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Drug Utilization Evaluation (DUE) of Captopril in Two Coronary Care Units (CCU) of Namazi Hospital, Shiraz, Iran

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Abstract

Captopril is one of the most important medicines prescribed for managing cardiovascular disorders. Therefore, its appropriate prescription, dosage, and other drug-related factors of captopril have indispensable importance in the management of cardiovascular disorders. Performing a drug utilization evaluation (DUE) study on captopril in a referral in-patient setting that may provide a strategy for optimizing captopril use and an insight into aspects of drug use and prescribing such as the pattern of use, quality, and outcomes. This survey was conducted in two cardiac care unit wards of Namazi Hospital, Iran within 2 years. The patients were selected for the survey based on their confirmed diagnosis by cardiologists. Twelve study criteria including indications, contraindications, drug interactions, dosage, dosing adjustment, pretreatment considerations, and monitoring parameters were evaluated for each patient and recorded in a questionnaire designed by the clinical pharmacist. 207 patients participated in this study. More than 85% of patients have correct indications for captopril prescriptions. The mean±standard deviation (SD) of hospitalization duration was 7.15±4.09 days. Statistical analysis revealed that in 27 (13.0%) of patients the blood potassium level was in an unacceptable range. For serum creatinine and blood urea nitrogen (BUN), the percentages for unacceptable amounts were 20.3 and 24.6%, respectively. Finally, the mean±SD of the final score for captopril utilization based on the standard guideline was 10.45±1.24 out of 12. The results suggest that to improve therapeutic outcomes with captopril, it is recommended to provide further education to specialists, adhere to captopril prescription guidelines, and implement appropriate monitoring methods.

Keywords: Drug Utilization Evaluation, Drug Utilization Review, Captopril, Angiotensin-converting enzyme inhibitor, Hypertension, Heart failure

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1. Introduction

In recent decades, irrational drug utilization has become one of the most challenging concerns in the healthcare systems of both developed and developing countries (1). In this regard, the use of drugs must be monitored in order to provide the most rational medication usage. Rational drug use is attributed to the proper indication, dose, frequency, and duration of administration considering the contraindications, cautions, potential side effects, and drug-drug and drug-food interactions (2). This issue is more important for drugs that have great economic and clinical impacts on healthcare systems such as high-cost drugs,

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frequently used drugs, and drugs with a narrow therapeutic index (1-5).

Drug Utilization Evaluation (DUE) (also known as Drug Utilization Review (DUR)) studies are systematic analyses of medication use patterns aimed at ensuring appropriate, safe, and effective drug therapy. These studies play a critical role in identifying deviations from standard treatment guidelines, optimizing prescribing practices, and minimizing medication-related errors (6). By evaluating drug usage, DUE studies help healthcare providers enhance clinical outcomes through evidence-based decision-making and improved patient care. They also facilitate the monitoring of medication adherence, adverse effects, and therapeutic efficacy, ensuring that patients receive the maximum benefit from their treatments (4). Furthermore, DUE studies contribute to cost-effective healthcare by reducing unnecessary drug expenditures and preventing wasteful practices. Overall, they serve as a vital tool for continuous quality improvement in clinical settings (7).

Captopril, a sulfhydryl-containing angiotensin-converting-enzyme inhibitor (ACEI), was the first orally active drug in its category, developed by Squibb. It has a short half-life and it needs to be administered multiple per day (8). Captopril inhibits the ACE which converts the angiotensin I to angiotensin II, a potent peripheral vasoconstrictor. By decreasing the angiotensin II, the aldosterone secretion would be suppressed and sodium and water renal reabsorption would be reduced. Consequentially, the blood volume and total peripheral resistance would be decreased which results in decreased cardiac preload and afterload with no reflex tachycardia. Captopril also increases the levels of bradykinin, a peripheral vasodilator, by inhibiting the breakdown of bradykinin (9, 10). Captopril has been widely prescribed for patients with essential hypertension, congestive heart failure (CHF), left ventricular dysfunction (LVD) after myocardial infarction (MI), and diabetic nephropathy. It is contraindicated in patients with bilateral renal artery stenosis, pregnancy, and patients with a history of angioneurotic edema.

