TALLINN UNIVERSITY OF TECHNOLOGY
School of Information Technologies

Gerda Joa 212097YVEM

ANALYSIS OF DRUG-DRUG INTERACTION ALERT SYSTEM: PRESCRIPTION OF CARDIOVASCULAR DRUGS IN PRIMARY HEALTH CARE

Master's thesis

Supervisor: Tanel Ross
MSc

Tallinn 2023

TALLINNA TEHNIKAÜLIKOOL
Infotehnoloogia teaduskond

Gerda Joa 212097YVEM

RAVIMITE KOOSMÕJU HOIATUSSÜSTEEMI ANALÜÜS: KARDIOVASKULAARHAIGUSTE RAVIMID PEREMEDITSIINI ERIALAL

Magistritöö

Juhendaja: Tanel Ross
MSc

Tallinn 2023

Author's declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

Author: Gerda Joa

09.05.2023

Abstract

Background: Clinical decision support systems (CDSS) can improve patient safety by assisting physicians in identifying potential drug-drug interactions (DDIs) and reducing the risk of harm to patients. **The aim of this thesis** is to analyze the CDSS effect on C-D category and cardiovascular disease (CVD) C-D category interaction rate in Estonian primary health care settings from 2017-2022. Two hypotheses were formulated: a null hypothesis that there is no significant effect of the system on interaction rates and an alternative hypothesis that there is a significant effect. **Methods**: Mixed method approach: Prescription centre data and end-user surveys were used to measure the relationship between the system and interaction rates. **The results**: The system significantly reduced D category interaction rates (all prescriptions by 45.8% and with CVD by 63.45%). Decrease in top 10 interaction pairs suggesting a more informed and cautious approach to prescribing medication. Older patients, especially those aged 70-84, were at a higher risk of receiving prescriptions with clinically significant interactions. Cancellation was an unreliable indicator for interactions. **Conclusion:** CDSS significantly reduces DDI rates in primary health care settings, especially for D category drugs and patients with CVD. The system is a valuable tool for physicians to ensure patient safety by providing alerts on potential interactions and prompting informed decisions. To further improve the system, incorporating patient-centred features is recommended.

This thesis is written in English and is 59 pages long, including 6 chapters, 9 figures and 8 tables.

Annotatsioon

Ravimite koosmõju hoiatussüsteemi analüüs: kardiovaskulaarhaiguste ravimid peremeditsiini erialal

Taust: CDSS võib parandada patsiendi ohutust, aidates arstidel tuvastada võimalikke ravimite koostoimeid ja vähendada patsientidele tekkivat kahju riski. **Käesoleva magistritöö eesmärk** on analüüsida kliinilise otsusetoe süsteemi mõju C-D kategooria ja kardiovaskulaarhaiguste C-D kategooria interaktsioonidele Eesti esmatasandi tervishoius aastatel 2017-2022. Sõnastati kaks hüpoteesi: nullhüpotees, et süsteemil ei ole interaktsioonimääradele märkimisväärset mõju, ning alternatiivhüpotees, et süsteemil on märkimisväärne mõju. **Metoodika:** kombineeritud meetodil uurimistöö: süsteemi ja interaktsioonimäärade seoste mõõtmiseks kasutati retseptikeskuse andmeid ja lõppkasutaja küsitlusi. **Tulemused:** Süsteem vähendas oluliselt D kategooria interaktsioonide sagedust (kõikide retseptidega 45,8% ja kardiovaskulaarhaigustega 63,45%). Vähenes ka top kümne interaktsioonipaaride arv, mis viitab arsti informeeritumale ja ettevaatlikumale lähenemisele ravimite väljakirjutamisel. Vanemad patsiendid, eriti vanuses 70–84, olid kõrgema riskiga, et saada retsepte kliiniliselt oluliste interaktsioonidega. Retseptide tühistamine ei olnud usaldusväärne näitaja interaktsioonide arvu kohta. **Järeldused:** CDSS vähendab oluliselt ravimite vaheliste interaktsioonide esinemissagedust esmatasandi tervishoius, eriti D-kategooria ravimite ja kardiovaskulaarhaigustega patsientide puhul. Süsteem on arstide jaoks väärtuslik tööriist, tagades patsientide ohutuse, pakkudes hoiatusi võimalike interaktsioonide kohta ja soodustades informeeritud otsuste tegemist. Süsteemi edasiseks täiustamiseks on soovitatav integreerida patsiendikesksed funktsioonid.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 59 leheküljel, 6 peatükki, 9 joonist, 8 tabelit.

List of abbreviations and terms

ADR	*Adverse Drug Reaction*
CDSS	*Clinical decision support system*
CVD	*Cardiovascular disease*
DDI	*Drug-drug Interaction*
EHIF	*Estonian Health Insurance Fund*
NSAID	*Non-steroidal anti-inflammatory drugs*

Table of Contents

List of figures

List of tables

1 Introduction

Medication therapy is beneficial for disease treatment and managing quality of life [1]. Nevertheless, the risks must be considered to achieve a balanced approach [1]. One possible risk might be the inappropriate medication use [1]. One of the important specific types of potentially inappropriate medication use is drug-drug interactions (DDI) which can increase the risk of adverse drug reactions (ADR), deterioration of functional status, health services use and mortality [1]. Different explicit criteria to define DDIs have been available for more than two decades, still has been little implemented to prescription in well-functioning community-dwelling [1].

There are two types on DDI: pharmacodynamic and pharmacokinetic [2], [3]. Pharmacodynamic interactions occur when the interaction of two drugs produces an additive or cancelling effect on the body [2]. Pharmacokinetic interactions occur when one drug affects the absorption, distribution, metabolism, or excretion of another drug [3].

To increase the practical use of DDI information in the form of clinical decision support system (CDSS), computerized DDI alert systems have been developed [3]. CDSS can increase the recognition of DDIs and improve patient safety. Automated alerts can reduce the incidence of significant interactions with increased recognitions of interacting drug pairs [4].

According to the World Health Organization, cardiovascular diseases (CVD) are the leading cause of death worldwide (32% of all global deaths) [5]. CVD include different diseases, and patients often have multiple risk factors (e.g., hypertension, diabetes, high blood lipids) [5]. Drug treatment is necessary to reduce the risk of CVD exacerbation, to prevent heart attack and strokes [5]. Studies show that a third of people over the age of 75 take at least six medications and over a million take eight or more medications daily, making polypharmacy an important risk factor for DDI [6].

