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CLINICAL PHARMACY INTERVENTIONS ON THE PREVALENCE OF POTENTIAL CLINICALLY SIGNIFICANT DRUG-DRUG INTERACTIONS IN OUTPATIENT CARDIOVASCULAR PATIENTS: A BEFORE-AND-AFTER STUDY

Vo Phat Dat[1], Nguyen Hoang Tuan Hung[2], Nguyen Thanh Duy[3], Tran Yen Hao[4*]

1. Tam Nong Regional Health Center

2. Nam Can Tho University

3. Kien Giang General Hospital

4. Can Tho University of Medicine and Pharmacy

**Corresponding author: tyhao@ctump.edu.vn*

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ABSTRACT

Background: *Potential clinically significant drug-drug interactions are highly prevalent among cardiovascular outpatients due to multimorbidity and polypharmacy, posing a significant threat to patient safety.* ***Objective:*** *To evaluate the impact of a multifaceted clinical pharmacy intervention on the prevalence and severity of potential clinically significant drug-drug interactions in a regional hospital setting.* ***Materials and methods:*** *A quasi-experimental before-and-after study was conducted at the outpatient department of Tam Nong Regional Medical Center, Vietnam. We analyzed 2,400 prescriptions (1,200 pre-intervention: June-August 2025; 1,200 post-intervention: January-March 2026). Drug-drug interactions were identified using the Vietnamese National Drug Interaction Database, UpToDate/Lexicomp, and Drugs.com. The multimodal intervention included the development of a cardiovascular-specific drug-drug interactions reference list, prescriber education, and the integration of electronic clinical decision support alerts. Binary logistic regression was used to identify factors independently associated with drug-drug interactions occurrence.* ***Results:*** *The prevalence of prescriptions containing potential clinically significant drug-drug interactions decreased significantly from 32.4% to 12.5% ($p < 0.001$), representing a 61.4% relative reduction. High-severity drug-drug interactions dropped from 6.1% to 0.8% ($p < 0.001$), while moderate-severity interactions decreased from 26.3% to 10.2% ($p < 0.001$). Risk factors for drug-drug interactions included advanced patient age (≥70 years; OR 4.92, 95% CI: 3.33-7.28), high comorbidity burden (≥3 comorbidities; OR 7.13, 95% CI: 4.61-10.92), and polypharmacy (OR 3.89, 95% CI: 3.01-5.03). Additionally, prescriptions issued by prescribers with a bachelor's degree were associated with significantly higher odds of drug-drug interactions compared with those issued by prescribers with postgraduate qualifications (OR 1.85, 95% CI: 1.43-2.39).* ***Conclusions:*** *The multifaceted clinical pharmacy intervention effectively reduced the prevalence and severity of potential drug-drug interactions among cardiovascular outpatients. Integrating electronic alerts with targeted education is a robust strategy for enhancing medication safety, particularly for high-risk patients.*

Keywords: *Potential clinically significant drug-drug interactions, clinical pharmacy intervention, cardiovascular disease, quasi-experimental study, before-and-after study.*

I. INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, accounting for a substantial proportion of hospital visits and long-term pharmacotherapy [1]. Patients with cardiovascular conditions frequently present with

multiple comorbidities such as hypertension, diabetes mellitus, dyslipidemia, and chronic kidney disease. As a result, polypharmacy is common in this population, increasing the risk of drug-drug interactions (DDIs). Clinically significant DDIs may lead to adverse drug reactions, reduced therapeutic efficacy, prolonged treatment, increased healthcare costs, and even life-threatening events [2].

In outpatient settings, the risk of DDIs is particularly concerning because patients often receive long-term prescriptions and may not be closely monitored compared to inpatients. The complexity of cardiovascular regimens such as combinations of antiplatelet agents, anticoagulants, beta-blockers, renin-angiotensin system inhibitors, and lipid-lowering drugs further heightens the likelihood of interactions [3]. Early identification and prevention of clinically significant DDIs are therefore essential to ensure medication safety and optimize therapeutic outcomes.

