International Journal of Clinical Pharmacy (2019) 41:1555–1561
https://doi.org/10.1007/s11096-019-00918-z

RESEARCH ARTICLE

# The role of the clinical pharmacist in the prevention of potential drug interactions in geriatric heart failure patients

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Received: 20 March 2019 / Accepted: 25 September 2019 / Published online: 8 October 2019


## Abstract

*Background* The treatment of heart failure patients is very complex and includes lifestyle modification as well as different pharmacological therapies. Polypharmacy is very common in such patients and they are at increased risk of potential drug–drug interactions and associated effects such as poor adherence, compliance and adverse events. *Objective* The aim of the present study is to investigate retrospectively the prescribed pharmacotherapy of the hospital discharged heart failure patients for possible drug interactions. *Settings* Clinic for Cardiology of the "Saint Marina" University Hospital in Varna, Bulgaria. *Method* Lexicomp® Drug interaction software was used for screening potential drug–drug interactions. Logistic regression was applied to determine the odds ratio for the association between the age and number of drugs taken and the number of potential drug–drug interactions. *Main outcome measure* Incidence and type of pDDIs in geriatric heart failure patients. *Results* A retrospective study was conducted by reviewing the medical records of 248 selected heart failure patients for the prescribed medicines for a 1-year period (January 2015–December 2015). The total number of potential drug–drug interactions was 1532, or approximately 6.28 (± 4.72 SD) per one person. The range of prescribed drugs was between three and fourteen, 92% of them have been taking more than five medicines, an average of 7.12 (± 2.07 SD) per patient. The average age was 72.35 (± 10.16 SD). The results have shown stronger association between the number of drugs taken (more than 7) and the occurrence of potential drug–drug interactions (more than 10)—37.84 (95% CI 9.012–158.896, $P \leq 0.001$). No statistically significant differences were found between age and occurrence of potential drug–drug interactions (more than 10)—1.008 (95% CI 0.441–2.308, $P = 0.848$). *Conclusion* The incidence of drug-drug interactions in heart failure patients is high. The clinical pharmacist, as a part of the multidisciplinary team, could reduce medication-related problems, such as drug interactions, and to optimize drug therapy by checking the treatment prescribed at the discharge of these patients.

**Keywords** Bulgaria · Clinical pharmacist · Drug–drug interactions · Heart failure · Polypharmacy

## Impacts on practice

- Patients with heart failure are predisposed to drug–drug interactions due to the complex pharmacotherapy and the advanced age of these patients. The physicians of these patients should always be alert for potential drug–drug interactions and check any new medication for possible ones.
- The potential for drug–drug interactions increases significantly with increasing the number of the prescribed medications.
- For reducing the risk of potential drug-drug interactions, appropriate software for prediction should be used. Another suitable option could be to include a clinical pharmacist in the multidisciplinary team.

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## Introduction

Heart failure (HF) is a complex syndrome secondary to structural and/or functional changes in the heart that cause circulatory hypoxia regardless of normal or elevated ventricular pressure. Clinical expressions are fatigue, dyspnea (especially at night), fluid retention (edema, pulmonary congestion), increased venous jugular pressure, cardiomegaly, reduced or preserved ejection fraction [1]. The treatment of HF is very complex and includes both lifestyle modification and multiple pharmacological therapies. Drugs used in the treatment of heart failure are divided into two groups: (1) those that improve prognosis—ACE inhibitors, $AT_1$-blockers, aldosterone antagonists, beta-blockers, blockers of the I(f) channels in the sinus node; and (2) those that improve the condition of the patient (diuretics, vasodilators, cardiac glycosides) [2]. In addition to standard treatment, patients may receive many other drugs to treat the accompanying conditions related to HF. The most common ones are hypertension, atrial fibrillation (AF), anemia, diabetes, chronic kidney disease and hyperlipidemia. Therefore, polypharmacy is very common in HF and patients are at an increased risk of potential drug–drug interactions (pDDIs) and associated effects such as poor adherence, compliance and adverse events [3].