Irrational use of captopril, such as incorrect dosing or inappropriate indications, can lead to serious clinical consequences, including severe hypotension, hyperkalemia, or worsening renal function. Adhering to standard therapeutic guidelines is essential to minimize these risks, optimize patient outcomes, and ensure the safe and effective use of captopril in clinical practice (11, 12). To date, as far as we know, no drug utilization evaluation study on captopril has been conducted and published. According to the various indications for captopril use, the present study aimed to evaluate the use of captopril concurrently based on standard therapeutic guidelines.

2. Methods and Materials

This cross-sectional study was conducted over a two-year period, from October 2011 to October 2013, and was divided into two phases: the development of a standard guideline and the collection of data from enrolled patients. The prescription of captopril served as the inclusion criterion. For each patient initiated on captopril, a standard guideline checklist was assigned, and data were gathered until the patient's discharge. Two hundred and seven patients receiving captopril in two coronary care units of Namazi Hospital were included in the present study.

2.1. Standard Guideline Checklist Preparation

A standardized guideline checklist was developed using credible scientific references and textbooks such as UpToDate, MedScape, AHFS Drug Information Handbook, and Braunwald's Heart Disease. This checklist included details on indications, contraindications, drug interactions, dosage, dose adjustments, pretreatment requirements, and side effect monitoring (Table 1). Exclusion criteria were defined as the discontinuation of captopril within 24 hours of prescription or patient death.

2.2. Data Gathering and Statistical Analysis

After gathering data, statistical analysis was conducted in SPSS software (v20, IBM company, USA). The scores of variables

Table 1. The standard guideline checklist data used in DUE of captopril.

Checklist data		Comment
Indications		Acute hypertension
		Essential hypertension
		Heart failure (HF) (Stage A to D AHA*/ACC† classification)
		LVD after MI
		Diabetic nephropathy
Contraindications		Hypersensitivity to captopril and any other ACEI or any components of the formulation- Angioedema history
		Pregnancy
		Hyperkalemia (K+ > 5.5 mmol/L)
		Bilateral renal artery stenosis or renal artery stenosis in patients with a solitary kidney
Drug interactions (Grade D)		Allopurinol
		Amifostine
		Cyclosporine
		Strong cytochrome P450 2D6 inhibitors (i.e. fluoxetine, paroxetine, quinidine)
		Iron-dextran complex
		Lithium
		Rituximab
Dosage‡	Hypertension	Initial dose: 12.5-25 mg 2-3 times per day
		Maximum dose: 150 mg 3 times per day
		Usual dose range: 25-100 mg in 2 divided doses
	HF	Initial dose: 6.25-12.5 mg 3 times daily
		Target dose: 50 mg 3 times per day
	LVD after MI	Initial dose: 6.25 mg 3 times per day
		Target dose: 50 mg 3 times per day
	Diabetic nephropathy	Target dose: 25 mg 3 times per day
Dose adjustment	10<ClCr <50 ml/min	75% of the normal dose is administered or the usual dose is administered every 12-18 hours.
	ClCr <10 ml/min	50% of the normal dose is administered or the usual dose is administered every 24 hours.
	Hemodialysis	The normal dose is administered post-dialysis or 25-35% of the supplement dose is administered.
	Peritoneal dialysis	The supplement dose is not necessary.
Pretreatment considerations		Pregnancy
		Lactation
		Drug allergy history (e.g. a history of angioedema)
		Collagen vascular disease
		Complete blood count (CBC)Serum creatinine
		Potassium
		Blood pressure
		Previous drug history (e.g. diuretics or nonsteroidal anti-inflammatory drugs [NSAIDs])
Monitoring	CBC	Close and periodical CBC monitoring in the first 3 months especially in patients with renal failure and collagen vascular diseases.
	Leukocytes	complete leukocyte counts with 2-week intervals in the first 3 months. (if the leukocyte count reaches 4000/mm3 or ½ pretreatment count, captopril must be discontinued.)

