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Original article

Identification and Evaluation of Drug-related Problems Associated with Angiotensin Converting Enzyme Inhibitor Use

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Abstract
Drug-related problems (DRPs) are relatively common among hospitalized patients, causing detriment to themselves and increased healthcare costs. Characterizing such problems allows for the development of remedial strategies aimed at minimizing their frequency and ensuring higher medication safety for the patients involved. This study focuses on inpatients receiving ACE inhibitors who are admitted to internal medicine wards, as the literature has a gap in this respect. Consequently, we provide a comprehensive assessment of the DRPs associated with the use of ACE inhibitors use hospitalized patients in the Sebha Medical Centre. Ethical approval was granted for the study, which was conducted for two months, during which 175 patient medical records were collected and reviewed. A specialized clinical pharmacist identified a total of 186 DRPs and classified these, revealing an average of 1.06 problems per patient. The most common DRPs were identified as drug interactions (78%), adverse drug reactions (17%), improper dose (3%), and improper indication (2%). Drug interaction problems were significantly associated with patients taking several medications (P <0.05). The high prevalence of DRPs among hospitalized patients in the Sebha Medical Center is alarming. This study highlights the importance of clinical pharmacy services to help identify and reduce DRPs. Additionally, patients with multiple medical conditions and patients using multiple medications should be closely assessed for DRPs.
Keywords: Drug-Related Problems, Angiotensin Converting Enzyme (ACE) Inhibitors, In-Patient, Clinical Pharmacy.

Introduction

Although many efforts have been made to enforce the rational use of drugs, many studies have reported drug-induced health problems [1-3]. Most problems are seen to occur with drug dispensing, administration, and the use of the particular medicinal product, but the lack of proper follow-up and reassessment of medical treatment by the physician is also a major issue [4,5]. Drug-related problems (DRPs) occur more frequently in hospitalized patients where multiple changes are made in the patient's medication regimen, and where there may also be a lack of continuity of a particular drug [6]. Accordingly, in clinical medicine, a wide range of DRPs may arise, and these not only lead to serious consequences for the patient but also promote additional costs to healthcare systems due to other outcomes, such as the need for re-hospitalization. Several DRPs are, however, preventable [7-10], and their prevention should be attempted to optimize drug therapy, positively influence health expenses, enhance each patient's quality of life, and potentially save lives [11-13].

The problems commonly associated with drug use include inappropriate medication prescribing, discrepancies between prescribed and actual regimens, poor adherence, drug interactions, inappropriate use, patient monitoring, and inadequate surveillance for adverse effects. Additionally, DRPs are influenced by other variables, such as polypharmacy (≥ 5 concurrent medications), female gender, age status (≥ 65 years old), renal insufficiency, and dementia [14,15]. In recent years, pharmaceutical care services have made significant strides forward in DRP prevention, and now many pharmacists provide patient-centered care by identifying potential and actual solutions to the possible DRPs they might encounter [16]. Indeed, several studies have shown the positive effect of pharmaceutical care interventions in reducing DRPs in different settings, especially in the hospital context [17-20]. The detection of DRPs is critical in pharmaceutical care because such problems can reduce the optimal patient outcome, resulting in increased morbidity and mortality, and hence, higher healthcare costs. When working in collaboration with other healthcare professionals, especially in clinical settings, clinical pharmacists play an important role in ensuring the rational use of drugs by identifying and resolving DRPs.

Angiotensin converting enzyme inhibitors (ACEIs) have been widely used for many years in patients with hypertension, coronary diseases, heart failure, or chronic kidney diseases. The ACEIs reduce blood pressure by modulating the hormones of the renin-angiotensin-aldosterone system. Renin is a hormone released by the juxtaglomerular cells of the kidney in response to decreased renal perfusion and increased sympathetic activity [21]; renin is also produced locally in tissues. Renin cleaves and activates angiotensin I. Angiotensin I is cleaved by the angiotensin-converting enzyme into angiotensin II [22]. Angiotensin II acts centrally and peripherally to increase vascular tone, thus elevating blood pressure [23]. Angiotensin II also promotes sodium retention through its effects on aldosterone [24] and volume expansion through its effects on the antidiuretic hormone [25].