Drug interactions occur with the concomitant use of two or more drugs and are manifested by a change in the pharmacological effect. They could be desirable or undesirable. For example, concomitant use of aspirin with clopidogrel reduces the risk of myocardial infarction and ischemic stroke (a desired effect), but also increases the risk of bleeding (undesirable effect) [4]. The demand for a balance between these two effects determines the beneficial therapeutic outcome of the treatment.

Clinical pharmacists are part of the multidisciplinary care team for HF patients in both inpatient and outpatient settings [5]. They are able to solve many drug-related problems, including those with drug interactions. As experts in pharmacotherapy, clinical pharmacists may prevent inappropriate use of medicines that could exacerbate symptoms and increase hospitalizations of patients. They could educate patients to be alert, when taking medications, including prescription, non-prescription and alternative medicines, which are contraindicated in HF. Clinical pharmacists have to collaborate with all members of the team, especially physicians, to improve the health outcomes for HF patients [6, 7].

## Aim of the study

The aim of the present study was to investigate retrospectively the prescribed pharmacotherapy of the discharged HF patients for possible drug interactions, as well as the prevalence, risk rating and severity of hazardous drug interactions.

## Ethics approval

The Committee on Research Ethics at the Medical University "Paraskev Stoyanov" Varna, Bulgaria approved the following study (Protocol Number 84/27.06.2019). The complete patient information was kept private and was not available to the public.

## Methods

### Design of the study

The medical records for a 1-year period (January–December 2015) of 971 cardiac disease patients who pass through the Clinic for Cardiology of the St. Marina University Hospital in Varna, Bulgaria were retrospectively analyzed for pDDIs in the prescription at hospital discharge using a computerized database for drug interactions—Lexicomp® Drug Interactions (Wolters Kluwer, Hudson, OH) [8]. Pharmacological groups with increased drug interaction potential, due to their complex pharmacological properties and life-threatening adverse effects, such as antihyperlipidemics, anticoagulants and antithrombotics, were the main subject of the study. Therefore, inclusion criteria in the study were: (1) the diagnosis of HF with 2–4 class of NYHA; (2) receiving standard treatment (e.g. ACE-inhibitors or AT1-blockers and/or beta blockers, and/or diuretics, and/or aldosterone antagonists, and/or nitrates, and/or ivabradine); (3) concomitant use of medications with a risk of pDDIs due to complex pharmacological properties and life-threatening adverse effects—statins, anticoagulants (acenocoumarol or NOACs) and antithrombotic drugs (clopidogrel or ticagrelor).

According to the risk rating of the Lexicomp® Drug Interactions software, DDIs were classified as category A (No known interactions), B (No action needed), C (Monitor therapy), D (Consider therapy modification) and X (Avoid combination). According to the severity of the reaction the categories were major, moderate, minor and N/A. The main measure criteria we have set, was the detection of pDDIs, which got into risk rating categories D (Consider therapy modification) and X (Avoid combination), or when the severity of the pDDI was classified as a major one.

The criteria for defining concomitant diseases are described in Table 1.

### Data analysis

Data were shown as numbers (n) and percentage (%) and results were presented as mean ± standard deviation (SD). Multivariate logistic regression analysis was done to determine the association between occurrence of potential

drug–drug interactions with increasing age (≤60 and >60) and number of drugs prescribed (≤7 and >7). For the statistical processing of the data, two softwares were used—Excel 2016 and SigmaPlot 11.0. $P < 0.05$ was selected as the level of statistical significance.

## Results

After reviewing the medical records and the prescribed medication at discharge of 971 patients who pass through the Cardiology Clinic at St. Marina University Hospital in Varna, Bulgaria, 248 patients were selected, based on the criteria mentioned above, and the risk of drug interactions was checked with the indicated software. The general patient characteristics are shown in Table 2.

