drugs and address patient's medication administration to improve thier knowledge on medication and to enhance their adherence [13]. It is suggested that as a member of the multidisciplinary care team, the pharmacist may improve patient care by medication review, identifying potentially harmful prescribed drugs, optimizing the patient's treatment plan according to current guidelines and ensuring that the necessary medications are prescribed. In a retrospective study of 378 hospitalized HF patients with worsening symptoms between 2012 and 2014, pharmacist-led medication adjustment significantly reduced inappropriate medication use [14].

Patient counseling may be defined as giving written or verbal information to patients about how to use their medication, its possible side effects, proper storage of the medication, and diet and lifestyle changes. As important parts of the pharmacist intervention, patient counseling and education promote the rational use of medications, which has the potential to enhance disease outcomes and medication adherence [15]. In a meta-analysis of 49 randomized controlled trials, pharmacist counseling was associated with decreases in 30-day hospital readmissions and emergency hospital visits, and a significant increase in medication adherence compared to no counseling [16].

According to the guidelines on good pharmacy practice from the International Pharmaceutical Federation/World Health Organization (FIP/WHO), pharmacists should provide recommendations to make sure that the patient receives adequate information, written or verbally, to maximize the treatment benefit [17]. A variety of interdisciplinary HF care programs include patient counseling and education to enhance the benefits patients derive from the medication therapy by individualizing care plans, providing information on the medication, and improving the knowledge on the disease and self-care. So, patient counseling and education comprise an important part of the pharmacist intervention services [18].

Pharmacist participations in a multidisciplinary care team have demonstrated to be beneficial in HF management, which includes optimization of guideline-directed medical therapy (GDMT) and medication adjustment [14] optimizing the transition of care (ToC) and medication reconciliation [19,20], and providing patient education [21]. Figure 1 summarizes these pharmacist involvements in HF management.

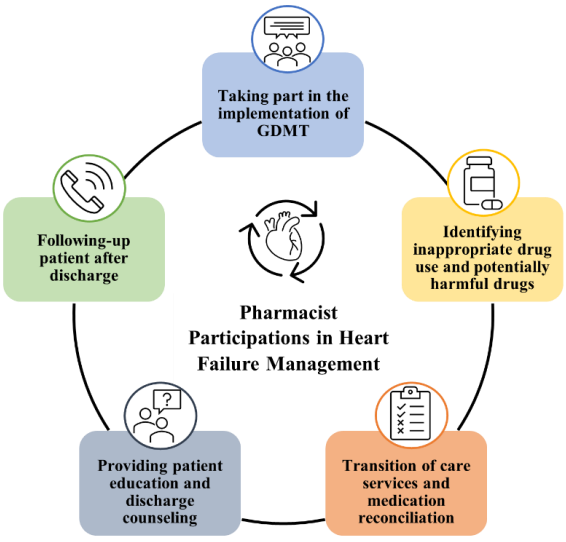

Figure 1. Pharmacist participations in HF management

Further, previous studies have shown that pharmacist contributions in HF management in a multidisciplinary team may reduce HF hospitalizations [22] and 30-day all-cause readmission rates [23].

The aim of this study is to review the available literature to investigate the impact of pharmacist interventions on HF, with the intention to improve clinical outcomes.

RESULT AND DISCUSSION

This study is designed as a literature review, English studies about the pharmacist's participation in HF care between the years 2010-2022 were screened. During the literature search, clinical studies were searched with the keywords "HF, clinical pharmacist, pharmaceutical care, drug-related problems, pharmacist intervention" in Pubmed®, Scopus®, Webofscience®, and Google Scholar® search engines. Animal studies and experimental models were excluded. The last screening was made on 20 February 2023.

Randomized controlled trials and meta-analyses evaluating the efficacy of pharmacist intervention in HF patients were reviewed. Only the studies that were available in full text are included. The data obtained from the studies are as follows: the characteristics of the people participating in the study (age, HF classification; the type, duration, frequency of pharmacist intervention; type of outcome measure (quality of life, medication adherence, all-cause and HF related hospitalization, length of hospital stay, prescription errors and medication discrepancies, all-cause and HF related mortality).

A total of 8 randomized controlled trials conducted to determine the benefit of pharmacist interventions in HF are included in this study [24-31]. The characteristics of the included trials are summarized in Table 1, which follows: the total number of participants, the environment that the intervention took place in, follow-up time, pharmacist intervention, and outcome measure. The main pharmacist intervention practices that were investigated in these studies include medication review, patient counseling, and patient education.