According to Eurostat, the rate of inpatients with CVD in Estonia in 2019 is in tenth place compared to other EU countries, the results reported by people themselves, CVD rate in Estonia is 21.1% [7]. With increasing age, the probability of developing chronic diseases (e.g., CVD) increases, both in the world and in Estonia [8]. Family physicians deal with early detection of disease, treatment and prevention of complications [8]. Consequently, CVD surveillance is one of the quality criteria for a family physician, aiming at detection of the disease and implementation of effective treatment to reduce complications and mortality [8].

In Estonia, the DDI CDSS has been mandatory for all outpatient prescribers since 2016 [9]. Although some hospitals have implemented a DDI alert solution on their own, the service is not available in inpatient settings [9]. Previous studies have shown that the number of clinically significant interactions identified by the system has remained relatively stable over time [10], [11]. Both studies compared three months of data in three different years.

Metsla found that family physicians are generally satisfied with the CDSS [10]. The system does not differentiate between systemic and topical use when considering the dosage form, leading to further inaccuracies in the alerts [10]. The DDI alert was frequently overridden for two main reasons: first, alerts were triggered for drugs that the patient was no longer taking, and second, no suitable alternative existed for the current drug pair [10]. In addition, physicians would like possibility of cancelling interaction notices in patients who do not take the drug that is transmitted in an alert, and the system currently misses potential DDIs with over-the-counter medicines, such as aspirin [10]. To improve the DDI alert system, alternative drug suggestions are desired [10]. Despite the study findings, which showed that 35% of all prescriptions contained clinically significant drug interactions, the number of such prescriptions did not decrease during the study period and remained stable [10].

Kurbatova also points out that while studying C -D interactions, the decline was seen with the level of interactions between C4 and D4, but number of drug interactions remained at the same level (31.4 % of all prescriptions) [11].

In Estonia, in case of health concern, first contact in healthcare system is his/her family physician who will referring to specialist if necessary [12]. Repeat prescriptions can be

extended by phone and e-mail to a patient with chronic disease or long-term treatment through a family physician [12]. The family physician also extends repeat prescriptions that were originally written by a specialist [12]. Therefore, family physicians have a much higher prescription load than other specialities.

Problem statement: The CDSS has been in use since 2016 [9], a comprehensive review of its functioning and effectiveness has not been conducted throughout this entire period.

The aim of this mixed methods study is to analyse the DDI alert system in primary health care in Estonia over the years of 2017, 2019-2022. In this study, prescription centre data will be used to measure the relationship between C-D category DDIs and CDSS. At the same time, the end-user survey will be explored using semi-structured interviews with family physicians in Estonia. The reason for combining both quantitative and qualitative data is to better understand this research problem by converging both DDI alert system data and family physicians views data.

Research question:

1. How does CDSS have effect on C-D category DDI rate over a five-year period in primary health care settings.

2. How does CDSS have effect on C-D category DDI rate on the occurrence in CVD prescriptions in primary health care setting.

Null hypothesis (H0): There is no significant effect of the CDSS system on the rate of C-D category DDIs over a five-year period in primary health care settings, and no significant effect on the occurrence of DDIs in CVD prescriptions.

Alternative hypothesis (H1): The CDSS system has a significant effect on the rate of C-D category DDIs over a five-year period in primary health care settings, and a significant effect on the occurrence of DDIs in CVD prescriptions.

2 Background

To fully comprehend how a DDI alert system can aid physicians in making informed decisions regarding drug administration in outpatient settings, it's essential to first grasp the fundamentals of DDIs. While CDSS tools are available globally, their effectiveness can be limited by certain challenges. To better understand these challenges and to create an overview of what should be done to modernize DDI alert systems with a focus on enhancing patient safety, a literature review was conducted. This section incorporates previous research findings and recommendations that could inform future improvements to these systems.

2.1 Drug-drug interactions

Hanlon et alles conducted a cross-sectional study and found that over a third (34%) of participants aged 70-79 had potential DDIs [1]. The risk of DDI increases with the number of medications, and it's estimated that 50% of people taking 5-9 drugs have at least one potential DDI, while the probability reaches 100% for those taking 20 or more drugs [13]. DDIs are common among older adults and are associated with hospitalization and ADRs [1], [2], [14]. Chronic conditions and the number of medications are factors associated with the likelihood of having a DDI [1]. Interestingly, older adults with less than 5 drugs in their regimen but with chronic conditions are also at higher risk of having a DDI. The most common drug classes affected by other drugs are CVD medications (24.2%) and non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin [1]. NSAIDs are commonly used by older adults, with over one in ten participants using them daily, and over a quarter of them being over-the-counter medicines. NSAIDs increase the risk of peptic ulcer disease, especially when taken with other medications, such as antithrombotic drugs (CVD medication) [1]. Each drug prescription increases the odds of having at least one DDI by 35-40% [1]. DDIs can have adverse effects on the cardiovascular system and other systems in the body [2]. Based on these findings, it is important to consider potential DDIs when prescribing medications, particularly for older adults with chronic conditions taking multiple medications.

Minimizing the risk of drug interactions is important in ensuring optimal patient care. Adhering to recommended guidelines and considering provided information when administering medications can help achieve this goal [15]. Some factors to consider when managing potential drug interactions include dose, duration, dosing times, and sequence [15]. It is important to note that almost all DDIs are dose-dependent, with increasing dose magnifying the interaction [15]. The duration of treatment can also be a determinant of DDI, with a single dose of a precipitating drug unlikely to have a clinically significant effect on the metabolized drug [15]. While dosing times may have little effect on metabolic DDIs, the sequence of administration may be important when titrating the target drug for optimal therapeutic response [15]. By taking these factors into account, healthcare professionals can minimize the risk of drug interactions and provide safer care for their patients.

2.2 Cardiovascular disease medications

Patients with CVD often have multiple pathophysiological conditions such as metabolic syndromes characterized by obesity, hypertension, dyslipidaemia and hyperglycaemia, which require health promotion or polypharmacy therapy [16]. Multimorbidity increases the prevalence of polypharmacy, and it is not uncommon for older patients with ischemic heart failure associated with atherosclerosis to receive multiple CVD drugs, such as antiplatelet therapy, high intensity statins, and beta blockers [14]. As the number of drugs increases, so does the risk of DDIs, which may have adverse effects on systems of the body, including cardiovascular [2], [15]. Therefore, it is important to know the risk factors for DDI and to find an effective treatment for the patient taking into account their CVD risk factors, lifestyle, and comorbidities, such as hypertension, hyperlipidaemia, and hyperglycaemia [2], [15].