ACEIs are the top oral cardiovascular drugs prescribed in the Sebha Medical Center. The identification of DRPs associated with ACEIs will allow for the selection of management plans that will achieve therapeutic

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objectives.To the best of the researchers' knowledge, there has been no evidence-based research on ACEIs-related problems. Therefore, the objectives of the present study are to identify and evaluate the DRPs associated with the use of ACEIs inpatients in the Sebha Medical Center.

Methods

Study Design and Setting

The study was conducted with patients on ACE inhibitors in the Sebha Medical Center located in Sebha City, which is an oasis city in southwestern Libya, 640 km from the country's capital, Tripoli. It is a retrospective study covering the period between 2017-2018 and December 2019 to February 2020. This study began after approval was obtained from the Research and Ethics Review Committee of the Faculty of Pharmacy, Sebha University. Permission to collect data was granted after official letters were approved by the Head of the Sebha Medical Center. All other concerned bodies were informed about the aim of the study. All the data collected during the study were handled confidentially and respectfully, and used for research purposes.

Study Population

A total of 175 patients were included in the study. The sample size was calculated as 1.96 (standard deviation/desired error) [2,] which provided a minimum sample size of 169 patients. Accounting for a standard error of 5%, the minimum sample size was estimated to be 169. However, we decided to include 175 patients to compensate for potential attrition and increase the precision of our results. This small increase allows us to detect significant effects and generalize the results more broadly.

Inclusion Criteria

Adult patients aged 18 years and above. In-patients on ACE inhibitors diagnosed with cardiovascular disease (hypertension, postmyocardial infarction, congestive heart failure) or diabetic nephropathy.

Exclusion Criteria

We excluded patients not on ACE inhibitors, and outpatients. Also, patients with incomplete records were not included.

Data Analysis

Descriptive statistics, such as frequency and percentages, were generated for the categorical variables. The number of DRPs was presented as n (%). A Pearson correlation model was used to investigate the possible association between drug interactions and polypharmacy. A p-value of <0.05 was considered statistically significant. All data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 22.

Results and Discussion

Patient demographics and baseline characteristics

A total of 175 inpatient medical records were included in this study. The demographic data of the patients appear in (Table 1), which shows that males represented 63.4% of the study population. As shown in (Figure 1), the majority of patients belonged to the age group of 61–70 years. The age range of the studied patients was from 18-96 years with a mean age of 19.44 (SD = 18.03) years, as shown in (Table 1) and (Figure 1).

Table 1. Demographic patient data (n = 175)

Gender	Frequency	%
Male	111	63.4
Female	64	36.6
Age	Mean 19.44±18.03	Range 18-96

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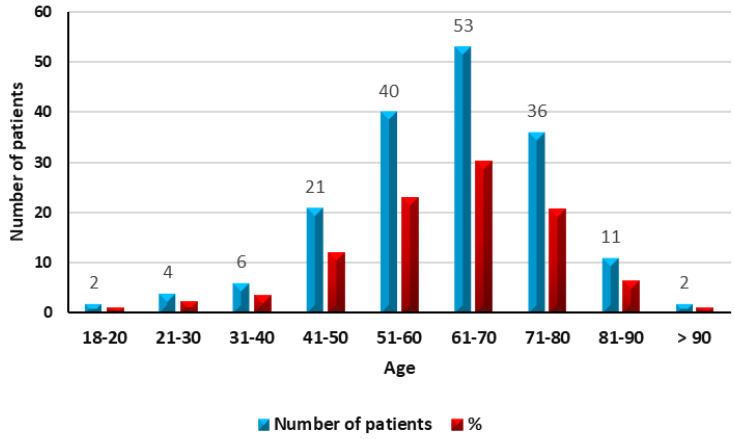

Figure 1: Distribution of age

ACEIs utilization pattern

Among 175 patients included in the study, 98 (56%) were taking captopril, 46 (26.3%) were taking lisinopril, 21 (12%) were taking enalapril, and the remaining 10 (5.7%) were taking ramipril (Figure 2).

