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Research Article

Enhancing Medication Safety: How Clinical Decision Support Systems and Clinical Pharmacists' Interventions Address Drug-Disease Interactions

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ABSTRACT

Drug-disease interactions (DDSIs) occur when a medicine aimed at treating one disease may worsen another comorbidity or condition. Clinical decision support systems (CDSS) to screen DDSIs have been demonstrated to be an effective and labor-saving method, while clinical pharmacist interventions help manage clinically relevant interactions. Incorporating both CDSS and clinical pharmacist interventions may serve as a good practice model to further improve DDSI management. This study aims to assess the impact of the CDSS and clinical pharmacist interventions in mitigating DDSI. A quasi-experimental study was conducted to compare the prevalence of DDSIs before and after the application of CDSS and clinical pharmacist interventions. The CDSS was developed by integrating a DDSIs database into the hospital software systems. The database was built by a multidisciplinary team based on thorough literature screening and discussions with healthcare experts. It included interaction pairs (medicine code – ICD-10 code) with their severity, details on clinical outcomes, and management strategies. The CDSS started to provide alerts for physicians in December 2022. In cases where the physicians ignore the alerts, clinical pharmacists are involved in consultation. A total of 139,136 and 150,934 prescriptions were included during the pre- and post-interventional periods, respectively. After interventions, there was a significant reduction in the prevalence of total DDSIs, from 0.14% (95% CI: 0.12% - 0.17%) in the pre-intervention phase to 0.015% (95% CI: 0.010% - 0.022%) in the post-interventional phase, with an odds ratio of 0.1 (95% CI: 0.07 – 0.16). The rate of contraindicated interactions decreased from 0.06% to 0.005% (OR: 0.08; 95%CI: 0.04 – 0.17), and major interactions were reduced from 0.08% to 0.009% (OR: 0.11; 95%CI: 0.07-0.20). In the post-intervention period, a continuous decrease in the number of interactions was also noted over 3 months. The utilization of CDSS for identifying drug-disease interactions and clinical pharmacist interventions have been shown to reduce the prevalence of DDSIs, thereby improving medication safety.

Keywords:
Drug Disease Interaction; Clinical Decision Support System; Clinical Pharmacist

1. INTRODUCTION

Drug-disease interactions (DDSIs) occur when a medicine aimed at treating one disease may worsen another comorbidity or condition[(1)]. These may be attributed to preventable medication errors[(2)]. They contribute to an increased risk of adverse drug reactions (ADR), which can lead to serious clinical consequences,

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including decreased quality of life, hospitalization, and even mortality, as well as economic consequences[3]. The prevalence of DDSIs varies significantly across studies, ranging from 3%[4] to 50%[5]. A study conducted in Sweden indicated that one in every ten elderly patients attending primary care has at least one DDSI[6]. Despite their serious consequences, DDSIs are preventable in most cases, and DDSI monitoring is considered a key element of optimal care, particularly for patients with multi-morbidities[7].

To mitigate DDSIs, Clinical Decision Support Systems (CDSS) have been adopted in various clinical settings as an efficient and labor-saving approach[8-11]. When integrated with Computerized Physician Order Entry (CPOE), CDSS enables prescribers to check for drug interactions in real-time when inputting orders into the system. This strategy has the potential to prevent inappropriate prescribing, as most preventable drug-related problems occur at the drug ordering stage[11].

Previous studies have highlighted the problem of alert fatigue, where clinically insignificant alerts are generated too frequently or lack credibility in clinical significance[12]. To avoid alert fatigue, it is necessary to construct a database integrated with relevant actionable clinical recommendations[1,13]. This can be achieved with the involvement of a multidisciplinary team; wherein clinical pharmacists play a pivotal role in recommending significant interaction pairs for database inclusion and in managing the interactions along with prescribers. A notable example of implementation is from the Netherlands, where hospital and community pharmacists played a major role in developing a comprehensive list of clinically relevant drug-disease interaction pairs and a best practice recommendation for a national program[1].

In Vietnam, monitoring drug interactions has been one of the primary activities of clinical pharmacists, primarily through the traditional method of reviewing medical records[14]. However, this practice may be insufficient to identify potential interactions due to the imbalance between the shortage within the clinical pharmacy workforce and the large number of prescriptions in hospitals, necessitating the need for additional support from a CDSS[15]. Some hospitals in Vietnam have developed databases of clinically relevant DDSIs that are incorporated into the CDSS to manage DDSIs. Moreover, clinical pharmacists are also involved in providing additional consultation for specific cases to optimize DDSI management. Our study aimed to evaluate the effectiveness of this practice model at a general hospital in Vietnam.