The demographic characteristics of the selected patients showed almost identical gender distribution, men versus women 1.12:1. According to age, the majority of patients were in the elderly group (>60)—211 (85%), as the number of those over 80 was 59 (23.8%). The average age was 72.35 (±10.16 SD). Regarding the stage of the disease, the majority of patients were in the third stage of HF (NYHA)—218 (87.9%). Almost all of the patients were with hypertension, the other accompanying diseases included atrial fibrillation (51.2%), anemia (40.7%), diabetes mellitus (39.9%) and COPD (10.5%). Reduced kidney function (eGFR < 60 mL/min/m$^2$) was detected in 75 (30.2%), while kidney failure (eGFR < 30 mL/min/m$^2$)—in 19 (7.8%) of the patients.

### DDIs detected by Lexicomp®

The total number of pDDIs was 1532, or approximately 6.28 (±4.72 SD) pDDIs per one person. The most common drug interactions with respect to the risk rating were in group C—1254 (81.85%), requiring careful monitoring of patients. In the most dangerous risk rating categories according the Lexicomp® software a total of 105 DDIs were detected—96 in category D and 9 in category X, respectively. The software also classified drug interactions based on the severity of the interaction as major, moderate, minor, and not classified. Based on this classification, the main interactions were in the moderate group—1302, while major DDIs were noted in 118 patients. All results are summarized in Table 3.

The most frequent drug interactions, with their possible mechanisms and results of interactions are presented in Table 4.

**Table 2** Main patient's characteristics included in the study

| Patients characteristics | Number (%); Mean ± standard deviation (SD) |
|---|---|
| *Gender* | |
| Male | 131 (52.8%) |
| Female | 117 (47.2%) |
| *Age* | |
| ≤60 | 37 (14.9%) |
| 61–79 | 152 (61.3%) |
| ≥80 | 59 (23.8%) |
| Average age | 72.35 (±10.16 SD) |
| Average age (males) | 71.51 (±10.06 SD) |
| Average age (females) | 73.29 (±10.24 SD) |
| *Number of prescribed drugs* | |
| ≤4 | 20 (8.06%) |
| 5–7 | 127 (51.2%) |
| 8–10 | 84 (33.9%) |
| ≥11 | 17 (6.85%) |
| Range | 3–14 |
| Average | 7.12 (±2.07 SD) |
| *Stage of heart failure (NYHA)* | |
| 2 | 24 (9.7%) |
| 3 | 218 (87.9%) |
| 4 | 6 (2.4%) |
| *Main comorbid condition* | |
| Hypertension | 247 (99.6%) |
| Atrial fibrillation | 127 (51.2%) |
| Anemia | 101 (40.7%) |
| Diabetes mellitus | 99 (39.9%) |
| COPD | 26 (10.5%) |
| *Kidney function* | |
| eGFR < 60 mL/min/m$^2$ | 75 (30.2%) |
| eGFR < 30 mL/min/m$^2$ | 19 (7.8%) |

**Table 1** Criteria for defining concomitant diseases

| Concomitant illness | Criterion |
|---|---|
| Hypertension | A history of hypertension or blood pressure higher than 140/90 mmHg in hospital trials |
| Diabetes mellitus | A history of diabetes mellitus or newly diagnosed such by blood glucose |
| Chronic obstructive pulmonary disease (COPD) | Anamnesis and/or COPD hospitalizations |
| Chronic kidney disease (CKD) | Anamnesis and/or hospitalizations due to CKD and eGFR of less than 60 mL/min/m$^2$ |
| Chronic kidney failure (CKF) | eGFR of less than 30 mL/min/m$^2$ |
| Anemia | A hemoglobin level of less than 130 g/L for men and 120 g/L for women |

The results from the performed multivariate analysis have shown stronger association between the number of drugs taken and the occurrence of pDDIs—37.84 (95% CI 9.012–158.896, $P \leq 0.001$). No statistically significant differences were found between age and occurrence of pDDIs—1.008 (95% CI 0.441–2.308, $P = 0.848$) (Table 5).