Clinical pharmacy services have been increasingly recognized as an effective strategy to enhance medication safety. Through activities such as medication review, development of reference guidelines, prescriber education, and implementation of electronic alert systems, clinical pharmacists can actively detect, prevent, and manage potential DDIs [4]. Evidence from various healthcare settings suggests that structured clinical pharmacy interventions can significantly reduce medication-related problems, including DDIs.

At the Tam Nong Regional Medical Center, a preliminary assessment of outpatient cardiovascular prescriptions revealed a concerning 32.4% prevalence of clinically significant DDIs [5]. Despite this high prevalence, a systematic, targeted strategy to address these interactions had not yet been implemented at the facility. Therefore, this study was designed to evaluate the effectiveness of a comprehensive, pharmacist-led clinical pharmacy intervention in reducing the prevalence and severity of DDIs. We hypothesized that a multifaceted approach—integrating educational training, context-specific reference guidelines, and electronic prescribing alerts—would significantly decrease both the occurrence and clinical severity of potential DDIs among cardiovascular outpatients.

II. MATERIALS AND METHODS

2.1. Study population

Study population: The study population comprised health insurance-covered outpatient prescriptions for patients aged ≥50 years with at least one diagnosed cardiovascular disease (ICD-10 codes I10-I79). The age threshold of ≥50 years was selected because cardiovascular risk tends to increase markedly from this age onward. This threshold is also consistent with contemporary cardiovascular risk stratification frameworks, including the 2021 ESC prevention guidelines [14].

Eligible prescriptions were those containing at least one cardiovascular medication. The unit of analysis was the individual prescription. Prescriptions containing only traditional or herbal medicines, as well as prescriptions with a single medication, were excluded from the analysis.

2.2. Research methods

- Study Design: This study used a quasi-experimental before-and-after design. The pre-intervention phase was conducted from June to August 2025, followed by an

intervention implementation period from October to December 2025. The post-intervention phase was conducted from January to March 2026.

- Samples: The sample size was recalculated using the formula for comparing two independent proportions, with p_1 representing the expected prevalence of potential clinically significant DDIs before the intervention and p_2 representing the expected prevalence after the intervention:

$$n = \frac{\left[Z_{1-\alpha/2}\sqrt{2\bar{p}(1-\bar{p})} + Z_{1-\beta}\sqrt{p_1(1-p_1)+p_2(1-p_2)}\right]^2}{(p_1-p_2)^2}$$

Where:

n = required sample size per study period
p_1 = expected prevalence of DDIs before intervention
p_2 = expected prevalence of DDIs after intervention
$\bar{p} = (p_1 + p_2)/2$
$Z_{1-\alpha/2}$ = Z value for the significance level, usually 1.96 for $\alpha = 0.05$
$Z_{1-\beta}$ = Z value for power, usually 0.84 for 80% power
$p_1 - p_2$ = expected absolute reduction in DDI prevalence

Based on the findings of Nguyen Thi Minh Khoa *et al.,* the prevalence of potential clinically significant DDIs among cardiovascular outpatients was approximately 42% [6] ; thus, p_1 was set at this value. The expected post-intervention prevalence (p_2) was established at 36%, reflecting a projected absolute reduction of 6%. Under these assumptions, a minimum sample size of 1,036 prescriptions per study period was required. To enhance statistical precision and account for potential data exclusions, the final sample was increased to 1,200 prescriptions per phase.

Due to the large and varying number of outpatients in each study period, a systematic two-stage random sampling procedure was employed to select 1,200 prescriptions for each phase. First, from the total pool of eligible cardiovascular outpatients, 1,200 unique patients were selected using a computer-generated random number sequence. Subsequently, for each selected patient, a single representative prescription from their clinical records during the study period was randomly extracted. This approach ensured that each patient contributed only one prescription to the analysis, thereby maintaining the independence of observations and preventing any single patient from disproportionately influencing the results.