2. METHODS

Study design and setting

A quasi-experimental study was conducted to evaluate the impact of a CDSS combined with pharmacist interventions on the prevalence of DDSIs with cardiovascular and endocrine drugs. This study was carried out at 19-8 Hospital – Ministry of Public Security, Vietnam. This leading Grade I general hospital, which is positioned as the flagship medical institution under the Ministry of Public Security, accommodates 900 to 1,000 outpatients daily and boasts a capacity of 600 beds. The hospital began to implement CDSS and pharmacist interventions to manage DDSIs of cardiovascular and endocrine drugs in December 2022. Data were collected from September 2022 to November 2022 for the pre-intervention period (phase 1) and from 13rd April 2023 to 30th June 2023 for the intervention period (phase 2). We selected a three-month period prior to the initiation of the CDSS and another three-month period during which the CDSS operated smoothly for comparison. These periods were close to each other, allowing for few differences in the routine practices and other conditions, except the application of the CDSS and pharmacist intervention practice model.

In the pre-intervention period, pharmacists briefly reviewed all prescriptions of inpatients and outpatients before dispensing. This process was time-consuming and usually lacked DDSI checking. Besides, clinical pharmacists in charge of a specific ward reviewed the medical records of some inpatients who were at high risk for drug-related problems, including DDSI. Similarly, at the dispensing and consultation area, clinical pharmacists did medication reviews for selected outpatients, such as those with poly-pharmacy or new patients with chronic diseases. In the post-intervention period, the CDSS was integrated into this practice to help send DDSI alerts to physicians and identify patients with DDSIs that need pharmacist interventions.

The CDSS + pharmacist interventions practice model

The CDSS for DDSI alert was developed following five steps (Figure 1). Firstly, a list of all cardiovascular and endocrine medications was extracted from the hospital formulary. Secondly, an initial list of contraindicated and major DDSIs, along with their descriptions and recommended management strategies, was created by hospital clinical pharmacists by screening each drug's summary of product characteristics from Vietnam, Europe, and the USA. Moreover, relevant guidelines, handbooks, and electronic databases were exhaustively examined for additional information. In the third step, the predefined list was validated by obtaining expert's opinion on whether they agreed or disagreed

with the severity of the DDSIs. The experts were physicians in the cardiology, endocrinology, and clinical pharmacists in the hospital. The DDSI pairs achieving over 90% consensus among the multidisciplinary team earned inclusion in the validated list. In the fourth step, all practitioners were duly informed about the impending implementation of DDSI recommendations before integration into the CPOE systems. The recommendations encompassed interaction pairs (medicine code – ICD-10 code), indicating the severity of DDSIs, and provided details on clinical outcomes or management strategies. The fifth step encompassed the ongoing evaluation and updating of recommendations. Pharmacists reviewed medical records of patients triggering alerts weekly to validate the accuracy of alerts. Any new medicines introduced at the hospital were also encoded into the system during this period.

Upon activation, the system categorized interactions based on severity, promptly alerting physicians to contraindicated or major interactions. When an interaction was identified, the prescriber received an immediate alert. The alert supplied vital information, facilitating immediate decision-making or Consultation with clinical pharmacists (Figure 2). In case of a contraindicated DDSI where the physician agreed with the alert, the CDSS alert necessitated either selection of an alternative medicine or discontinuation of the current order. If a physician disagreed with alert recommendations, a clinical pharmacist would be needed to consult before the physician decided to adjust or continue the original prescription with the documented reason. For major DDSIs, decisions could be tailored based on patient-specific conditions and alert recommendations. However, immediate discussions with the in-charge clinical pharmacists on DDSI management were strongly recommended (Figure 3).