Table 1. Characteristics of the included studies

Study	Participants	Intervention Setting	Follow-up Time	Pharmacist Intervention	Outcome Measure
Yassin et al.[24]	93 CHF* patients with NYHA** class II or III, 47 in intervention group, 46 in usual care group	Hospital	6 weeks	Medication review, patient counseling	Hospitalization, length of hospital stay, medication discrepancies
Schulz et al. [25]	237 CHF patients, 110 in intervention group, 127 in usual care group	Community pharmacy	Median follow-up: 2.0 years	Medication review, patient counseling	Medication adherence, QoL***, hospitalization, all-cause mortality
Roblek et al. [26]	51 HF**** patients, 26 in intervention group, 25 in usual care group	Hospital	6 months	Recommendations on clinically relevant DDIs*****	Number of clinically relevant DDIs at discharge, all-cause mortality, hospitalization
Vinluan et al. [27]	16 HF patients aged ≥65 years, 7 in intervention group, 9 in usual care group	Hospital	Four times total: at day 3, 30, 60 and 90	Patient counseling	HF rehospitalization, medication adherence, mortality

Table 1 (*continued*). Characteristics of the included studies

Study	Participants	Intervention Setting	Follow-up Time	Pharmacist Intervention	Outcome Measure
Barker et al. [28]	120 hospitalized CHF patients, 64 in intervention group, 56 in usual care group	Home	Two times total: 1 and 6 months after discharge	Medication review	Mortality, CHF and all-cause hospitalizations, health related QoL
Lowrie et al. [29]	2164 HF patients with left ventricular systolic dysfunction, 1090 in intervention group, 1074 in usual care group.	Within National Health Service	Median follow-up: 4.7 years	Medication review	All-cause mortality, HF hospitalization, CV hospitalization, all-cause hospitalization
Korajkic et al. [30]	70 HF patients, 35 in intervention group, 35 in usual care group	Outpatient clinic	Three times total: at week 4, 8 and 12	Patient education	Number of correct weight-titrated furosemide dose adjustments, HF rehospitalization for fluid overload, HF-related QoL, HF knowledge
Eggink et al. [31]	85 HF patients, 41 in intervention group, 44 in usual care group	Hospital	6 weeks	Medication review	Total sum of prescription errors and medication discrepancies, estimated adherence

*CHF: Chronic heart failure, **NYHA: New York Heart Association, ***QoL: Quality of life, ****HF: Heart failure, *****DDIs: Drug-drug interactions

Yassin et al. conducted a study with chronic heart failure (CHF) patients in Iraq, to evaluate the role of medication review and patient counseling provided by a clinical pharmacist in the management of HF care. Patient's medications were reviewed by a clinical pharmacist to identify and resolve any prescribing errors. The counseling included an interview with the patient to provide information about how HF medications work, side effects, appropriate route of administration, and dosing frequency. Pharmacist interventions resulted in significant reductions in hospitalization and length of hospital stay. Additionally, significant reductions in medication discrepancies were observed, which were: incorrect dosing, discontinuation of prescribed medication, and restarting discontinued medication [24].

In a German study investigating the benefit of medication review and patient counseling provided by a pharmacist in a multidisciplinary team on hospitalizations, QoL, medication adherence, and all-cause mortality in chronic HF patients, pharmacist participations caused a significant increase in medication adherence to the three HF drug classes (beta blockers, angiotensin-converting enzyme inhibitors [ACEi] or angiotensin receptor blockers [ARBs], and mineralocorticoid receptor antagonists [MRAs]), which were the recommended drugs of choice according to the guidelines at that time. Pharmacist participations also led to improvement in the QoL of the HF patients. The results did not show a significant difference in hospitalizations and all-cause mortality [25].

In a study with HF patients in Slovenia, pharmacist's effect on reducing clinically relevant drug-drug interactions (DDIs) was evaluated. At discharge, pharmacist contributions caused a significant reduction in clinically relevant drug-drug interactions. The most common clinically relevant DDIs include the interaction between ACEi/ARBs and spironolactone, which caused hyperkalemia, renal impairment, and arrhythmia; and the interaction between loop diuretics and spironolactone, which led to renal impairment, hypovolemia, and electrolyte imbalance. The results showed no significant

difference in hospitalization and all-cause mortality [26].

An American study conducted to assess the benefit of pharmacist patient counseling on therapy adherence in HF. Pharmacists provided inpatient counseling on pathogenesis and symptoms of the disease, medication therapy, possible side effects, necessary diet and lifestyle changes, weight monitoring, and when to seek help, and followed up patients via phone after discharge. The data demonstrated a higher medication adherence in the intervention group at day 3, 30, and 60 compared with the control group. At day 90, the data showed a reduction in medication adherence in both groups, and the adherence in the intervention group was lower compared to the control group. After the overall follow-up period, hospital readmissions were not significantly different. However, mortality rates were lower in the intervention group [27]

Barker et al. conducted a study with chronic HF patients to determine the impact of medication review led by pharmacist on HF outcomes in Australia. In the study, pharmacist participations did not cause a significant difference in mortality, hospital admissions, and health related QoL [28]. Similarly, in a study with HF patients with left ventricular systolic dysfunction in the UK, medication review provided by a pharmacist did not cause a significant difference in all-cause mortality, all-cause, HF, and cardiovascular related hospitalizations [29].