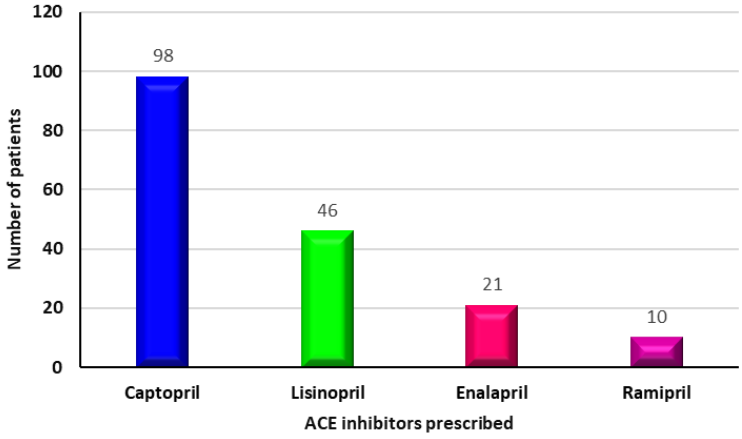

Figure 2: Distribution of ACEIs

Detection and evaluation of DRPs associated with ACEI therapy

The total number of identified DRPs in this study was 186, with an average of 1.06 such problems per patient. The major categories and frequencies of these DRPs appear in (Table 2) which shows ACEIs-drug interactions and adverse drug reactions-related problems to be the most frequently identified categories.

Table 2: DRPs Associated with ACEIs (Total number of DRPs = 186)

DRPs	Frequency	%
Drug interactions	145	78
Adverse drug reactions	32	17
Improper dose	6	3
Improper indication	3	2

Indications

(Table 3) showed the indications of ACEIs. It reveals that in this study, there were three examples of ACEIs being used improperly with patients suffering from end-stage renal disease (ESRD), which has been shown in a previous study to be inappropriate [26].

Table 3. Indications of ACEIs

Indication	Number of patients	%
Hypertension	102	58.3
Congestive heart failure	45	25.7
Post-myocardial infarction	27	15.4
Diabetic nephropathy	1	0.6

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ACE inhibitors are considered among the most potent antihypertensive drugs and, apart from their major action, exhibit beneficial lateral effects in the prevention of cardiovascular disease in various classes of hypertensive patients. Additionally, ACEIs have proven more effective than other hypertensive substances in reducing proteinuria and retarding the progression of renal damage in patients with various types of nephropathies. They have a wide usage despite being inappropriate, and the study by Huri and Wee In 2013 [26] was the only one to show their inappropriateness for diabetic nephropathy, because if they are widely prescribed for it, and yet only one study 8 years ago finds they aren't suitable.

Dosing Problem

Of the six cases of inappropriate dosing identified, some of the ACEIs were prescribed at a higher dose than required, particularly in patients with existing renal impairment. A high dose of enalapril (20 mg/day) was given in two (1.14%) elderly hypertensive patients having a CrCL of 25.8 and 27.4ml/min, respectively. In addition, an inappropriate ACEIs dosage was administered in 1.71% (three) of the patients, despite there being no indication for this (captopril). Additionally, lisinopril was prescribed at a higher dosage than required in a patient (0.57%) with congestive heart failure (CHF). Due to age-related reductions in renal function, the elderly may be particularly susceptible to ACEIs-induced reduction in blood pressure and renal function. The elderly has reduced elimination half-life, and the area under the serum concentration-time curve (AUC) is 15-40% higher in patients with poor renal function [27,28].
Enalapril has a recommended starting dose of 2.5 to 5mg/day. However, a starting dose of 2.5mg/day is appropriate for older patients or those with other risk factors (i.e., systolic blood pressure < 100 mmHg; those taking large doses of either loop diuretics or potassium-sparing diuretics; or with pre-existing hyponatremia, hyperkalemia, or renal impairment) [29]. In respect of captopril, the dose in a patient having a CrCL 10-50 ml/min should be decreased by 50% of the normal dose [30]. For lisinopril, the dose in a patient having congestive heart failure (CHF) should have been administered 5-20mg/day as a single dose [30].

ACEIs-induced adverse reactions

Adverse drug reactions were also observed in this study. Hyperkalemia is a commonly observed adverse effect among patients receiving ACEIs and is followed in frequency by cough and hyponatremia. Such adverse reactions are repeatedly reported in previous studies [31,32]. Therefore, these potential responses to ACEIs should be taken into consideration, especially in the elderly who might suffer significant deleterious effects.

ACEIs-induced hypotension

Hypotension occurs most commonly with the first dose, although it may arise at any time during therapy. As the information necessary to determine this particular adverse effect (e.g., blood pressure and some other values) was not recorded in our study, it was not possible to identify whether this had occurred in any of the research population.