Research and clinical investigations have improved the knowledge of CVD pharmacogenomics and microarrays, which have shown that dosing drugs at specific times, such as during wakefulness or sleep, not only affects their pharmacokinetics and pharmacodynamics but also affects DDI events [14]. Patients with an average age of 65 (n=698) who were taking CVD medications used an average of six different medications, with 98.1% using five or more, 39.9% using ten or more, and 6.2% using 15 or more [14]. In addition, the effect and absorption of many CVD drugs are affected by waking time,

lifestyle, and comorbidities [2]. To minimize the risk of DDI, it is important to adhere to recommended guidelines and take into consideration provided information when administering medications [15]. Teaching patients to recognize DDI can also improve their compliance with medication regimens.

2.3 Clinical decision support systems

2.3.1 Main outcomes and drawbacks

The family physician's handbook highlights that studies have demonstrated a significant variation among physicians in the assessment of probabilities and the utilization of information [17]. Physicians are not always able to accurately estimate and predict probabilities. In contrast, CDSS can be more effective than clinical assessment by offering DDI information along with a comprehensive anamnesis and clinical examination [17].

CDSS that are embedded into electronic health-record systems have been shown to improve physicians ability to detect and manage DDIs [18]. However, to ensure the effectiveness of such systems, it is crucial that they provide high-quality, accurate, and clinically relevant information presented in a premeditated way [19]. Therefore, CDSS that offer carefully sorted, structured, and evaluated information on DDIs and clinically-based recommendations would help improve prescribing performance [18].

While CDSS have the potential to improve the ability of physicians to detect clinically significant DDIs, they are not fail-safe [3]. CDSS can fail to reduce DDIs if physicians do not follow or use the alerts [4]. Often missing important interactions, leading to fatigue and dismissal which contributes to the inconsistency of the database [3]. Common problems with CDSS include a poor signal to noise ratio and many false positive alerts, which can cause alert fatigue and display irrelevant alerts [4]. Moreover, software programs that evaluate only two drug profiles at a time cannot assess multidrug combinations, leaving physicians with incomplete information to manage DDIs in patients with polypharmacy [3]. Lack of understanding of the alerts importance can also be a problem [4].

According to a systematic review by Poly et alles, current CDSS generates alerts that are frequently overridden by physicians, with override rates ranging from 56.3% to 95.6%

for DDI alerts [20]. One way to improve the accuracy of DDI alerts is by using coded override reasons, but many systems use the same list of reasons for all categories of medication alerting, leading to inaccurate overrides [19]. A retrospective cohort study conducted in New York City on primary care physicians revealed that DDI alert override rates were not associated with general workload, but rather with the increased number of repeated reminders for the same patients and overall complexity of patient diseases [21]. On average, primary care physicians received one-quarter of DDI alerts, and one-third of the alerts were repeats for the same patient within the same year [21]. Despite the potential benefits of CDSS, a high number of alerts can affect physicians mental state and consume too much time, leading to the override of both significant and clinically irrelevant alerts [20]. Ancker et alles concluded that physicians find it challenging to identify relevant information in the large quantity of irrelevant information [21]. To address this issue, organizations and CDSS vendors should investigate the overriding reasons for DDI alerts and improve the options available to users [19]. Wright et alles conducted studies and found that when mandatory free-text reasons are required, users often enter space or random characters to move to the next step of prescribing the medicine [19]. However, optimizing the types and frequencies of alerts based on clinical context can improve their relevance and reduce alert fatigue, ultimately enhancing patient safety [20].

Table 1 provides an overview of the main override reasons for DDI alerts [19].

Table 1. Overview of main override reasons for DDI alerts.

Categories of DDI reason	**Examples**
Will monitor or take precaution	Will monitor patient for DDI; interaction noted; aware of interaction
Not clinically significant	Not clinically significant DDI, this alert is not useful; inaccurate alert
Benefit overweight's risk	Potential benefit overweighs the risk; no good alternative
Patient tolerated previously	Patient tolerated before; current therapy
Dose adjusted	Dosage adjusted; dosing intervals adjusted; have or will adjust dose
Not related to DDIs	New active cases in same unit; expect improved renal function; clearance wrong due wrong length; irrelevant to patient
Not ordering a medication	Entering historical medication; patient expired
Alert is not the recipient's responsibility	Treatment plan requirement; defer to primary physician;
Agreement, though alert was overwritten	Ordering this but will stop other drug; consultation with pharmacist
Order is urgent	Deferring to other priorities; emergency
Error in data	Error in data

2.3.2 Strategies to mitigate system fatigue

Study in the Netherlands, in primary care settings were conducted to determine which events need DDI (re)assessment and whether CDSS can affect the event [22]. There were 49,9% of polypharmacy when prescribing medicine, of which 61,6% had DDI alerts. CDSS should provide recommendations for specific management, to support physician [22]. For example, when first prescribing the drug, CDSS should guide to monitoring,

second time guide to evaluate the DDI effect. However, CDSS should not result in one-size-fits-all protocol, it should take into account the situation and preferences of individual [22].

Secondly, CDSS should offer the possibility to manually overrule the settings [22]. Alerts can be different, taking into account individual patient. DDI alerts are a tool to help and to detect problems but cannot replace physicians assessment. By changing the alert generation, the top 10 drug pairs, DDI alerts were decreased by 28,3% [22].

Several strategies to optimize alert burden have been evaluated and is supported by pre-post study contacted in university hospital in Brussels, Belgium by Muylle et alles [23]. They found out that DDI screening in CDSS is often too sensitive, generating a high alarm burden and low specificity alerts, leaded to alert fatigue and high override rates [23]. Physicians override both clinically significant and irrelevant alerts, compromising the goal of patient safety [23]. The improvement of alert burden changed when alerts changed to more patient-specific, taking into account the characteristics of the patient and the results of laboratory tests [23]. The design of highly serious and serious alerts was changed, the recommendations presented were more distinguishable. Highly serious alerts suggested an absolute contraindication, while serious alert often suggested a relative contraindication or patient monitoring. Overriding highly serious alerts was more difficult, where the reason for the override had to be written out with password conformation to continue the recipe. By adjusting the alert severity classification, the proportion of very serious alerts decreased from 92% to 38.4% [23].

Poly et al. recommended improving CDSS by incorporating patient-specific factors into dose recommendation alerts, optimizing alert types and frequencies, reducing alert fatigue, categorizing frequent alerts, providing clear and concise information, reviewing override reasons, identifying malfunctions and failure patterns, removing repetitive alerts, using hard-stop alerts, refining alerts based on clinical relevance, encouraging reasons for cancellation, forming a multidisciplinary planning committee, and integrating with various departmental data. [20].

By conducting a literature review, Table 2 illustrates common strategies for reducing medication errors using CDSS.

Table 2. Benefits of CDSS, possible harm, and mitigation strategies.