Identification and classification of DDIs

The presence and severity of potential DDIs were assessed using three reference databases: the Vietnamese National Drug Interaction Database [15], UpToDate/Lexicomp® (Wolters Kluwer Health) [16], and Drugs.com [17]. Only clinically significant DDIs were included in the outcome analysis, defined as DDIs classified as either severe or moderate.

A severe DDI was defined as an interaction classified as “contraindicated” in the Vietnamese National Drug Interaction Database, “avoid combination” or “consider therapy modification” in UpToDate/Lexicomp®, or “major” in Drugs.com.

A moderate DDI was defined as an interaction classified as “monitor therapy” in UpToDate/Lexicomp® or “moderate” in Drugs.com.

When severity classifications differed across databases, the highest severity rating was used for analysis. For example, if an interaction was classified as "major" in Drugs.com but as "monitor therapy" in UpToDate/Lexicomp®, it was categorized as severe.

Intervention strategy

Following analysis of the pre-intervention data, clinically significant cardiovascular DDI pairs were identified and used to develop a multifaceted intervention strategy. The development of the DDI reference list involved identifying high-frequency and clinically relevant DDI pairs from the pre-intervention dataset, followed by verification against multiple evidence-based databases (Vietnamese National Drug Interaction Database, Drugs.com, and UpToDate) to ensure clinical validity and consistency.

The intervention included (1) the development of a context-specific reference list of clinically significant cardiovascular DDIs which were extracted from the results of the pre-intervention period; (2) Educational training sessions for prescribers on high-risk interaction pairs and appropriate management strategies; and (3) Integration of an electronic DDI alert system into the prescribing software.

The physician training was conducted through structured sessions, including presentations and case-based discussions, focusing on high-risk DDI pairs, their clinical consequences, and recommended management strategies. Training materials were standardized and delivered by clinical pharmacists prior to the post-intervention phase. The electronic alert system was integrated into the hospital prescribing software and provided real-time notifications when potential clinically significant DDIs were detected during prescription entry. Alerts included information on interaction severity and recommended management actions to support clinical decision-making.

The intervention targeted prescribing physicians in the Outpatient Department. Physicians eligible to participate were those actively prescribing cardiovascular medications during the study period. Physicians were excluded if they were on maternity leave, long-term study leave, not providing outpatient services during the data collection period, or declined to participate in the intervention.

Clinical pharmacists were responsible for developing the DDI list, conducting training sessions, and supporting the implementation of the alert system. Where applicable, pharmacist recommendations regarding DDI management were communicated to prescribers, and the acceptance of these recommendations was recorded to assess intervention feasibility.

- Study content: Data were extracted from the hospital's electronic prescribing and medical record systems using a standardized data collection form. Variables extracted for analysis included prescription-level information (study period: pre-/post-intervention; total number of medications per prescription; presence and number of clinically significant DDI pairs; and severity classification).

- Statistical Analysis

Data were analyzed using SPSS version 20. Descriptive statistics were used to summarize patient, prescriber, and prescription characteristics. These characteristics were compared between the pre- and post-intervention periods using the chi-square test. A p-value <0.05 was considered statistically significant.

Binary logistic regression was performed to identify factors associated with the occurrence of clinically significant DDIs. Candidate variables included patient-related factors (age group, sex, and number of comorbidities), prescription-related factors (number

of medications), and prescriber-related factors (age group, professional qualification, and years of professional experience). Prescriber age was categorized as <40 and ≥40 years, while years of professional experience were categorized as <10 and ≥10 years for regression analysis. Associations were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Variables with 95% CIs that did not include 1 were considered statistically significant.

The effectiveness of the intervention was evaluated using an effectiveness index, calculated as follows:

$$\text{Effectiveness index (\%)} = \frac{P_{pre} - P_{post}}{P_{pre}} \times 100$$

where P_{pre} and P_{post} represent the proportions of prescriptions containing potential clinically significant DDIs in the pre-intervention and post-intervention periods, respectively.