Continued Table 1.

Neutrophils	The neutrophil counts must also be higher than 1000/mm3 otherwise, captopril must be discontinued.
Potassium	An increase in K+ to <5.5mmol/L is acceptable. If: K+ <5 mmol/L; check the K+ levels at about 7 days after starting captopril. 5 <K+ <5.5; recheck in 7-day intervals. K+ ≥5.5; stop the captopril.
Serum creatinine	The serum creatinine must be checked in 4 and 7-day intervals in high-risk and low-risk patients, respectively. An increase in serum creatinine up to 35% of the pretreatment level is safe and anticipated, otherwise, captopril must be discontinued.
Blood urea nitrogen (BUN)	If urea does rise excessively consider stopping concomitant nephrotoxic drugs (e.g. NSAIDs) or potassium supplements/retaining agents (e.g. triamterene, amiloride, spironolactone, eplerenone, etc.)
Blood pressure (BP)	If: Systolic BP <90mmHg, captopril must be stopped until the systolic BP reaches levels higher than 90 mmHg.
Cough	Check the pulmonary-induced cough In the case of a troublesome cough, captopril must be discontinued and angiotensin receptor blockers must be substituted.
Angioedema	In the case of angioedema, captopril must be discontinued and angiotensin receptor blockers or any other alternative must be substituted.

* AHA: American Heart Association † ACC: American College of Cardiology ‡ Use the lower initial dose if the patient is dehydrated or on a diuretic.

that were in accordance with the standard guideline were considered as 1, otherwise, the score 0 was allocated. Quantitative and qualitative variables were described as Mean±SD and percentages, respectively. To evaluate the normality of the data collected in the study, the Kolmogorov-Smirnov test was performed. In order to determine the significant differences between the means of groups independent-sample T-test was used. Furthermore, for the screening of each adverse effect, the Naranjo Scale was exploited based on the following Table 2. The scores equal and more than 9 were known as definite adverse drug reaction (ADR), 5-8 as probable ADR, 1-4 as possible ADR, and 0 as doubtful ADR.

Table 2. Naranjo Scale for estimation of adverse drug reaction probability.

Question	Yes	No	Do not know or not done
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse events appear after the suspected drug was given?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0
Did the adverse reaction appear when the drug was re-administered?	+2	-1	0
Are there alternative causes that could have caused the reaction?	-1	+2	0
Did the reaction reappear when a placebo was given?	-1	+1	0
Was the drug detected in any body fluid in toxic concentrations?	+1	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0

Table 3. The demographic data of patients included in the DUE study.

Criteria		Number of patients (%)
Age	<65 y.o.	108 (52.2%)
	>65 y.o.	99 (47.8%)
Sex	Male	102 (49.3%
	Female	105 (50.7%)

3. Results

Two hundred and seven patients were included in this study. The demographic data (Table 3) revealed that out of the patients included in the study, 102 (49.3%) were male and 105 (50.7%) were female. Additionally, 99 patients (47.8%) were over 65 years old, while 108 (52.2%) were 65 years old or younger.

3.1. Diagnosis

The diagnosis of patients included in the present study is divided into three major diagnoses including acute coronary syndrome, heart failure, and hypertension. The diagnosis distributions are presented in figure1.

3.2. Indications and Contraindications

In the present study, 180 out of 207 patients (86.96%) had the indication for captopril use based on the captopril standard guideline. The other 27 patients (13.04%) had no indication for captopril use. Eight out of 207 total patients had a contraindication for captopril use. Five patients had hyperkalemia with K+>5.5 mmol/L, 2 patients had renal artery stenosis (both with solitary kidney), and 1 patient with angioedema history.