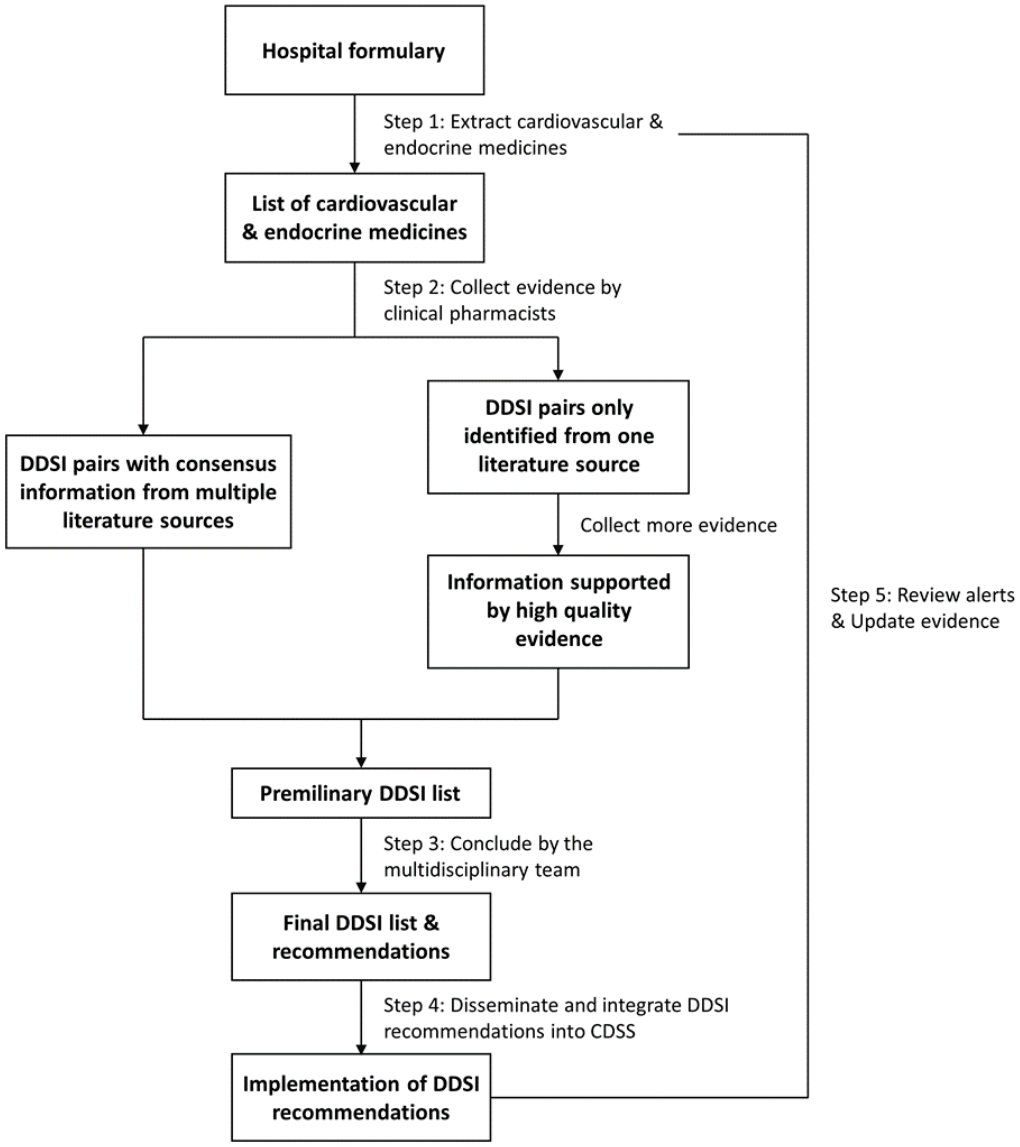

Figure 1. Development process of drug – disease interaction recommendations

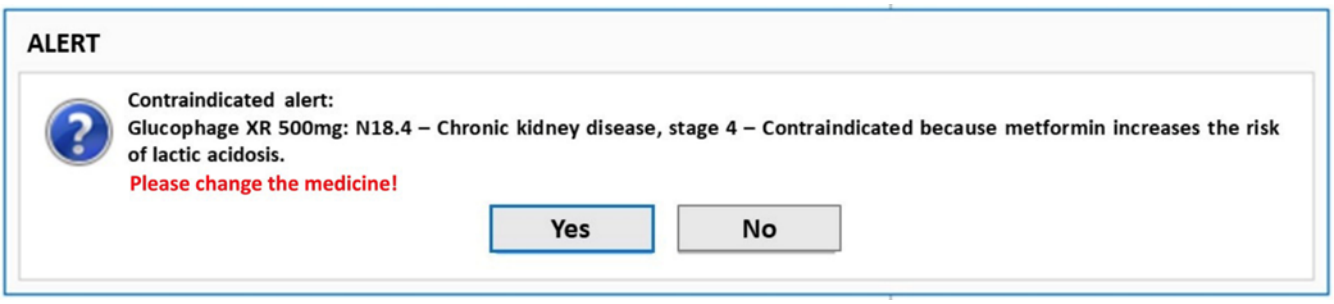

Figure 2. Screen displays of the alert box for DDSIs recommendation. This mock alert appears when a physician prescribes metformin to a patient with stage 4 chronic kidney disease. The box displays the interaction pairs, the severity of the DDSIs, and the rationale behind the alert. If the doctor clicks "Yes", they must change metformin to an alternative drug. Otherwise, a pharmacist consultation is required.

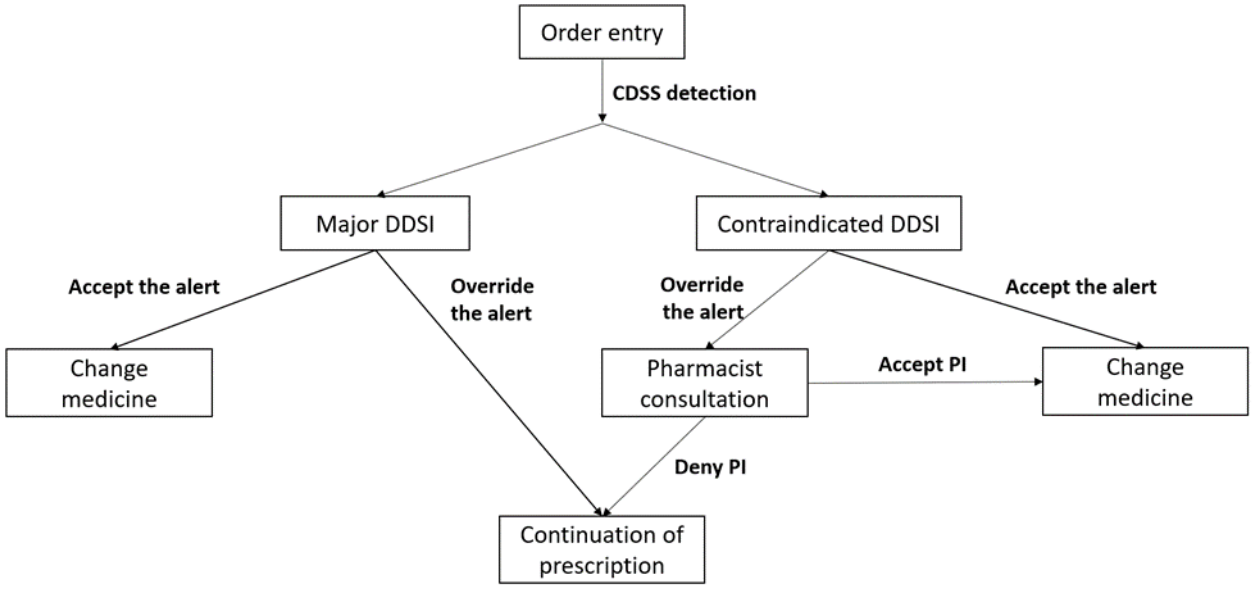

Figure 3. Workflow of the CDSS combined with pharmacist intervention for DDSI management. Noted: CDSS: clinical decision support system, DDSI: drug-disease interaction, PI: Pharmacist's Intervention.

Data collection and DDSIs identification

All outpatient prescriptions during the study periods were used for data collection. Prescriptions usually include patients' demographics, diagnosed diseases at admission and comorbidities with ICD-10 codes, and drug names with hospital codes, dosage, prescription dates, and ward details. Those with at least one cardiovascular or endocrine drug and fulfill information were included and compiled into Excel spreadsheet files for the phase 1 & 2. DDSIs in each prescription in both phases were identified based on the validated DDSIs list integrated into the CDSS.

Outcome measures

Our primary outcome was to assess how the CDSS affected the proportion of DDSIs incidents during two specific time periods. We counted all interaction episodes, including prescriptions of drug combinations dispensed to the same patient on multiple occasions. Secondary outcomes included analyzing DDSIs by time and department, as well as examining the most common drugs and diseases involved in these interactions

Statistical analysis

Descriptive statistics were presented as proportions or as means (± SD) or medians with corresponding ranges. Chi-squared test and Wilcoxon test were employed to identify statistical differences in patient characteristics between the two periods. The prevalence rate of DDSIs before and after CDSS implementation were computed. Odds ratios for the count of DDSIs were calculated for both periods to investigate the impact of the intervention using Chi-squared test. The significance level was set at $p<0.05$. All statistical analyses were conducted using R-Studio and Excel 2013.