- **Ethical Approval:** The study was approved by the Ethics Committee in Biomedical Research of Can Tho University of Medicine and Pharmacy (Approval No. 25.019.HV/PCT-HĐĐĐ in 2025).

III. RESULTS

A total of 2,400 outpatient cardiovascular prescriptions were analyzed, including 1,200 prescriptions in the pre-intervention phase and 1,200 prescriptions in the post-intervention phase.

Table 1. Patient characteristics

Characteristics	Pre-intervention (n=1200)	Post-intervention (n=1200)	p-value
Age (years)			0.99
50-59	335 (27.9%)	330 (27.5%)	
60-69	548 (45.7%)	552 (46.0%)	
≥70	317 (26.4%)	318 (26.5%)	
Sex			0.90
Male	536 (44.7%)	540 (45.0%)	
Female	664 (55.3%)	660 (55.0%)	
Cardiovascular diagnosis			0.78
Hypertension	844 (70.3%)	850 (70.8%)	
Coronary artery disease	211 (17.6%)	205 (17.1%)	
Heart failure	46 (3.8%)	45 (3.7%)	
Number of comorbidities			0.92
0	227 (18.9%)	230 (19.2%)	
1-2	404 (33.7%)	398 (33.2%)	
≥3	569 (47.4%)	572 (47.6%)	

No statistically significant differences in patient characteristics were observed between the pre- and post-intervention periods (p>0.05). In both periods, most patients were aged 60-69 years, and slightly more than half were female. Hypertension was the most common cardiovascular diagnosis, followed by coronary artery disease and heart failure. Nearly half of the patients had three or more comorbidities, indicating a high burden of multimorbidity in this outpatient cardiovascular population.

Table 2. Prescription characteristics

Characteristics	Pre-intervention (n=1200)	Post-intervention (n=1200)	p-value
Number of prescribed medications			0.86
<5	615 (51.2%)	620 (51.7%)	
≥5	585 (48.8%)	580 (48.3%)	

Prescription characteristics were comparable between the pre- and post-intervention periods (p=0.86). Approximately half of the prescriptions contained five or more medications.

Table 3. Prescriber characteristics

Characteristics	Pre- intervention n (%)	Post- intervention n (%)
Sex		
Male	10 (66.7%)	9 (60.0%)
Female	5 (33.3%)	6 (40.0%)
Age group (years)		
<40 years	8 (53.3%)	7 (46.7%)
≥40 years	7 (46.7%)	8 (53.3%)
Years of professional experience		
<10 years	6 (40.0%)	5 (33.3%)
≥10 years	9 (60.0%)	10 (66.7%)
Professional qualification		
Bachelor	8 (53.3%)	9 (60.0%)
Postgraduate	7 (46.7%)	6 (40.0%)
Postgraduate qualifications included Specialist I/Master's degree and Specialist II physicians (n = 2).		

The characteristics of prescribers are presented in Table 3. The distributions of sex, age group, years of professional experience, and professional qualification were generally comparable between the pre- and post-intervention periods. In both study phases, male prescribers accounted for the majority. Approximately half of the prescribers were aged ≥40 years, and most had ≥10 years of professional experience. Regarding professional qualification, bachelor-level physicians slightly predominated over those with postgraduate qualifications.