	Potential harm of CDSS	**Solution(s) to mitigate harm, Explanation of solution(s)**
Patient Safety Preventing medication and prescription errors and side effects [24].	**Alert fatigue** [24]. Information overload can cause providers to ignore even important alerts or CDSS recommendations [24].	Prioritizing critical alerts while minimizing nuisance alerts for non-critical indications **Explanation:** Prioritize critical alerts and personalize them to specific specialties and severities to prevent alert fatigue [24], [23], [20], [22]. DDI software should include concomitant medications, lab values, demographics, and administration times for accuracy [24], [22].
Management	**Negative impact on user skills** [24]**.**	**Explanation:** Systems must be physician-friendly, avoiding being too prescriptive or restrictive, with ongoing performance analysis to identify accuracy issues and design changes if needed [24], [20], [22].
	System and content maintenance challenges [24]**.**	**Explanation:** Implement regular reviews, streamline knowledge acquisition, gather physician feedback, educate users on data entry, monitor performance and usage changes, and ensure repository data quality [24], [20].
	User distrust of CDSS [24]**.**	**Explanation**: Provide users with verifiable sources for recommendations to increase trust and knowledge [24], [20].

2.4 Estonian drug-drug interaction system

From June 2016, an e-service for DDI is available to all physicians in outpatient settings, consisting of automatic reminders in the user information system [9]. The database has been developed in cooperation between the clinical pharmacologist of the Swedish Karolinska Institute and the Finnish University of Turu Central Hospital and has been in clinical use in Finland and Sweden for over ten years [18]. The database is updated four times a year [25].

In order for physicians to be able to better assess the interactions of the drugs used by the patient and to improve the quality of treatment, all drug prescribers have been enabled to use the free DDI evaluation database SFINX-PHARAO [9]. Since 2017, the new name of the SFINX interaction database is INXBASE. The name change was suggested to expand the international distribution of the datasets [25]. Alerts about the risks of all possible and theoretical drug combinations are not helpful to clinicians who have to treat patients with more than one symptom or disease [18]. The main purpose of INXBASE is to include well-established and documented interaction risks and theoretical risks if they are considered clinically significant [9]. Consequently, the aim is to provide brief and practical recommendations for dealing with each possible DDI [18]. Therefore, structured texts have been created in the alerts, which provide information about the consequence of the DDI, recommendation, mechanism of interaction and the background of scientific source [18].

The database is connected to the digital prescription [26]. At the moment of prescribing the drug, the system checks the patient's prescriptions and gives an automatic notification to the physicians in the event of significant interactions [26]. The database finds combinations in patients' regimens that may result in potential interactions, and also provides guidance on how to adjust the regimen if necessary [26], [17]. Sometimes it is necessary to replace the drug with another drug, but often it is enough to adjust the dose [17].

The interaction request is submitted by the healthcare facility to the prescription centre as soon as the physicians has selected the active ingredients or preparation code or drug from of the new prescription [27]. DDI alerts are displayed with pair of interacting drugs and according to the classification of clinical significance and documentation, starting with

the most important interaction (order: D4, D3, D2, D1, D0, C4, C3, C2, C1, C0) [18], [27] and are listed on Table 3.

Table 3. Classification categories in INXBASE for clinically significant (C-D) and level of documentation.

Classification	Definition
C	Clinically significant interaction that can be handled e.g., by dose adjustments [18]
D	Clinically significant interaction. The combination is best avoided [18]
0	Data derived from extrapolation on the basis of studies with similar drugs [18]
1	Data derived from incomplete case reports and/or in vitro studies [18]
2	Data derived from well-documented case reports [18]
3	Data derived from studies among healthy volunteers and/or pilot studies among patients [18]
4	Data derived from controlled studies in relevant patient populations [18]

The clinically significant classifications must be colour distinguishable, with the D level classification shown in red and the C level classification in yellow [28]. Only class C and D interactions are automatically displayed [28]. If the data of the prescription to be approved is related to a level C or D interaction, the physicians can approve the prescription if they confirm that they are aware of the interactions [28].

The interaction alert of bought-out prescriptions is calculated according to the length of the treatment course: a fixed number of days or 90+ days by default for drugs that are used when necessary/consistently [27]. When purchasing a repeat prescription, calculations are made only according to the first prescription purchased [27].

3 Methods

Analysis to assess the DDI alert system in Estonia were carried out using the Estonian Health Insurance Fund (EHIF), prescription centre database. This paragraph is divided into subsections to address study design, data from prescription centre and semi-structured interviews. Subsections that give overview of study design, data collection and about ethical considerations.

3.1 Research design

The research question for this study is to investigate how the CDSS have effect on DDI rates overall and in CVD in primary health care settings during a five-year period, using a pragmatism worldview. Pragmatism places an emphasis on problem-solving and practical applications, rather than on methods [29]. It employs a variety of approaches to gain a deeper understanding of the problem at hand [29]. The study is a retrospective mixed method approach, which combines qualitative and quantitative data to gain greater validity and provide a more comprehensive picture of the research topic.

The benefits of using mixed methods in this study are to gain more complete and comprehensive insights into the research question, and to provide a greater repertoire of tools to meet the study's aims and objectives [30], [29]. To obtain quantitative results, interactions were analysed for DDI in C-D category pairs in general and later for CVD drug pairs across five years. From the quantitative results, author can see the frequency of prescription of drugs with DDI and the change over time, but there is no data on whether prescription changes have been made due to an DDI alert. The qualitative study was conducted to improve the validation of the research questions and provide further clarity to the findings. Semi-structured interviews were used as a research method to gather information from a small sample size, to explore personal experiences, attitudes, and perceptions related to the research topic [31].

The study used thematic analysis to analyze the semi-structured interviews. Thematic analysis is a method well-suited for identifying patterns and generating insightful findings, tailored to the research question [32]. The quantitative results analysed the frequency of prescription of drugs with DDI and changes over time, while semi-structured interviews helped to validate study findings and provide deeper insights. The mixed

method in this study aimed to generate understanding through different perspectives and stances and to look for answers to the research question regarding the effect of the DDI alert system in Estonia.

3.1.1 Prescription centre data

The aim of this quantitative analysis is to evaluate the impact of the CDSS on drug interactions in the category C-D drugs prescribed in family medicine. The CDSS has been available since the summer of 2016, and the analysis period selected for this study is 2017-2022, covering the first full year when the system was in use. Two previous studies have already investigated the DDI alert system in family medicine [10], [11], which provide relevant input to this study. By analysing the data, author of this study can compare results with previous research and determine whether a three-month data analysis is sufficient or a longer period is necessary to evaluate the impact of the alert system.