3. RESULTS

Prescription characteristics

During pre- and post-intervention period, there were 139,136 and 150,934 prescriptions in cardiovascular and endocrine drugs, respectively. The median (IQR) age of patients in the pre-intervention period was 64 (57-71) years, which increased slightly to 65 (58-72) years in the post-intervention period (p <0.001). Females constituted 42.8% and 42.3% of the patients in the pre-intervention and post-intervention period, respectively. The number of diagnosed diseases per prescription showed a median (IQR) of 4 (2-5) in both periods. Prescriptions were primarily distributed across various departments, with the majority from the Outpatient department (74.2% in pre- and 73.5% in post-intervention period).

There were major changes in the distribution of prescriptions across department during the post-intervention period, including the Faculty of Traditional Medicine (4.1% to 1.1%; p<0.05), Emergency Department (1.4% to 0.6%; p<0.05), Gastroenterology (0.4% to 1.1%; p<0.05). The distribution of prescriptions over time demonstrated stability, with no significant differences observed after 90 days after commencing the study (Table 1).

Table 1. Prescription characteristics in the pre-intervention and post-intervention periods

Characteristic	Pre-intervention period (N = 139136)	Post-intervention period (N = 150934)	p-value
Age, median (IQR) in years	64 (57-71)	65 (58-72)	<0.05*
Female, No (%)	59489 (42.8%)	63879 (42.3%)	0.01849
Number of diagnosed diseases per prescriptions (median, IQR)	4 (2-5)	4 (3-6)	<0.05*
Distribution of prescriptions by departments			
Outpatient department	103223 (74.2%)	110973 (73.5%)	0.032
Geriatric department	25381 (18.2%)	29564 (19.6%)	<0.05
Faculty of Traditional Medicine	5673 (4.1%)	1621 (1.1%)	<0.05
Emergency Department	1949 (1.4%)	938 (0.6%)	<0.05
Department of Internal Nephro-Rheumatology	1625 (1.2%)	1699 (1.1%)	0.293
Gastroenterology	592 (0.4%)	1652 (1.1%)	<0.05
Other departments	693 (0.5%)	4487 (3.0%)	-
Distribution of prescriptions by time periods			
The first 30 days	45581 (32.8%)	50592 (33.5%)	0.88
The second 30 days	46538 (33.4%)	49569 (32.8%)	<0.05
The third 30 days	47017 (33.8%)	50775 (33.6%)	0.39

*: Wilcoxon test

DDSIs prevalence before and after the implementation of CDSS and pharmacist interventions

Table 2 provides an overview of cardio-endocrine drug interaction rates with comorbidities in outpatients before and after the intervention. There was a significant reduction in the prevalence of total DDSIs, decreasing from 0.14% (95% CI: 0.12-0.17) in the pre-intervention period to 0.015% (95% CI: 0.010-0.022) in the post-intervention period, with an odds ratio of 0.1 (95% CI: 0.07-0.16). Specifically, in the Outpatient department, the rate dropped from 0.08% to 0.01% post-intervention (OR: 0.11; 95%CI: 0.07-0.20)

DDSIs occurrence over the study periods

Over a 3-month study period, a continuous decrease in the number of interactions was noted. Contraindicated interactions were reduced from 3 to 2 and ultimately to 1 during the 3-month intervention period. Similarly, major interactions decreased from 7 to 6 and concluded with 3 cases (Figure 3)

The most common drugs and diseases involved with DDSIs

The predominant medication implicated in DDSIs was rosuvastatin, representing 29.5% of all drugs identified in DDSIs (Table 3). It was found to be inappropriate in patients with severe renal impairment and those with myopathy or muscular disorders. Subsequently, levothyroxine (mainly interacting with

diabetes and hyperthyroidism) and candesartan plus hydrochlorothiazide (interacting with gout/hyperuricemia) accounted for 24.5% and 23.0% of the total, respectively. Meanwhile, diabetes and gout/hyperuricemia also emerged as the most prevalent diseases associated with DDSIs, constituting 24.5% and 23% of the total, respectively. Additionally, DDSIs involved other diseases, including renal impairment, myopathy, and Parkinson's disease