3.3. Drug Interaction

No captopril grade D drug-drug interaction was found in 207 patients included in this study.

3.4. Dosage

The results of the analysis of the dosage of captopril showed that the drug dose has the highest rate of non-compliance with the standard guideline. In 116 patients, the dose was incorrectly prescribed according to the drug indication. The dose match and mismatch for each indication are presented in Figure 2.

3.5. Dose Adjustment

After analysis of the data, the dose should have been adjusted for 13 patients based on the estimated glomerular filtration rate (GFR), but no dose adjustment had been performed. Eleven out of 13 patients had creatinine clearance 10 to 50 ml/min and 2 patients were on renal dialysis. The GFR was calculated according to the Cockcroft-Gault equation (Equation 1).

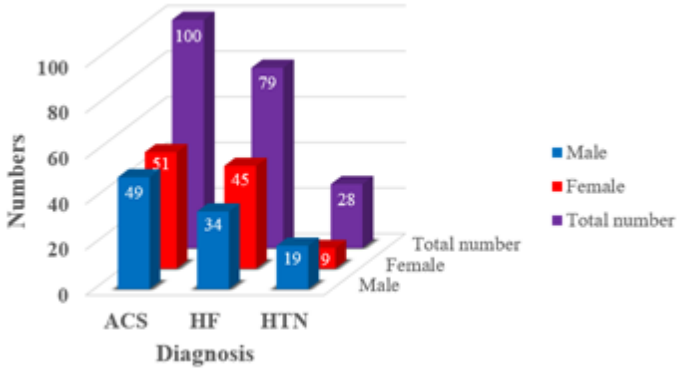

Figure 1. Diagnosis distribution for 207 patients included in the DUE study of captopril.

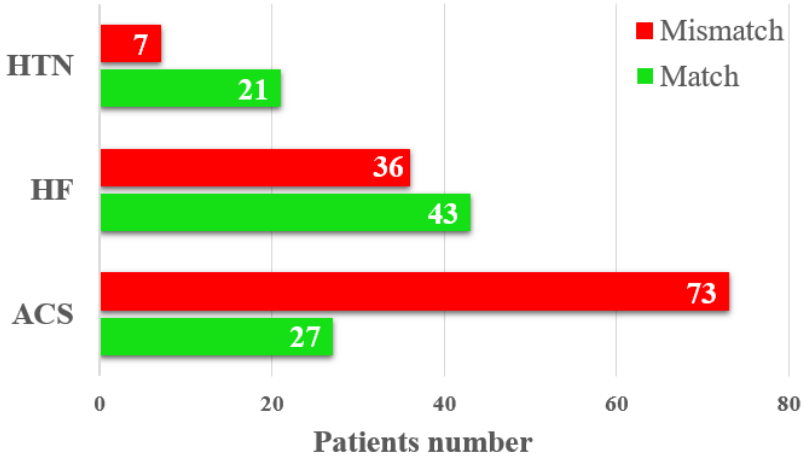

Figure 2. The match and mismatch of dose for each indication of captopril (HTN, hypertension; HF, heart failure; ACS, acute coronary syndrome).

$$GFR = \frac{(140 - age) \times weight \times (0.85\ if\ female)}{72 \times serum\ \text{creatinine concentration}} \quad \text{(Eq. 1)}$$

3.6. Pretreatment Considerations

The pretreatment considerations were checked for all 207 patients included in this study and no error was found regarding the pretreatment considerations.

3.7. Side Effects Monitoring

3.7.1. Serum Levels of Potassium

Although captopril must be discontinued in the case of patients with K+ ≥ 5.5 mmol/L, the serum potassium levels of 27 out of 207 patients had exceeded 5.5 mmol/L and captopril had not been discontinued.