ACEIs-induced hyperkalemia

In this study, 15 (8.6%) cases of hyperkalemia were reported as adverse reactions to ACEIs. We found that hyperkalemia developed in 10 (5.7%), 2 (1.14%), 2 (1.14%), and 1 (0.6%) patients, respectively, who were receiving captopril, enalapril, lisinopril, and ramipril (Figure 3).

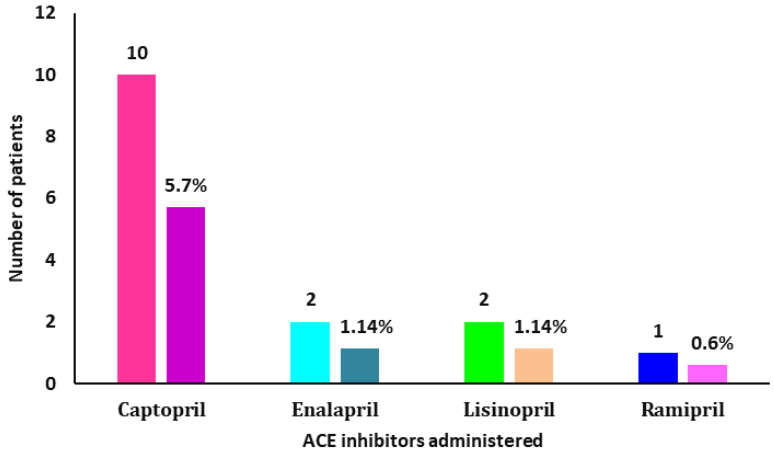

Figure 3. ACEIs-induced hyperkalemia

Although the definition of hyperkalemia is not always consistent, it is generally defined as a serum potassium level >5.0 [33,34]. Hyperkalemia can be further classified as mild (5.6-6.0 mEq/L), moderate

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(6.1-7.0 mEq/L), and severe (>7.0 mEq/L) [33]. In terms of severity, the majority of hyperkalemia cases reported in this study were mild as seen in 11 patients (73.3%), whilst moderate levels were observed in 4 patients (26.7%). These findings reflect those in several published studies that have reported lower incidences of hyperkalemia (8.2%, 7.2%, 5.2% and 9.8%) in patients who received ACEIs [35-38].

In the current study, the four prescribed ACEIs were seen to cause hyperkalemia. This adverse effect is due to the suppression of adrenal aldosterone release caused by ACEIs. This adverse effect rarely occurs in patients with normal renal function. Our study shows that these patients may experience hyperkalemia secondary to either ACEIs drugs or potassium-sparing diuretics. In addition, most of the patients were elderly and found to have heart failure, reduced kidney function, and a high prevalence of other leading risk factors such as the presence of other comorbidities, polypharmacy, and associated drug-drug interactions, all of which may contribute to hyperkalemia.

These findings concur with those from earlier studies that also revealed hyperkalemia to be a frequent consequence of multi-drug use, especially in elderly patients, patients with reduced kidney function [39] and heart failure [33], and in patients prescribed non-steroidal anti-inflammatory drugs and anti-hypertensive agents targeting the renin–angiotensin–aldosterone system (RAAS), including ACE inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) [40].

ACEIs-induced hyponatremia

Eight (4.6%) members of the study population receiving ACEIs developed hyponatremia, showing a predisposition to this reaction, which was similar in males (50%) and females (50%). However, the incidence of hyponatremia was greater (62.5%) in the older age group compared to the lower age group (37.5%). Of the population of patients prescribed captopril, 87.5% developed hyponatremia, and of the population of patients prescribed ramipril, only one patient developed it and that none of the patients using enalapril or lisinopril developed it (Figure 4).