To conduct the analysis, the author requested data from EHIF on January 9, 2023. However, on February 8, 2023, EHIF reported a technical problem with the 2018 data in the database. As a result, the author excluded 2018 data from the analysis. On February 10, the prescription centre data arrived in Excel format, but it was found to be incomplete. The author contacted EHIF on February 11 and received the missing data on February 13.

In order to ensure the reliability of the data, EHIF was asked to present the data in a structured form, highlighting separately the drugs used to treat cardiovascular diseases identified by the International Classification of Diseases (I10-I89). The request for data was as follows:

- Prescriptions for drugs with prescribed and realized status by physician's specialty and the number of prescriptions prescribed with all interactions (strength of interaction C0-D4). i.e., that one data row = speciality, strength of interaction, more precisely interaction (C0-D4), persons, number of unique prescriptions, number of all prescriptions with interaction.
    - In addition, similar data request for drugs with cardiovascular diseases
- Prescriptions of prescribed and realized status medicines by age group and in the specialty of family medicine (E300). i.e., that one data row = age group (in

increments of 5 years, i.e., 0-4 years; 5-9 years, etc.), interaction more precisely, number of unique recipes, number of all recipes with interaction
    - In addition, similar data request for drugs with cardiovascular diseases
- Prescriptions of drugs with the top 10 prescribed and realized status by family physicians in the specialty of family medicine (E300). i.e., that the first column presents the TOP10 list, data row = in non-personalized form, e.g., family physician nr1, persons, number of unique prescriptions, number of prescriptions with all interactions
    - In addition, similar data request for drugs with cardiovascular diseases
- Pairs of interactions (C0-D4), prescriptions of drugs with prescribed and realized status in the specialty of family medicine (E300). i.e., data row = interaction more precisely (C0-D4), active substance, persons, number of unique prescriptions, number of prescriptions with all interactions.
    - We know, at this point, that the interaction is considered a unique recipe in addition to the recipe that creates the interaction, we would like to get the data regardless of what is unique or what is the recipe on which the interaction occurs, given that the interaction pair is still one.
    - In addition, similar data request for drugs with cardiovascular diseases.
- Cancellation, total number of cancelled prescriptions with reason for cancellation. i.e., data line = reason for cancellation, number of prescriptions
    - In addition, similar data request in the specialty of family medicine (E300).
    - In addition, similar data request regarding drugs with cardiovascular diseases in the specialty of family medicine (E300).

Data management

Data analysis was conducted using Microsoft Excel's Pivot Table feature. The structured data allowed for data analysis using various filters, including period, strength of interaction, active substance pairs, number of patients, number of prescriptions, and total number of prescriptions with interactions. The study utilized full calendar years (period), specifically 2017, 2019, 2020, 2021, and 2022.

To determine the top 10 specialties, each year was filtered separately. The results were then filtered to show the top 10 values, and a separate table was created to display the top

5 specialties. From 2017-2019, rheumatology was consistently in the top 5, but it dropped out in 2020. Therefore, to provide a more comprehensive overview of prescribing frequency per specialty compared to family medicine, the decision was made to include the top 6 specialties in the research.

To conduct the C-D category drugs prescribing analysis, filters were applied to examine category C and D drugs separately, as well as by period and strength of interaction. The interaction strengths for C0, C1, C2, C3, C4 and D0, D1, D2, D3, D4 were then filtered separately. The results were compiled into a single table, which offers a comprehensive overview of drug prescribing patterns. Using the results from the filtered category C and D drug prescriptions for each period, a figure was created that included the r-squared value to indicate the trend line outcome.

The top 10 active ingredient pairs were analysed using a periodic filter and a top 10 filter based on the number of prescriptions with all interactions. This yielded the most frequently prescribed interaction pairs. Using these periodic results, a separate table was created to display the top 10 prescribed drug pairs, with each drug pair compiled into a single row and the total number of prescriptions noted in columns for each period. A figure was then generated to illustrate the number of prescriptions for each drug pair in each period.

To analyze changes in clinically significant interaction classification over time, we considered all years as the study period. Drug pairs were organized in rows, with columns representing interaction categories for each year. The number of columns was counted for each interaction category, and any change in the column count indicated a change in the interaction category. To verify the changes, original data were reviewed to determine the exact year when the change occurred for each drug pair. Based on this information, table were created that included the study period, the strength of the interaction, and the amount of the prescriptions.

The age group data was filtered by period to obtain the total number of prescriptions with interactions per age group. Using this data, a table was created and used to generate a chart that shows the rate of drug interactions by age group. To calculate the assumed average amount of drugs prescribed per age group, the total number of prescriptions with interactions was divided by the number of unique prescriptions. Unique prescriptions

were counted only once, based on EHIF's definition, even if the physician provided three prescriptions at once. The resulting value represents the estimated average amount of drugs prescribed per age group, based on the registered interactions.

To analyze cancellations, periodic filtering was applied to compare all cancelled drugs with drugs cancelled in the family medicine specialty. From the filtering results, a table were prepared to compare the number of cancelled prescriptions in each period for all drugs and for drugs prescribed by family physicians.

3.1.2 Interviews

The purpose of the interviews with family physicians was to collect information about acceptability and usability with the Estonian DDI alert system based on a literature review in an individual semi-structured interview. The interview consisted of 10 questions (Appendix 2). The interview guide was developed following DeJonckheere et alles recommendations, and included a set of open, neutral, and clear guiding questions, complemented by follow-up and probing questions that were tailored to each participant's responses [33].

On February 27, the author wrote to Family Physician Association of Estonia to send out an e-mail inviting family physicians to participate in the study. The invitation to the study was accompanied by a cover letter (Appendix 3). The cover letter introduced the study and the author, provided information that the survey was coordinated with the ethics committee, and participation was voluntary and anonymous. To streamline study participation, the author utilized the Calendly platform to offer a registration option. The platform featured available time slots that were convenient for potential participants, and required an email address to complete the registration process.

The criteria for including family physicians in the sample were:

- The participant uses the software where the DDI alert system is implemented
- The participant agreed to participate in the study

The semi-structured interview questions were formulated and validated based on a research conducted in 2018, which examined CDSS satisfaction, use, and system efficiency from family physicians [10]. The questions were refined after the first

interview to receive feedback and improve wording, ensuring that the same meaning issues were removed.

Data management

Interviews were conducted with 7 family physicians by the author in March 2023.

Face-to-face interviews were conducted in Estonian with family physicians using a semi-structured format. The interviews lasted on average 30 minutes, and all participants were asked the same questions, which could lead to additional follow-up questions. The interviews were audio-recorded in the Teams environment.

The audio recordings of the interviews were transcribed using a web-based speech recognition program developed by the Phonetics and Speech Technology Laboratory of the Cybernetics Institute at Tallinn University of Technology [34] and following the steps described by Braun and Clark [32].