3.8. Serum Creatinine Levels

In this study 42 out of 207 patients had a rise of more than 35% of normal serum creatinine levels, however, captopril had not been discontinued.

3.9. BUN

BUN had increased in 51 patients (24.64%) and no intervention such as discontinuation of K-sparing diuretics (e.g. spironolactone) had been considered. About 34% of these patients had been found to have increased BUN levels between 30-50% of the normal BUN upper limit.

3.10. Hypotension

Hypotension is one of the important side effects of ACEIs. The systolic blood pressure in 26 patients (12.56%) was found to be lower than 90 mmHg, however, the drug had not been discontinued.

3.11. Angioedema

Two female patients showed angioede-

Table 4. The probability of adverse drug reaction (ADR) based on Naranjo Scale.

Adverse drug reaction	Naranjo score	Probability according to the Naranjo Scale
Hyperkalemia	8	Probable
High serum creatinine	7	Probable
High BUN levels	7	Probable
Hypotension	4	Possible
Angioedema	3	Possible
Cough	3	Possible

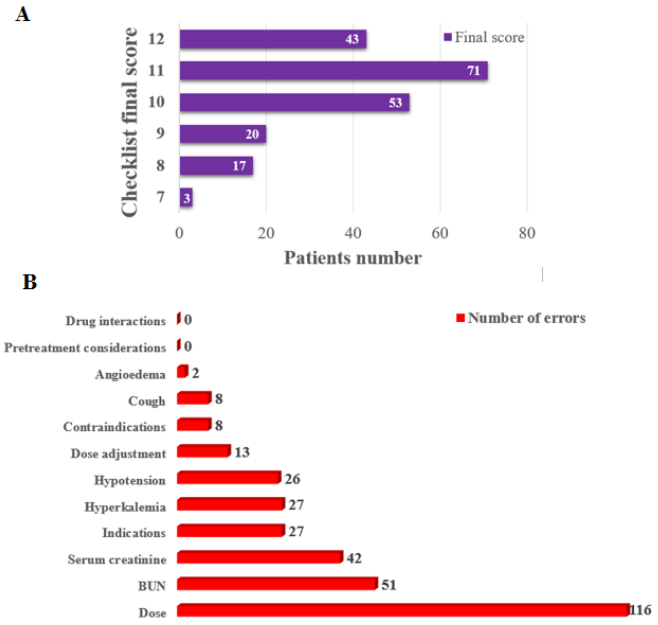

Figure 3. (A) The checklist final scores distribution (Min=7/12, Max=12/12), reflecting adherence to the standard guidelines for captopril use and (B) the number of errors for 12 evaluated factors in DUE of captopril, highlighting areas of deviation from the recommended practices .

ma during the present study and no intervention (such as captopril discontinuation) had been considered. However, intravenous injections of hydrocortisone, antihistamine, and in severe cases, epinephrine have been considered to control the angioedema.

3.12. Cough

The nonproductive cough is one of the annoying adverse effects of captopril. The cough had a lower incidence in patients using angiotensin receptor blockers. In this study, 8 patients (3.86%) of patients had a cough with captopril.

As described earlier, the screened adverse effects were classified into four groups based on their probability of appearing (Table 4).

3.13. The Checklist Final Scores

In this study, 12 factors including indication, contraindication, drug interactions, dosage, dose adjustment, pretreatment considerations, serum potassium levels, serum creatinine levels, BUN, hypotension, angioedema, and cough were checked. After determining the accuracy or inaccuracy of each factor, the summation of 12-factor scores was recorded. If all the factors were followed correctly for a patient, his/her final score would be 12. If a factor did not match the content of the standard guideline, the final score of 11 would be considered. The average final scores for male and female patients were calculated 10.31 ± 1.34 and 10.60 ±1.11, respectively. However, the average final scores in male and female patients were found not to be statistically significant (p-value=0.11). The average of the checklist final scores was found to be 10.45 ±1.24. The final score distribution and the number of errors of each factor are presented in Figure 3.