Table 2. Drug-disease interaction prevalence of Cardio-endocrine drugs among outpatients in the pre-intervention and post-intervention periods

Characteristic	Pre-intervention period (N = 139136)	Post-intervention period (N = 150934)	OR (95% CI)
Prevalence rate (95% CI) by severity			
Contraindicated DDSIs	0.06 (0.05-0.08)	0.005 (0.002-0.011)	0.08 (0.04-0.17)
Major DDSIs	0.08 (0.07-0.10)	0.009 (0.005-0.016)	0.11 (0.07-0.20)
Total DDSIs	0.14 (0.12-0.17)	0.015 (0.010-0.022)	0.1 (0.07-0.16)
Prevalence rate (95% CI) by department			
Outpatient Department	0.08 (0.07-0.1)	0.01 (0.007-0.018)	0.14 (0.08-0.23)
Geriatric Department	0.04 (0.03-0.06)	0.003 (0.001-0.008)	0.08 (0.03-0.19)
Internal Nephro-Rheumatology	0.02 (0.01-0.03)	0 (0.0-2.4)	-

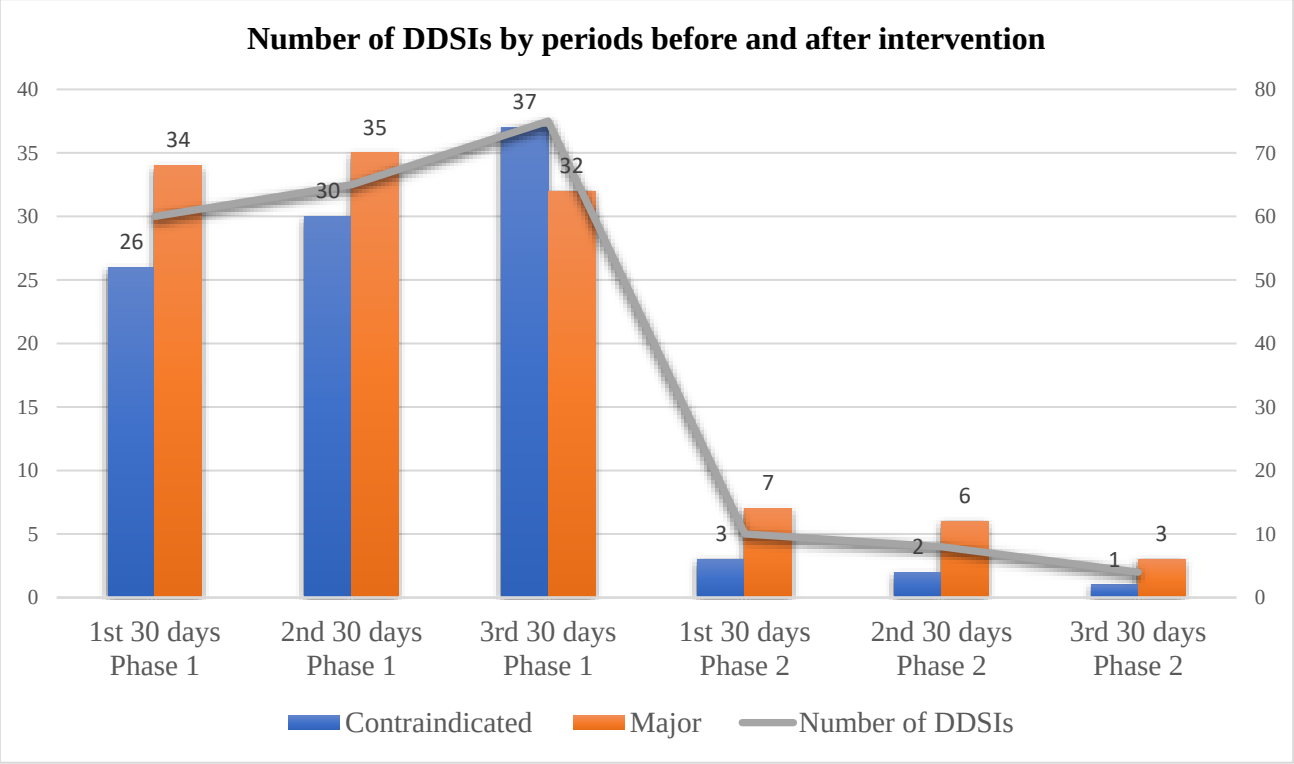

Figure 3. Number of cardio-endocrine drug interactions with comorbidities in outpatients by month. Noted: Phase 1: pre-intervention period, Phase 2: post-intervention period.