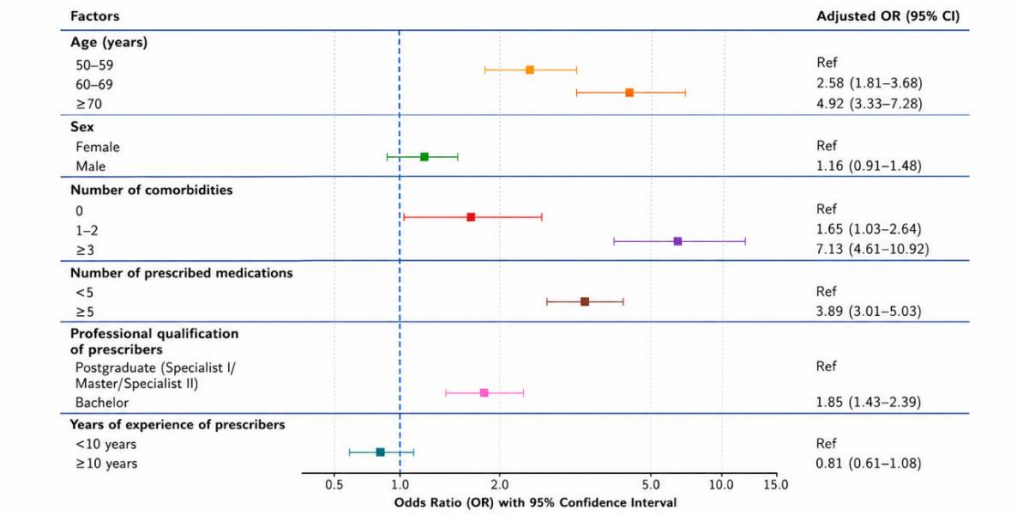

Figure 1. Factors associated with the presence of potential clinically significant DDIs (before the intervention)

Figure 1 demonstrates that, before the intervention, several patient-, prescription-, and prescriber-related factors were associated with the presence of potential clinically significant DDIs. Older patient age, higher comorbidity burden, polypharmacy, and prescriber professional qualification were significantly associated with increased odds of DDIs. Compared with patients aged 50-59 years, those aged 60-69 years and ≥70 years had significantly higher risks of DDIs. The strongest associations were observed among patients with ≥3 comorbidities and prescriptions containing ≥5 medications. In addition, prescriptions issued by bachelor-level prescribers were more likely to contain clinically significant DDIs than those issued by prescribers with postgraduate qualifications. In contrast, patient sex, prescriber age group, and prescriber years of experience were not significantly associated with DDI occurrence, as their 95% confidence intervals included the null value (OR = 1).

Table 4. Prevalence of prescriptions with clinically significant DDIs in the outpatient prescriptions before and after the intervention

Types of DDIs	Pre-intervention (n=1200)	Post-intervention (n=1200)	p-value	Effectiveness index
Clinically significant	389 (32.4%)	150 (12.5%)	<0.001	61.4%
Severe	73 (6.1%)	10 (0.8%)	<0.001	86.9%
Moderate	316 (26.3%)	122 (10.2%)	<0.001	61.2%

As shown in Table 4, the prevalence of prescriptions containing clinically significant DDIs decreased significantly after the clinical pharmacy intervention. The proportion declined from 32.4% (389/1200) before intervention to 12.5% (150/1200) after intervention ($p<0.001$), corresponding to a relative reduction (effectiveness index) of 61.4%. A marked reduction was also observed in contraindicated or major DDIs, which decreased from 6.1% to 0.8% ($p<0.001$), representing an effectiveness index of 86.9%. Moderate DDIs also declined from 26.3% to 10.2% ($p<0.001$), corresponding to a 61.2% relative reduction.

IV. DISCUSSION

The present study demonstrated a substantial reduction in the prevalence of prescriptions containing clinically significant DDIs following the clinical pharmacy intervention. The prevalence declined from 32.4% before the intervention to 12.5% after implementation, corresponding to a 61.4% relative reduction. This relatively high baseline prevalence reflects the complexity of cardiovascular pharmacotherapy, where multimorbidity and polypharmacy frequently increase the risk of DDIs. The significant reduction observed after the intervention suggests that structured clinical pharmacy activities, including prescriber education and integration of electronic interaction alerts, can effectively improve prescribing safety. Similar benefits of pharmacist-led interventions in reducing medication-related problems have been reported in previous studies evaluating clinical pharmacy services and medication safety programs [7].