## Discussion

HF is the most significant problem in cardiology and internal medicine because of biological (high mortality), medical (disability and high hospitalization) and economic (high health care budget) causes. The treatment is complex and includes many and various pharmacological groups. Patients with cardiovascular diseases, especially those with HF, are more prone to pDDI. The reason for this is older age, complex drug regimens (polypharmacy) and in addition—altered pharmacokinetics in patients with HF because of impaired hepatic and renal blood flow, resulting in a change in drug elimination processes [9].

In the present study, 85% of the selected patients were elderly (median age 72). The range of prescribed drugs was between three and fourteen, 92% of them have been taking more than five medicines with an average of 7.12 (±2.07 SD) per patient, and the average of pDDIs were 6 per one person (Table 1). The average age and the average number of drugs per patient were approximately overlapped with the data previously published. Straubhaar et al. [10] have reported 79 years median age and medium 8 drugs per patient at discharging. The pDDI per patient at discharge they found to be 3. Our results have shown twice as many pDDIs, namely 6.28 (±4.72 SD), and are similar to those reported by Roblek et al. [11]. Of course, it should be taken into account the fact, that the selection of the patients in the two cited studies are based primary on the diagnosis of HF, while our study is based on prescribed medications in HF patients with a high risk of interactions. Therefore we treated these patients, as patients more prone to hazardous drug interactions and in need of careful monitoring.

**Table 3** Classification of pDDIs in HF patients

| Classification | pDDIs (1532 detected DI by Lexicomp® software) |
|---|---|
| Risk rating | A—34 (2.22%) |
| | B—139 (9.07%) |
| | C—1254 (81.85%) |
| | D—96 (6.07%) |
| | X—9 (0.59%) |
| Severity of the interaction | N/A—35 (2.28%) |
| | Minor—77 (5.03%) |
| | Moderate—1302 (84.99%) |
| | Major—118 (7.7%) |

The most prevalent types of pDDIs were in category C—1254 (81.85%) and moderate in severity—1302 (84.99%) (Table 3). Both pDDI groups did not have serious and fatal consequences, but required careful monitoring of patients' symptoms. This result corresponds to the findings of similar reports [12].

As can be seen from Table 4, drugs, which we have set as a main subject of the study—statins, anticoagulants and antithrombotics, cover ~ 37% of major DDIs and ~ 66% of pDDIs in category D. These outcomes have positive match to previous studies. Abovementioned study of Sharma et al. [12] has indicated the most common drugs among hospitalized cardiac patients (Western Nepal) involved in DDIs to be atorvastatin (33.3%), enalapril (31.2%), digoxin (8.3%), furosemide (8.3%), clopidogrel (6.3%) and warfarin (6.3%). The pharmacological groups of statins, anticoagulants and antithrombotics cover nearly half of the pDDIs. The other study, conducted by Mateti et al. [13], have found the most common drug classes involved in DDIs in hospitalized cardiac patients (Manipal, India) to be anti-platelets (76.13%) and anticoagulants (72.72%). Interestingly, the most common drugs among these groups, responsible for DDIs were heparin and aspirin, not warfarin and clopidogrel, as the authors stated. Nevertheless, the last two were involved in the majority of the drug pairs resulting in DDIs and the bleeding was the main clinical adverse effect reported in the study. As illustrated above, the main pharmacological groups, subject of the study—statins, anticoagulants and antithrombotics are responsible for the most of DDIs among cardiac patients, including HF patients and therefore, patients treated with them should be carefully monitored for signs of toxicity.

In order to show the association of pDDIs with patients' age and number of drugs taken, we have performed a multivariate analysis. In our study, we found stronger association between the number of drugs taken (more than 7) and the occurrence of pDDI (more than 10) (Table 5). The association of pDDI and number of drugs is supported by other published studies. Ismail et al. [14] and Murtaza et al. [15] demonstrated significant associations of pDDIs with old age, longer hospital stay, and increased number of prescribed medications. In our study, we didn't observe statistically significant association between old age and occurrence of pDDI (more than 10). Based on our study findings, we recommend an increased alertness in patients taking more than 10 drugs and closely monitoring for pDDIs.