4. DISCUSSION

Given potential clinical and economic implications of DDSIs, and large volumes of prescriptions to screen for, CDSS in conjunction with clinical pharmacist expertise, has the potential to prevent interactions by identifying major interactions and providing real-time evidence-based practice recommendations

To our knowledge, this is the first study evaluating the impact of a CDSS combined with pharmacist interventions in mitigating the occurrence of DDSIs in the Southeast Asian region. Our findings indicated a notable 90% reduction (OR= 0.1; 95%CI: 0.07-0.16) in the prevalence of DDSIs following the integration of DDSI recommendations into the CPOE system. We followed the six-step procedure described by Van Tongeren to develop these DDSI recommendations[16]. Clinical pharmacists first developed a drug compendium, which was then reviewed by a multidisciplinary team to ensure its clinical significance. The finalized recommendations were disseminated to all physicians for practical implementation. Involvement of a multidisciplinary panel of experts and advance buy-in from physicians may in large part have contributed to the significant reduction in the prevalence of DDSIs in our study. This collective approach resulted in a favorable impact on the management of drug-drug interactions (DDIs), with an 83% decrease in the proportion of high-severity DDIs[10]. Previous studies in community pharmacy have demonstrated the impact of CDSS in reducing inappropriate prescriptions in the vulnerable population[8]. However, the effectiveness of CDSS was notably diminished where a multidisciplinary approach is not employed in crafting recommendations[17]. Desmedt et al. established drug dosage recommendations for patients with renal impairment. Notably, only two clinical pharmacists were involved in the development process, lacking insights from other professionals. The implementation of CDSS in that study did not lead to statistically significant reduction in appropriate prescribing rates (OR:0.97; 95%CI: 0.72-1.29)[17]. Future studies and implementation of CDSS should focus more on a collaborative development process to facilitate the success of this system.

Table 3. The most common drugs and diseases involved with drug-disease interactions in the pre-interventional period

Interaction element	Number (%) (N=200) *
Medication involved in DDSIs	
Rosuvastatin	59 (29.5%)
Levothyroxine	49 (24.5%)
Candesartan plus hydrochlorothiazide	46 (23.0%)
Beta-blockers	15 (7.5%)
Trimetazidine	8 (4.0%)
Disease involved in DDSIs	
Diabetes	49 (24.5%)
Gout/hyperuricemia	46 (23.0%)
Renal impairment	36 (18.0%)
Myopathy	29 (14.5%)
Parkinson's disease	8 (4.0%)

* Total DDSIs

Before the implementation of the CDSS, the prevalence of DDSIs in our study was 0.14%. This is in line with previously published literature, although substantial variability exists in the prevalence rates of DDSIs, ranging from 0.19% to 27.3% in different studies[18-20]. It is crucial to acknowledge that studies were not homogenous; disparities in medical settings, databases for DDSIs identification, and patient characteristics may contribute significantly to these variations. For instance, Lau et al. specifically focused on patients aged 75 years or older who were taking more than 5 medications [19]. Similarly, the study by Hanlon et al. included a patient population aged 70 years and older [18]. Meanwhile, the median age of our patients was 62 (41-68) in the pre-interventional period and 63 (43-68) in the post-interventional period. Older individuals are prone to having multimorbidity[21], making them more susceptible to polypharmacy and drug interactions[8, 22].

In this study, we primarily focused on building a DDSI database with cardiovascular and endocrine medications. In Vietnam, cardiovascular diseases and diabetes stand out as the most prevalent noncommunicable diseases, exposing patients to a heightened risk of drug-related problems due to polypharmacy and polymorbidity in this population. Furthermore, cardiovascular drugs accounted for the largest drug group in a previously published list of significant drug-disease interaction pairs[1].