The impact of patient education on patient-guided diuretic dose adjustment in HF was investigated in Australia with HF patients receiving furosemide diuretic therapy. The pharmacist intervention consisted of an educational session about HF and HF medications, improving patients' self care, how to recognize fluid retention symptoms, daily weight measurement, and adjusting the furosemide dose according to the changes in their signs and symptoms. Pharmacist interventions resulted in significantly higher appropriate self-adjustments of furosemide dosing. Without the pharmacist intervention, the number of patients readmitted to the hospital due to fluid overload was significantly higher. Moreover, the interventions resulted in significantly improved HF knowledge and the HF-related QoL [30].

In a study in the Netherlands, the effect of discharge medication review provided by a clinical pharmacist in HF was investigated. Patients' discharge medication was reviewed by a clinical pharmacist to identify any discrepancies and prescription errors. Medication discrepancies included deflections in medication use, such as discontinuation of prescribed medication, restarting discontinued medication, incorrect dosing, and incorrect time of taking medication. Prescription errors included errors that occured during prescribing, such as dosage form errors, contraindications, and medication duplications. The most common problem identified was prescription errors. Subsequently, discontinuation of prescribed medication and incorrect dosing were common for the intervention group. After the pharmacist intervention, prescription errors or medication discrepancies was reduced. However, the results did not cause a significant difference in estimated adherence [31].

The included studies demonstrated that pharmacist interventions may reduce prescribing errors, medication discrepancies [24,31] and drug-drug interactions [26]. Additionally, studies demonstrated that patient counseling and education provided by the pharmacist may improve QoL [25,30] and patient knowledge in HF [30]. The rest of the outcomes lacked significance between the study group and the usual care group [25-29,31]. These findings may be caused by the heterogenous and progressive nature of HF. In addition to the chronic progression of HF over time, other comorbidities that HF patients often have contribute to the poor disease outcomes, which may be associated with poor survival rates, high hospitalization rates, and deterioration in QoL. It should be noted that since the publications of the included studies, guidelines for the treatment and management of HF have been updated and new treatment recommendations have been made that were shown to reduce the risk of HF hospitalization or cardiovascular death in randomized controlled trials [32]. This may also explain why the results in the included studies were not significantly different.

The lack of significance in outcomes do not indicate that pharmacist participations in HF care may not be beneficial. In a chronic disease such as HF that causes a burden on patients, quality of life is an outcome that should be focused on. Improvements in QoL may be achieved with pharmacists who are knowledgeable about the disease and patients' comorbidities, can evaluate patients' complex drug regimens and detect drug-related problems, know current treatment strategies, and provide effective patient education about drug use and the disease. Moreover, pharmacists are accessible healthcare providers, so it is convenient for patients to receive health care services from a more accessible source.

Compared with health care professionals such as physicians and nurses who have other duties and responsibilities, pharmacists may provide counseling and education in a patient-based manner for a longer period of time and alleviate the burden of other health care providers since interventions like medication review and patient counseling are pharmacist's responsibilities.

Study Limitations

There are several differences among the included randomized controlled trials that may prevent a general conclusion from being drawn. The included studies vary in terms of sample size, study period, sociodemographic characteristics of the participants, and disease severity. Some of the included studies had small sample sizes and short follow-up periods, which may affect the generalizability of the findings. The studies included HF patients from different countries, which could have affected the accessibility of the health services and the pharmacist intervention for each study. The HF severity of the patient population varied within some of the included studies between the control and intervention groups. This may have affected the accurate reflection of whether pharmacist interventions objectively improved clinical outcomes. For a better comparison, these elements should be equivalent in the participants.

Future Perspectives

Pharmacist participations in HF care have the potential to improve disease outcomes and alleviate the burden of the disease. In order to develop this issue further, large-scale randomized controlled trials and meta-analyses should be conducted involving pharmacist interventions in HF. The potential impact of pharmacist interventions should be investigated not only in the management of HF alone, but also in the presence of HF and different comorbidities. So, a more evidence-based approach can be taken in different scenarios accompanying HF.

Additionally, protocols for HF management should be established that include pharmacist interventions to improve disease outcomes, and disease management teams in which the pharmacist plays an active role should become widespread. Thus, clearer approaches can be created in medication review and patient counseling practices carried out by the pharmacist and can be made a regular practice.

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that ethics committee approval is not required for this study.

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