In 2015, the Bulgarian Ministry of Health issued a regulation that required from hospitals with more than 400 hospital beds to appoint clinical pharmacists to track the medical care. A grace period of 3 years has been envisaged to enter

**Table 4** The most frequent drug interactions, the result of interaction and their possible mechanisms

| pDDI | Severity/risk category | Frequency | Result of interaction | Possible mechanism of DDI |
|---|---|---|---|---|
| *ACE inhibitors* | | | | |
| ACE-inhibitors + allopurinol | Major/D | 6 (2.4%) | ↑Risk of hypersensitivity | N/A |
| *Beta-blockers* | | | | |
| Beta-blocker + $I_1$-agonists | Moderate/D | 16 (6.5%) | ↑Risk of bradycardia | PD |
| Beta-blocker + $Alfa_2$-agonist | Moderate/D | 2 (0.8%) | ↑Risk of bradycardia | PD |
| Carvedilol + dabigatran | Major/D | 4 (1.6%) | ↑Risk of bleeding | P-gp |
| *Cardiac glycosides* | | | | |
| Digoxin + amiodarone | Major/D | 2 (0.8%) | ↑Risk of digoxin toxicity | P-gp |
| *Diuretics* | | | | |
| Loop diuretic + NSAIDs | Moderate/D | 3 (1.2%) | ↑Risk of nephrotoxicity/↓ effects of loop diuretics | PD |
| Loop diuretic + desmopressin | Major/X | 1 (0.4%) | ↑Risk of hyponatremic effect of desmopressin | PD |
| *Antiarrhythmics* | | | | |
| Amiodarone + levofloxacin | Major/X | 4 (1.6%) | ↑Risk of QTc-prolonging effect | PD |
| *The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins)* | | | | |
| Simvastatin + 1,4-DHP-CCB | Major/D | 6 (2.4%) | ↑Risk of statin toxicity | CYP3A4 |
| Statin + verapamil | Major/D | 3 (1.2%) | ↑Risk of statin toxicity | CYP3A4 |
| Statin + fenofibrate | Major/C | 9 (3.6%) | ↑Risk of statin toxicity | PD |
| Rosuvastatin + amiodarone | Major/B | 3 (1.2%) | ↑Risk of statin toxicity | CYP2C9 |
| *Anticoagulants* | | | | |
| Acenocoumarol + allopurinol | Moderate/D | 2 (0.8%) | ↑Risk of bleeding | CYP2C9? |
| Acenocoumarol + fenofibrate | Major/D | 4 (1.6%) | ↑Risk of bleeding | N/A |
| Acenocoumarol + amiodarone | Major/D | 4 (1.6%) | ↑Risk of bleeding | CYP2C9/PD? |
| Acenocoumarol + thiamazole | Moderate/D | 2 (0.8%) | ↓Effect of acenocoumarol | PD |
| Acenocoumarol + NSAIDs | Moderate/D | 3 (1.2%) | ↑Risk of bleeding | N/A |
| *Non-vitamin K oral anticoagulants (NOACs)* | | | | |
| Apixaban + aspirin | Major/D | 2 (0.8%) | ↑Risk of bleeding | PD |
| Apixaban + clopidogrel | Major/D | 2 (0.8%) | ↑Risk of bleeding | N/A |
| Dabigatran + amiodarone | Major/D | 2 (0.8%) | ↑Risk of bleeding | P-gp |
| Dabigatran + aspirin | Major/D | 2 (0.8%) | ↑Risk of bleeding | PD |
| Dabigatran + carvedilol | Major/D | 4 (1.6%) | ↑Risk of bleeding | P-gp |
| Dabigatran + fluconazole | Major/C | 1 (0.4%) | ↑Risk of bleeding | CYP3A4?, P-gp? |
| *Antithrombotic drugs* | | | | |
| Clopidogrel + proton-pump inhibitors | Moderate/D | 24 (9.7%) | ↓Effect of clopidogrel | CYP2C19 |
| Clopidogrel + apixaban | Major/D | 2 (0.8%) | ↑Risk of bleeding | N/A, PD? |
| Clopidogrel + aspirin | Moderate/C | 10 (4%) | ↑Risk of bleeding | N/A, PD? |
| Ticagrelor + aspirin | Major/D | 1 (0.4%) | ↑Risk of bleeding | N/A, PD? |