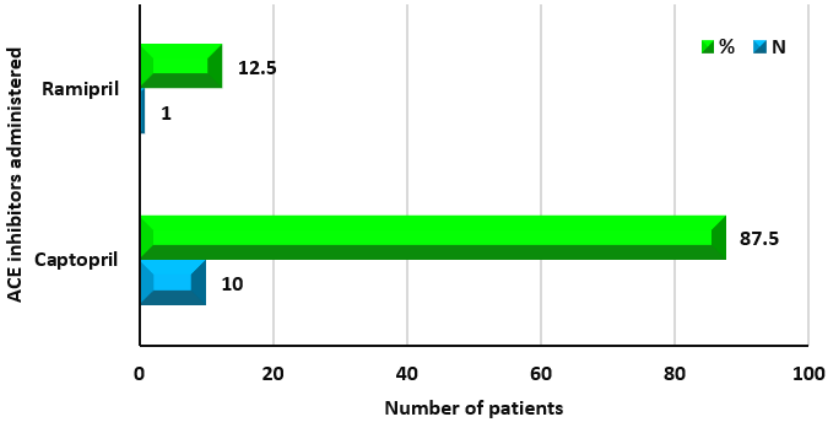

Figure 4: ACEIs-induced hyponatremia

Hyponatremia is defined as a serum sodium concentration below 135 mmol/l and may be associated with low, normal (275 to 290 mmol/kg), or high osmolality [41]. Clinical severity is dependent both on the magnitude of the hyponatremia and the rate at which the serum sodium level has declined. When the decrease in serum sodium is marked (≤125 mmol/l) or acute (occurring over <48 h), serious neurological complications can ensue as a result of cerebral oedema.

ACEIs have been found to cause significant hyponatremia occasionally, alone or in combination with diuretics or salt restriction. The study revealed that captopril had a higher association with hyponatremia compared to other drugs. It is often considered that there is no effect of ACEIs on serum sodium levels. One of the patients in our study who was receiving captopril was notable for not being on any medications known to commonly cause hyponatremia. In our study, hyponatremia was induced in 4.6% of patients taking ACEIs.

The incidence of hyponatremia in this study was notably lower than that featured in earlier case reports on ACEIs-induced hyponatremia [42-46]. The cessation of medication combined with the initiation of fluid restriction typically results in the normalization of hyponatremia without significant adverse effects [42]. This study revealed that monitoring of serum sodium levels in patients medicated with ACEIs will help to prevent unexpected adverse reactions like hyponatremia.

ACEIs-induced acute renal failure

No case of acute renal failure due to the administration of ACEIs was detected in this study. However, this does not indicate that no case existed, as much information was missing from the data, and we had no access to the patient's daily follow-up histories.

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ACEIs-induced cough

In this study, 9 (5.1%) cases of dry cough were reported as the adverse effect of ACEIs. We found that dry cough developed in 8 (4.6%) and 1 (0.6%) patients receiving captopril and enalapril , respectively. We observed that the incidence of ACEIs-induced cough was higher in heart failure patients (6, 66.7%) compared to those with hypertension (3, 33.3%). The prevalence of dry cough caused by ACEIs as detected in this study was in agreement with a previous study, which reported that the incidence of dry cough in patients treated with ACEIs was 6% for captopril [47] and 10% for enalapril [48]. Likewise, it has been demonstrated that the incidence of ACEIs-induced cough was higher in heart failure patients compared to those with hypertension [49]. Given that heart failure itself can cause coughing, the true incidence of ACEIs-induced cough is difficult to estimate in these patients. The incidence of cough varies based on the individual ACEIs used. ACEIs are categorized into three groups based on the presence of a sulfhydryl, carboxyl, or phosphoryl group, but the clinical relevance of this structural difference remains unclear [50].

This result agrees with that obtained in India, which demonstrated that the carboxyl group-containing ACEIs (enalapril, lisinopril, and ramipril) were associated with a lower incidence of cough compared with other groups [51]. It is reasonable to use ACEIs that induce cough less frequently. In this context, perindopril has been associated with a relatively low incidence of cough and has extensive evidence supporting its cardiovascular benefits and tolerability.

In our study, cough is more frequent in male patients. However, our finding is not in line with other studies that have demonstrated ACEIs-induced cough to be more frequent in female patients [52-55]. These variations may originate from heterogeneity in the study design and population or from the measurement of cough; additionally, there is the fact that ACEIs are likely to be a trigger in susceptible individuals, rather than a direct cause of cough [56].

ACEIs-induced angioedema

There was no detection of angioedema in this study.

ACEIs-drug interactions

The analysis of DRPs in this study revealed drug–drug interactions to be the most frequently-identified problems (78%) (Table 2). ACEIs were prescribed concomitantly with other drugs with known potential interaction risk in 145 patients (83% of the study sample). The ACEIs most implicated in drug-drug interactions for the current study are shown in (Figure 5). The drug interactions identified in this study were mostly based on established literature and evidence.