The resulting text data were analysed using thematic analysis. This involved developing a categorization based on the research questions. The categorization involved identifying patterns with the data, and interpreting the responses to draw conclusions related to the research questions. The analysis process included several rounds of revision to ensure the reliability and validity of the findings. Ethical considerations were taken into account throughout the study, including obtaining informed consent from participants and ensuring confidentiality and anonymity of the data.

3.2 Ethical considerations

Considering that the research uses health data, although it is in a depersonalised form, the author requested permission from the Research Ethics Committee of the National Institute for Health Development to carry out the research.

In a quantitative study, data processing is carried out without personal data. The data is sent from the EHIF to the email address of the author. The data contains information: date; physicians specialty; prescribed prescription drugs; prescription drugs that interact; DDI classifications. The study does not use personalised data where there is no risk of breach of confidentiality.

The participants in the qualitative study provided verbal consent at the start of the interview. Personal information was excluded from the interview recordings. The email used to recruit participants included details about the research purpose, data usage, and the author conducting the study. The author is available to address any questions or concerns raised by the participants.

This study was given approval by the Research Ethics Committee of the National Institute for Health Development on November 1, 2022 (Appendix 4).

4 Results

This chapter presents the findings of the study, which involved an analysis of prescription centre data and semi-structured interviews. The data analysis focused on prescriptions of C-D category drug pairs by family physicians, while the semi-structured interviews gathered feedback from family physicians regarding the acceptability and usability of the CDSS. The results of both the data analysis and the interviews are discussed in this chapter.

4.1 Prescription centre data

From 2017 to 2019-2022, the Prescription Centre recorded 52,647,151 fulfilled prescription orders, excluding data from 2018 due to a database issue with EHIF. Of those fulfilled prescriptions, 36,978,995 were issued in family medicine, with 13,547,237 containing CVD drugs.

The study examines DDIs prescribed in the field of family medicine. To understand how category C-D interacting prescriptions are prescribed across different specialties, the study analysed data from 59 specialties, including nurses, midwives, family nurses with additional prescription rights, and physicians with unspecified specialties. Figure 1 displays the average results for the top 6 specialties over a 5-year period, focusing on the proportion of prescription renewals by family physicians, which is why this sample was chosen for the research.

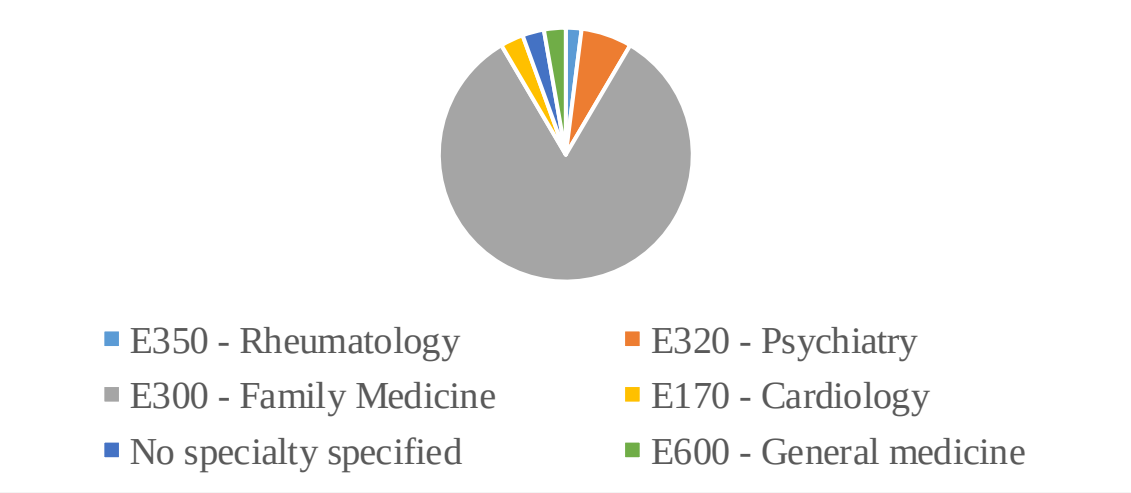

Figure 1. Prescribing DDI prescriptions, 5 years average, speciality top 6.

Table 4 displays total prescriptions in family medicine with C-D category interactions. Data is presented in millions (10^6).

Table 4. Prescriptions with issued in family medicine.

	2017		2019		2020		2021		2022	
Total prescriptions (E300)	**7,06**	**100%**	**7,41**	**100%**	**7,47**	**100%**	**7,55**	**100%**	**7,49**	**100%**
of which all C-D interactions	2,47	35,00%	2,38	32,10%	2,10	28,10%	2,30	30,40%	2,43	32,50%
of which all CVD C-D interactions	1,11	45,00%	1,03	43,50%	0,88	42,00%	0,91	39,80%	0,90	36,90%
All C-D interactions	**2,47**	**100%**	**2,38**	**100%**	**2,10**	**100%**	**2,30**	**100%**	**2,43**	**100%**
of which all C interactions	2,21	89,50%	2,18	91,60%	1,96	93,10%	2,16	94,10%	2,29	94,30%
of which all D interactions	0,26	10,50%	0,20	8,40%	0,15	6,90%	0,13	5,90%	0,14	5,70%
C - C0	1,24	50,20%	1,15	48,50%	1,06	50,20%	1,22	53,30%	1,29	53,20%
C - C1	0,06	2,50%	0,08	3,30%	0,07	3,40%	0,07	3,10%	0,08	3,10%
C - C2	0,09	3,80%	0,08	3,40%	0,07	3,10%	0,06	2,70%	0,06	2,60%
C - C3	0,39	15,70%	0,46	19,50%	0,41	19,60%	0,41	17,70%	0,41	16,90%
C - C4	0,43	17,30%	0,40	16,80%	0,35	16,70%	0,40	17,30%	0,45	18,50%
D - D0	0,09	3,60%	0,12	5,20%	0,09	4,10%	0,08	3,60%	0,09	3,70%
D - D1	0,01	0,50%	0,01	0,40%	0,01	0,40%	0,01	0,30%	0,01	0,30%
D - D2	0,01	0,50%	0,01	0,30%	0,01	0,30%	0,00	0,20%	0,01	0,20%
D - D3	0,11	4,40%	0,04	1,60%	0,03	1,50%	0,03	1,20%	0,03	1,10%
D - D4	0,04	1,40%	0,02	0,80%	0,01	0,60%	0,01	0,50%	0,01	0,40%
All CVD C-D interactions	**1,11**	**100%**	**1,03**	**100%**	**0,88**	**100%**	**0,91**	**100%**	**0,90**	**100%**
All CVD C interactions	0,95	85,50%	0,94	90,40%	0,82	93,30%	0,86	94,30%	0,85	94,70%
All CVD D interactions	0,16	14,50%	0,10	9,60%	0,06	6,70%	0,05	5,70%	0,05	5,30%
C - C0	0,50	45,20%	0,45	43,70%	0,41	47,00%	0,47	51,60%	0,47	52,00%
C - C1	0,02	2,00%	0,03	3,00%	0,03	3,10%	0,03	2,80%	0,03	2,80%
C - C2	0,06	5,80%	0,05	4,50%	0,03	3,80%	0,03	3,30%	0,03	2,80%
C - C3	0,14	12,40%	0,18	17,50%	0,15	16,90%	0,14	15,70%	0,14	15,90%
C - C4	0,22	20,10%	0,23	21,80%	0,20	22,50%	0,19	20,90%	0,19	21,20%
D - D0	0,04	3,50%	0,06	5,90%	0,03	3,40%	0,03	3,00%	0,03	2,90%
D - D1	0,01	0,60%	0,00	0,50%	0,00	0,50%	0,00	0,40%	0,00	0,40%
D - D2	0,00	0,30%	0,00	0,20%	0,00	0,10%	0,00	0,10%	0,00	0,10%
D - D3	0,10	8,60%	0,02	2,20%	0,02	2,10%	0,01	1,60%	0,01	1,40%
D - D4	0,02	1,50%	0,01	0,80%	0,01	0,60%	0,00	0,50%	0,00	0,40%