In our study, rosuvastatin was most frequently involved in drug interactions, accounting for 29.5% of the total DDSIs, comprising both contraindicated and major cases. It was found to be inappropriate in patients with severe renal impairment and patients with myopathy or muscular disorders. There are reported

risks of rhabdomyolysis, acute renal failure, and myoglobinuria associated with the use of HMG-CoA reductase inhibitors[23]. Meanwhile, in a study conducted in Poland, the most prevalent DDSI pairs involves beta-blockers, accounting for 12.8% of total DDSIs, followed by ACE inhibitors at 10.4%, and diuretics at 6.7%[24]. We attribute these differences to variations in patient populations, as the demographic profiles of patients in our hospital differ significantly from that in community pharmacies in Poland. The second-most common interacting drug in our population was Levothyroxine, involved in 24.5% of total DDSIs. This may be explained by the prevalence of thyroid dysfunction in patients with diabetes. A recent meta-analysis, based on data from 10,920 patients with diabetes, reported a mean frequency of thyroid disease at 11%[25]. Of these patients, up to one-third of those with type 1 diabetes experience thyroid dysfunction[26]

Mechanistically, hyperthyroidism can impair glycemic control in diabetic patients, while hypothyroidism may increase the risk of hypoglycemia, posing challenges for healthcare professionals in managing diabetes[27]. Surprisingly, gout and hyperuricemia accounted for 23% of the total disease-involved interactions. It was classified as a major interaction with the compound preparation of candesartan and hydrochlorothiazide (HCTZ). Angiotensin II receptor blockers (ARB) were shown to exhibit a favorable impact on either reducing serum uric acid levels or increasing fractional excretion of uric acid[28] Our final DDSI list did not include their interaction with gout/hyperuricemia. Whereas single-active ingredient HCTZ preparation was not available in this hospital and Vietnam, no DDSI with the single HCTZ was produced. However, Jiao et al. suggested that both ARB and diuretics may be associated with an increased risk of gout, hyperuricemia, and related adverse events[29].

One of the major strengths of our study is that the concise list of cardiovascular-endocrine drug interactions with comorbidities was developed based on a procedure that has been implemented in numerous European hospitals[16]. The procedure incorporated details on interaction pairs, consequences, and management, based on a combination of literature and consensus from a multidisciplinary expert panel. This ensured a highly reliable list tailored to the hospital's clinical context, facilitating practical application and convenience for physicians to avoid unfavorable interactions when prescribing. With the use of the hospital software, the research team could efficiently review hundreds of thousands of prescriptions, accurately identifying interactions within just a few minutes. The study design, comprising two phases (pre-intervention and post-intervention), allowed healthcare professionals to observe the real-world effects of the study interventions on cardiovascular-endocrine drug interactions with comorbidities in outpatient settings. Additionally, it facilitated an assessment of the impact of clinical pharmacists on optimizing pharmacotherapy decisions. Generally, the positive outcomes of managing DDSIs in cardiovascular and endocrine medications have demonstrated the effectiveness of CDSS - pharmacist interventions in routine practice. These promising results suggest that such intervention could be extended to other drug classes. Moreover, to solidify the effectiveness of CDSS, future research should focus on long-term and continuous evaluations.

However, there are limitations to consider in our study. As the alert system relied on ICD codes, certain DDSI pairs without assigned ICD codes were not integrated into the system, even though these pairs were documented in literature. Therefore, the current status of managing these interactions may not be fully assessed. Furthermore, due to the lack of resources and time, our study has not yet investigated physicians' acceptance rates of CDSS alerts and clinical pharmacist interventions, which are also crucial metrics for assessing the intervention's effectiveness. This highlights the need for further research, such as exploring physicians' perspectives or identifying associated factors influencing physician decisions, to provide a comprehensive view of CDSS implementation and clinical pharmacist support in mitigating DDSIs.

Finally, the durations of the two compared periods were three months, which may cause bias as the drug use patterns can be seasonal. However, to minimize the difference in routine practices, we chose the two short periods close to each other. Moreover, this study assessed the interactions of the cardiovascular and endocrine medications, which might be affected by season to a small extent. Although the prescriptions were distributed differently among the departments between the two phases, the top two departments were Outpatient and Geriatrics department. Furthermore, a reduction in DDSI was consistently seen in these departments and in the whole hospital, demonstrating robust findings on the effects of the new model.

5. CONCLUSION

The utilization of CDSS and active clinical pharmacist intervention, designed with an intentional process that involved multidisciplinary input, significantly reduced the prevalence of DDSIs.

6. ACKNOWLEDGMENT

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethics approval
This research was reviewed and approved by the Board of Hanoi University of Pharmacy, under the approval number 909/QĐ-DHN.

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