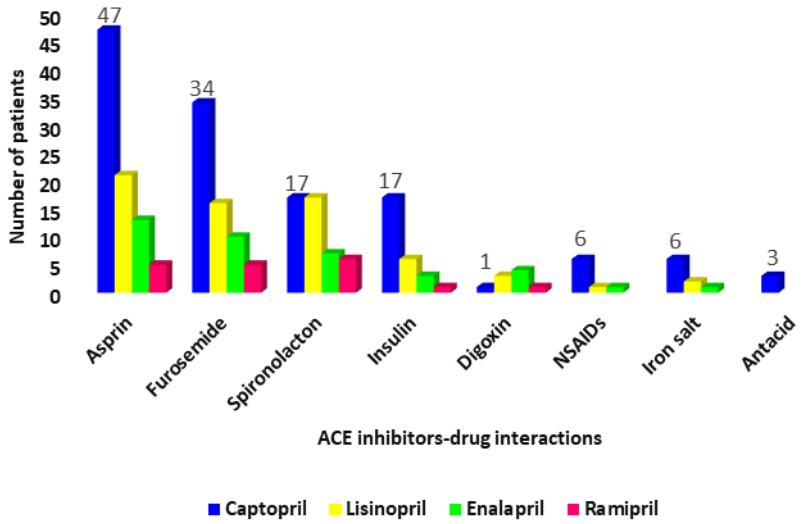

Figure 5: ACEIs- drug interactions

As expected, aspirin was the most frequently prescribed NSAID due to its anticoagulant properties and indication as either primary or secondary prophylaxis therapy against major cardiovascular events and stroke among the elderly. The most frequently prescribed combination of this kind was ACEIs with aspirin in 86 (59.3%) patients. It is worth noting that the results also included cases of drug interactions resulting from using of ACEIs with furosemide (65 patients, 44.8%), spironolactone (47 patients, 32.4%), insulin (27 patients, 18.6%), digoxin (9 patients, 6.2 %), NSAIDs (diclofenac sodium in 8 patients, 5.5%), iron salt (9 patients, 6.2 %) and antacid (3 patients, 2.1 %) (Figure 6).

The high percentage of potential drug-drug interactions in this study is probably related to the fact that patients had a higher number of comorbid conditions, were taking more drugs (91.4%), and were generally older than average, as more than half were ≥ 60 years (58.3%). In addition, polypharmacy ($p < 0.05$) was

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found to be associated with drug interactions (Table 4). Patients in this category were more susceptible to potential drug interactions than those outside it. These results are in line with other studies, which also showed that drug-drug interactions are more frequent in older patients who take multiple medications [57,58].

There is some evidence that the co-administration of aspirin with ACEIs may negatively impact the hemodynamic and survival benefits of ACEIs [59,60]. This is seen in patients with severe heart failure, where aspirin may interfere with prostaglandin synthesis [59]. Another suggestion is that NSAIDs promote sodium retention and so negatively affect the blood pressure-lowering features of several classes of antihypertensive drugs, including ACEIs [61].

ACE inhibitors increase the hypotensive effects of diuretics, which are often used synergistically to control blood pressure. Concomitant captopril and furosemide therapy has been reported to result in a potentiation of the hypotensive effects of captopril [62]. ACE inhibitors, NSAIDs, and diuretics, individually or in combination, are implicated in over 50% of cases of iatrogenic acute renal failure [63]. Several reports have revealed that NSAIDs can alter kidney function, leading to renal impairment, particularly when co-utilized/prescribed with other nephrotoxic agents, including ACEIs and diuretics [64,65]. Furthermore, all NSAIDs except aspirin can increase the risk of major cardiovascular (CVS) events such as edema, stroke, myocardial infarction, and congestive heart failure [66, 67]. NSAIDs also interfere with both the pharmacokinetics and dynamics of furosemide. They compete for proximal tubular secretion, shift the dose response curve, and impair the natriuretic and increased renal blood flow normally induced by furosemide [68]. Thus, both the control of hypertension by ACEIs and diuretics and their unloading effects in heart failure are antagonized by NSAIDs [59].