A particularly notable finding of this study was the marked reduction in high-severity DDIs. Contraindicated or major interactions decreased from 6.1% to 0.8%, while moderate interactions declined from 26.3% to 10.2%. This indicates that the intervention was especially effective in preventing potentially dangerous drug combinations. Prior to intervention, moderate DDIs accounted for the majority of clinically significant interactions, which is consistent with findings reported in cardiovascular populations in Pakistan where

74.06% of interactions were classified as moderate and 17.33% as major [8]. Similar patterns have been observed in other studies involving cardiovascular patients with polypharmacy, where moderate interactions represent the largest proportion of DDIs [8]. In elderly ambulatory cardiac patients in Ethiopia, potential DDIs were reported in 90.1% of patients, including 15.1% severe interactions [9]. Compared with these findings, the post-intervention rate of major or contraindicated DDIs observed in the present study (0.8%) was considerably lower. Because high-severity DDIs are strongly associated with adverse clinical outcomes, their substantial reduction highlights the potential of pharmacist-led interventions to enhance medication safety [10].

The intervention also resulted in a substantial reduction in the number of interaction pairs and prescriptions containing multiple DDIs. The number of major interaction pairs identified by Drugs.com decreased from 73 to 12, while contraindicated pairs according to UpToDate declined from 18 to 3. These findings confirm that the burden of high-risk DDIs in outpatient cardiovascular prescriptions was clinically relevant before intervention. Previous studies have also reported a high prevalence of severe DDIs among cardiovascular patients, particularly in populations with extensive polypharmacy [11]. For example, studies conducted among elderly patients with cardiovascular diseases in the United States identified a high proportion of severe potential DDIs, while Pakistani cardiovascular cohorts reported notable frequencies of major and class X interactions [8]. These findings support the view that cardiovascular pharmacotherapy is particularly prone to DDIs. The marked reduction in high-risk interaction pairs in the present study suggests that the intervention successfully targeted commonly reported high-risk combinations such as antiplatelet-proton pump inhibitor interactions and renin-angiotensin system inhibitor combinations with potassium-sparing diuretics [12].

The intervention also improved the clinical management of contraindicated DDIs through active pharmacist-physician collaboration. Although a small number of contraindicated interactions were still detected after the intervention, all cases were reviewed and appropriately managed through drug discontinuation, substitution, or protective therapy. These results highlight the importance of integrating pharmacist review into routine prescribing workflows. Similar outcomes have been reported in Vietnamese hospitals where clinical pharmacy activities combined with computerized warning systems significantly reduced cardiovascular drug-related interactions and ensured appropriate clinical management of remaining cases [13]. Previous studies have also demonstrated that computerized clinical decision support systems alone may lead to alert fatigue, whereas combining electronic alerts with pharmacist review significantly improves clinical acceptance and intervention outcomes [4].

This study has several limitations. First, the study was conducted at a single healthcare center, which may limit the generalizability of the findings to other healthcare settings. Second, the pre-post study design without a parallel control group makes it difficult to completely exclude the influence of external factors such as changes in prescribing practices or institutional policies during the study period. Third, DDIs were identified using electronic databases rather than clinical outcome data; therefore, the actual occurrence of adverse drug events related to these interactions was not evaluated. Finally, although efforts were made to ensure comparability between the two study periods, residual confounding factors may still exist. Despite these limitations, the study provides important real-world evidence demonstrating that structured clinical pharmacy interventions combined with

electronic prescribing alerts can significantly reduce the prevalence and severity of clinically significant DDIs in outpatient cardiovascular patients.

V. CONCLUSION

These findings demonstrate that clinical pharmacy intervention significantly reduced both the prevalence and severity of DDIs in outpatient cardiovascular patients. The development of a context-specific interaction list combined with electronic prescribing alerts represents an effective strategy to enhance medication safety and should be sustained and expanded.

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