Table 4 provides an overview that the average number of prescriptions in consistent over the years, except for 2017, which had fewer prescriptions but more interaction alerts. The middle part of the table shows all C-D category interactions, with separate interaction classifications. Category D interactions decreased by 45,8% in five years. C category drug pairs remain constant over the years with a small increase by 5,09%. Category C-D prescriptions remain steady (average 31,67%). The bottom part of the table shows CVD category interactions with a decrease in D category interactions by 63,45% and with increase in C category interactions by 9,71%.

On a little more detailed approach C-D category drugs pairs are analysed with a trend line. Figure 3 shows an overview of the results of all C-D category drug pairs.

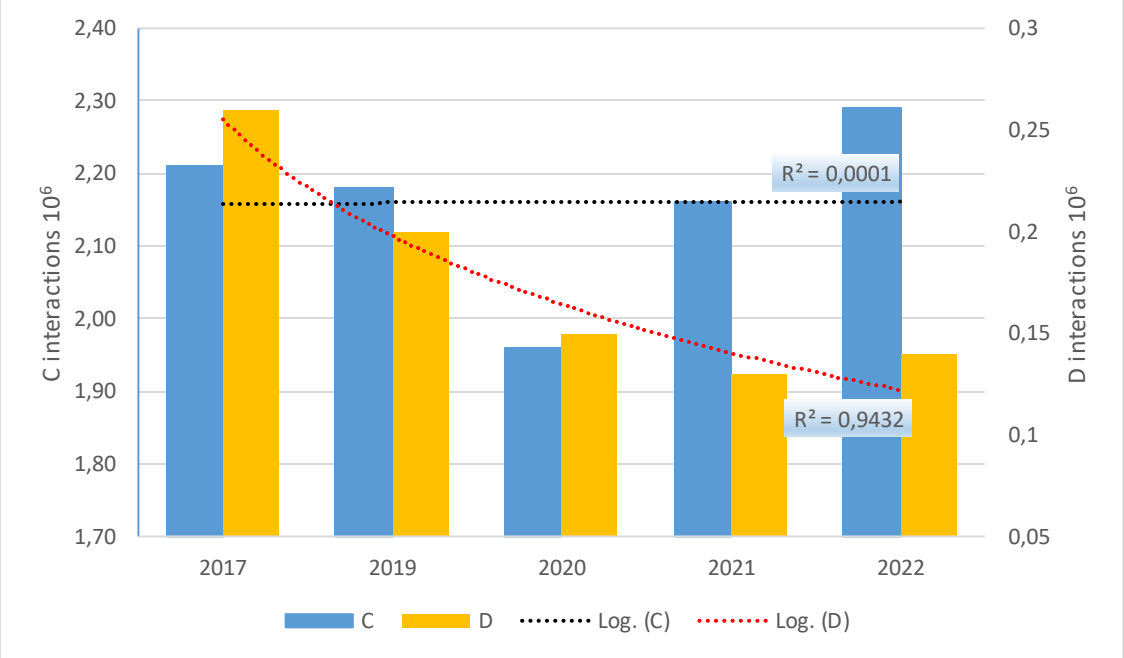

Figure 2. C-D category trendline.

Figure 3 reveals a decreasing trend of DDIs over the period from 2017-2022 When examining the trend lines for C and D category DDIs, there are differences in the strength of the correlation between the two categories. A correlation coefficient of +0.0001 for the C category suggests that there is no significant correlation between the variables, while a coefficient of -0.9432 for the D category indicates a strong negative correlation between the variables. This suggests that the use of the CDSS system has had a significant impact on reducing DDI rates for the D category drugs, but not for the C category drugs.

Figure 4 provides an overview of the trend line for the CVD C-D category drug pairs.

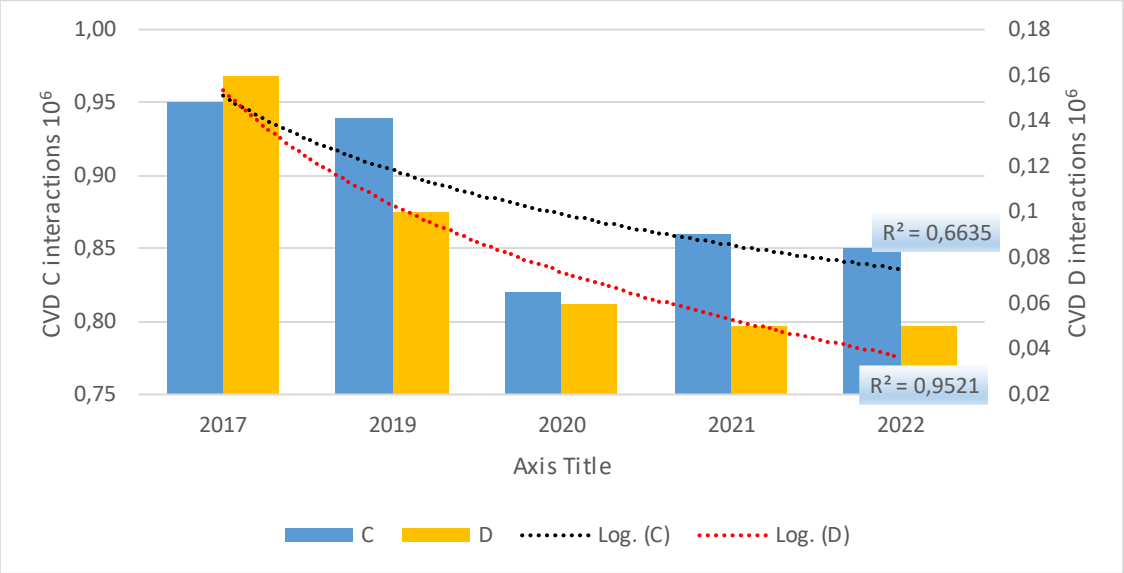

Figure 3. CVD C-D category trendline.