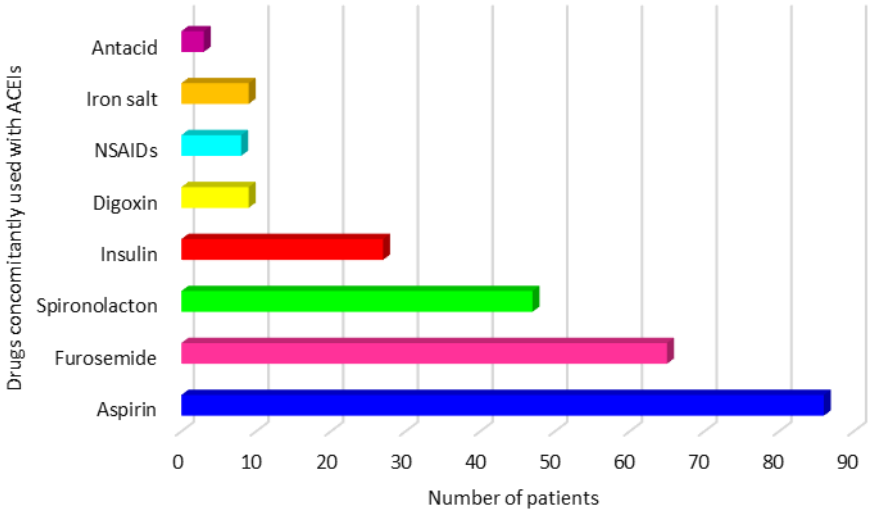

Figure 6: Drugs concomitantly used with ACEIs

***Table 4:* Correlation between drug interactions and polypharmacy**

		Drug Interaction	Polypharmacy
Drug interactions	Pearson Correlation 2-tailed)) .Sig	1	.186* .014
	N		175

**Correlation is significant at the 0.05 level (2-tailed).*

The concomitant use of potassium-sparing diuretics (such as spironolactone) and ACEIs has been reported to increase serum potassium by 1 to 1.5 mEq/L when compared to either drug used alone. This has occasionally resulted in significant arrhythmias and death [69]. The association of ACEIs and digoxin can either increase or decrease the plasma digoxin level through the deterioration of renal function [70].

Patients need to be closely monitored for manifestations such as lack of therapeutic efficacy or toxicity, especially for drugs whose therapeutic effects may be diminished or augmented when used in those combinations. Drug interactions are a major factor that might cause ADR, therapeutic failure, and drug-related harm to patients [71]. These can affect a patient's clinical outcome, quality of life, and contribute to unnecessary healthcare costs.

Conclusion

This study has highlighted the critical status of DRPs among hospitalized patients in the Sebha Medical Center and demonstrates the urgent need for strategies to be developed to minimize the problem. The findings also point to the importance of routine participation of clinical pharmacists in clinical rounds to

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identify and prevent DRPs. Additionally, this study has managed to identify DRPs associated with ACEIs and has revealed correlations between the most common medications. These outcomes of the study will help guide clinical pharmacists in their screening of vulnerable patients who require more attention. Additionally, the study provides a platform for further research in which the rate of acceptance and implementation of clinical pharmacists' interventions by physicians can be established. We hope that this study will influence policymakers to encourage the development of clinical pharmacy units in Libya.

Finally, some potential limitations must be considered, these being: (1) the study was conducted in a single hospital, and the patterns of DRPs may not be generalizable for other hospitals in Libya, (2) the external validity of the study may have been limited by the small sample size, short study duration, follow-up and inadequate data in the patient records, (3) the retrospective nature of this study prevents the assessment of patients' adherence to medications and knowledge of self-care activities, (4) the study includes only those patients on ACEIs and other drugs may have had an interactive effect, and (5) the study has focused only on identifying DRPs and not on applying interventions, which is understandable given that the role of the clinical pharmacist in Libyan hospitals has not yet been fully implemented. Future studies are needed to determine interventions that can successfully resolve the DRPs that arise in the hospital setting. In these, it would be helpful to include prospective studies that would allow for the longer monitoring of patients and reflect a more accurate profile of the natural timeframe of the medication's effects, and to include other drugs that can be evaluated similarly to ACEIs, using the methodology applied in this study.

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Conflicts of Interest

The authors declare no conflicts of interest.

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