4. Discussion

This study was a prospective observational study and did not include a control group. Instead of comparing specific groups, the study focused on evaluating the patterns of captopril utilization, including adherence to standard guidelines, prescribing practices, and clinical outcomes, within the two CCUs of Namazi Hospital. While no formal com-

parison between groups (e.g., based on adherence levels, demographic characteristics, or different CCUs) was conducted, the data were analyzed to identify trends, deviations from guidelines, and areas for improvement in captopril use. The hypothesis of this study questioned how closely ongoing captopril pharmacotherapy adhered to the standard guidelines. In the present study, although in most patients (86.96%) the drug was properly selected and prescribed according to its indications, in 116 patients the dose of the drug was not selected correctly. Newman et al. evaluated the effect of captopril on the survival of patients with HF. In that double-blind study, a 90-day captopril administration, and the placebo revealed that captopril reduced mortality by 17% (9). Since the dose mismatch in patients with ACS had the highest rate compared to other indications, the appropriate education regarding the correct dose in patients revealing unstable angina and non-ST elevation MI could be effective in improving the therapeutic outcome. Setting the standard guideline which would be available for the healthcare team could also be beneficial.

As described earlier, 13% of patients who received captopril showed increased serum potassium levels with no intervention. A study conducted by Lawrence et al. showed that 11% of patients had developed hyperkalemia (10). Although there is evidence for the beneficial therapeutic effects of captopril and spironolactone (K-sparing diuretic) combination in patients with normal renal function and younger ages (<65 y.o.) (11-16), the enhanced mortality is reported due to hyperkalemia in patients received captopril and spironolactone simultaneously (17, 18).

First-dose hypotension is an important side effect of captopril with a 38% incidence rate that occurs during the first hour of captopril ingestion and must be considered especially in patients with a history of MI. Patients who received losartan also experienced first-dose hypotension with a lower incidence rate (24%) (19, 20). Since the blood pressure of patients was measured at predetermined time points in this study, the hypotension after the first dose was probably missed and a lower incidence rate was obtained.

This study had several limitations. As a prospective observational survey designed to evaluate adherence to standard guidelines for captopril use, it did not include a control group, which may increase the risk of subjectivity in the evaluation criteria. The absence of a control group also limits the ability to establish causal relationships between medication use and clinical outcomes. Nonetheless, prospective studies offer advantages over retrospective studies, which are often constrained by incomplete or inaccurate data and are more susceptible to documentation biases. Finally, DUE studies are often conducted in single-center settings, which may not reflect prescribing practices or patient characteristics in other healthcare environments. Despite these limitations, DUE studies remain a critical tool for identifying areas for improvement in medication use and guiding evidence-based interventions.

5. Conclusion

In this study, the use of captopril in two coronary care units was evaluated and compared with the standard guideline. Although in most patients captopril was selected correctly, the dose was incorrectly selected and this is a possible reason for limited therapeutic outcome.

It seems that holding periodic educational courses is beneficial in order to improve the quality of pharmacotherapy. Setting the standard guidelines in CCUs must be considered to avoid the drug's adverse effects and to help the healthcare team choose the correct dose.

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Ethical Approval

This study, conducted under thesis number 708, supported by Vice-chancellor for Research and Innovation, Shiraz University of Medical Sciences. Ethical approval from the Ethics Committee of Shiraz University of Medical Sciences was received (No. 708. SUMS.1392.146). The research protocol was reviewed and approved in accordance with ethical standards and guidelines to ensure the protection of participants' rights, confidentiality, and welfare. All procedures adhered to the principles outlined in the Declaration of Helsinki.

Authors' Contributions

•SN:Soha Namazi verified the standard guideline, supervised the clinical and patient affairs and also edited the preliminary draft. MM:Moein Masjedi conceived the presented idea, conducted the patients' affairs and fullfilled the checklists and proofread the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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