The calculated percentage is based on 248 selected patients for the study

*N/A* not available data, *PD* pharmacodynamic mechanisms, *P-gp* P-glycoprotein

into force this regulation. Such a policy aimed to save up to 30% of the money for treatment and to prevent the side effects of certain medications [16, 17]. Reviewing the entire pharmacotherapy of the patients, the pharmacists can reduce hospital readmission and length of hospital stay [18, 19]. Roblek et al. [20] have demonstrated in a randomized, double-blind, controlled study, that clinical pharmacists could reduce clinically relevant DDIs in HF patients. The primary endpoint of the study were DDIs, secondary—re-hospitalization or death during follow-up. Results represented by the authors, have shown significant reduction of clinical DDIs in the group with pharmacist intervention versus control group (8 vs. 18; $P=0.003$). Regarding secondary endpoint, 11 versus 9 (intervention vs. control) patients were re-hospitalized or died ($P=0.2$). This study confirms that intervention of clinical pharmacists could reduce the number of clinically

**Table 5** Predictors associated with pDDIs

| Variable | Total number of patients (n = 248) | | Multivariate | |
|---|---|---|---|---|
| | Detected pDDIs ≤ 9 | Detected pDDIs > 10 | OR (95% CI) | *P* value |
| Patients' age | | | | |
| ≤ 60 | 29 | 8 | 1.008 (0.441–2.308) | (*P* = 0.848) |
| > 60 | 165 | 46 | | |
| Number of drugs | | | | |
| ≤ 7 | 135 | 2 | 37.84 (9.012–158.896) | (*P* ≤ 0.001) |
| > 7 | 49 | 52 | | |

*OR* odds ratio, *CI* confidence interval

significant DDIs among HF patients, but regarding the clinical endpoints 6 months from discharged, remains to be clarified.

As in heart failure cases, in oncology practice, patients are elderly and receive polypharmacy. Lopez-Martin et al. [21] have demonstrated the potential role of clinical pharmacist to prevent and manage the drug–drug interactions in oncology setting, as they take an active part in the modification or termination of drug prescriptions. A review of impact of clinical pharmacists in outpatient oncology practices by Gatwood et al. [22] has confirmed the benefit of integrating the clinical pharmacists into healthcare models.

Therefore, a specialist, as clinical pharmacists, with a very good knowledge of the principles of pharmacology/pharmacotherapy should be involved for better outcome in the patient care. In order to keep a high professional level in clinical pharmacy it is necessary to innovate the training to meet the increased clinical requirements for the profession [23].

### Limitations of the study

In the present study, a single program for the analysis of potential drug interactions was used. The reason for this was the detailed information provided by the software, the precise mechanisms of interaction (where known), the available information, the recommendations and the many available references. Another limitation of the study was that no data was provided for these patients after their discharge from the hospital. However, a significant number of patients were included in the study in order for the conclusions to be made.

## Conclusions

The incidence of drug-drug interactions in HF patients is high. The therapy of these patients should be carefully monitored for possible interactions. The clinical pharmacist, as specialist in pharmacology/pharmacotherapy and drug–drug interactions, could contribute to the reduction of medication-related problems, such as drug interactions, and optimize the drug therapy by checking the treatment prescribed at the discharge of these patients.

**Acknowledgements** The authors would like to thank the colleagues from the Cardiology Clinic at St. Marina University Hospital in Varna, Bulgaria for the provided data.

**Funding** None.

**Conflicts of interest** The authors have no conflicts of interest to disclose.

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