Figure 4 reveals a decreasing trend of CVD DDIs over the period from 2017-2022. In terms of CVD prescriptions, a correlation coefficient of -0.6635 for the C category and -0.9521 for the D category suggests a significant negative correlation between the variables, indicating that the use of the CDSS system has had a significant impact on reducing DDI rates for CVD prescriptions, particularly for the D category drugs. However, the impact on reducing DDI rates for C category drugs appears to be less significant.

To gain a better understanding of which age groups are most at risk for DDI, next was analysed the proportion of C-D and CVD interactions compared to all prescriptions issued in different age groups and are shown on Figure 5.

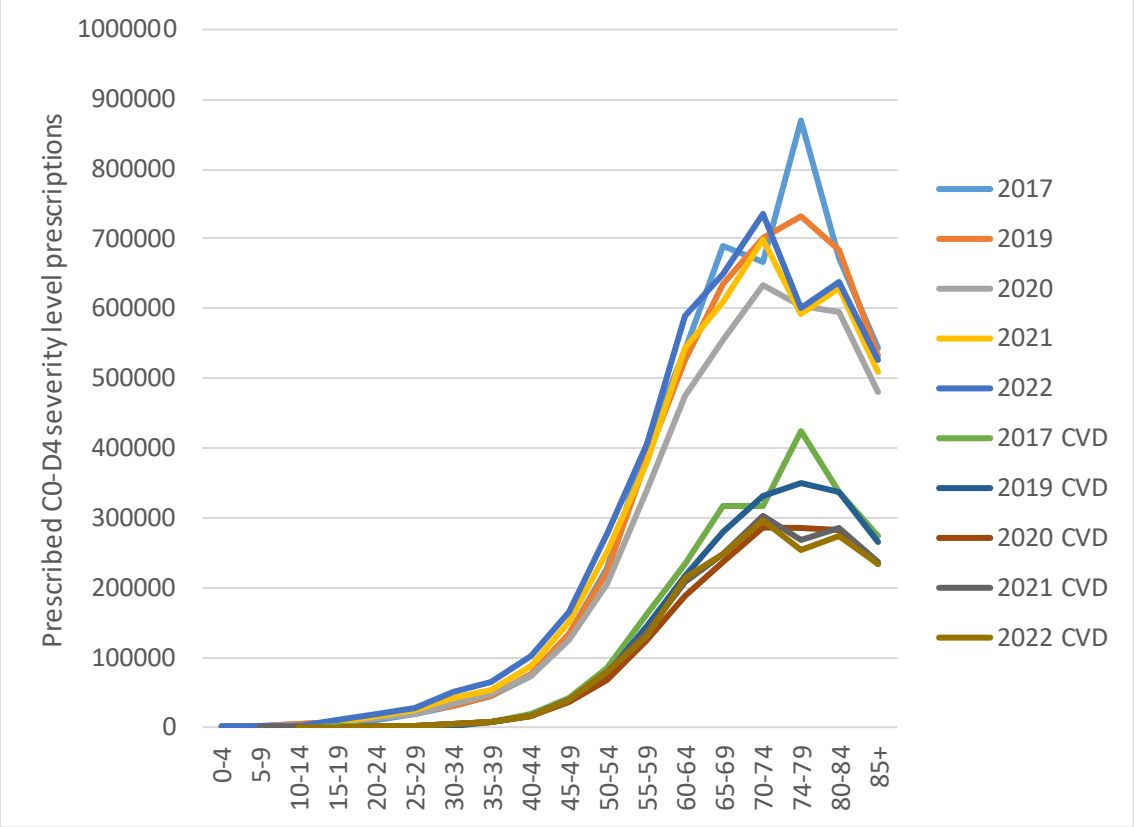

Figure 4. Number of C0-D4 severity level prescriptions according to age groups.

Figure 5 displays the results, which indicate that older patients are at a higher risk of receiving a prescription with a clinically significant interaction, particularly those aged 70-84. However, the risk starts to increase already at age 50. The proportion of interacting drugs prescribed by age is similar for all C-D and CVD interacting drugs.

Table 5 provides an estimated average number of medications taken by age group, based on the number of drug interactions in each group.

Table 5. Overview of how many medications patient takes on average by age group.

	2017	**2019**	**2020**	**2021**	**2022**
50-54	7,01	7,37	7,02	7,20	7,12
55-59	7,62	8,00	7,56	7,68	7,63
60-64	8,43	8,64	8,13	8,21	8,09
65-69	9,18	9,24	8,70	8,67	8,49
70-74	9,76	10,02	9,32	9,25	9,06
74-79	10,24	10,49	9,86	9,79	9,44
80-84	10,43	10,62	9,85	10,05	9,79
	2017 CVD	**2019 CVD**	**2020 CVD**	**2021 CVD**	**2022 CVD**
50-54	6,42	6,76	6,28	6,27	5,83
55-59	6,64	6,99	6,72	6,68	6,18
60-64	7,28	7,57	6,93	7,01	6,61
65-69	7,65	7,84	7,33	7,24	6,83
70-74	7,96	8,41	7,65	7,60	7,14
74-79	8,11	8,45	7,95	7,86	7,32
80-84	8,17	8,40	7,75	7,82	7,41

The data only includes drugs with C-D category interactions, so the actual number of medications taken may be higher. Patients aged 50-84 who are prescribed C-D category drugs take an average of eight interacting drugs, while those prescribed CVD C-D interacting drugs take an average of seven. As CVD risk and treatment are more common in the elderly, CVD drugs are likely to be involved in all category C-D interactions.

To gain further insight, the drug pairs were analysed in changes over a period of five years. Figure 6 displays all category C prescriptions, while Figure 7 shows all CVD category C prescriptions. Similarly, Figures 8 and 9 illustrate all category D and CVD category D prescriptions. The top 10 drug pairs of each year were considered. Although the main drug pairs remain relatively stable from year to year, visible changes can be observed.

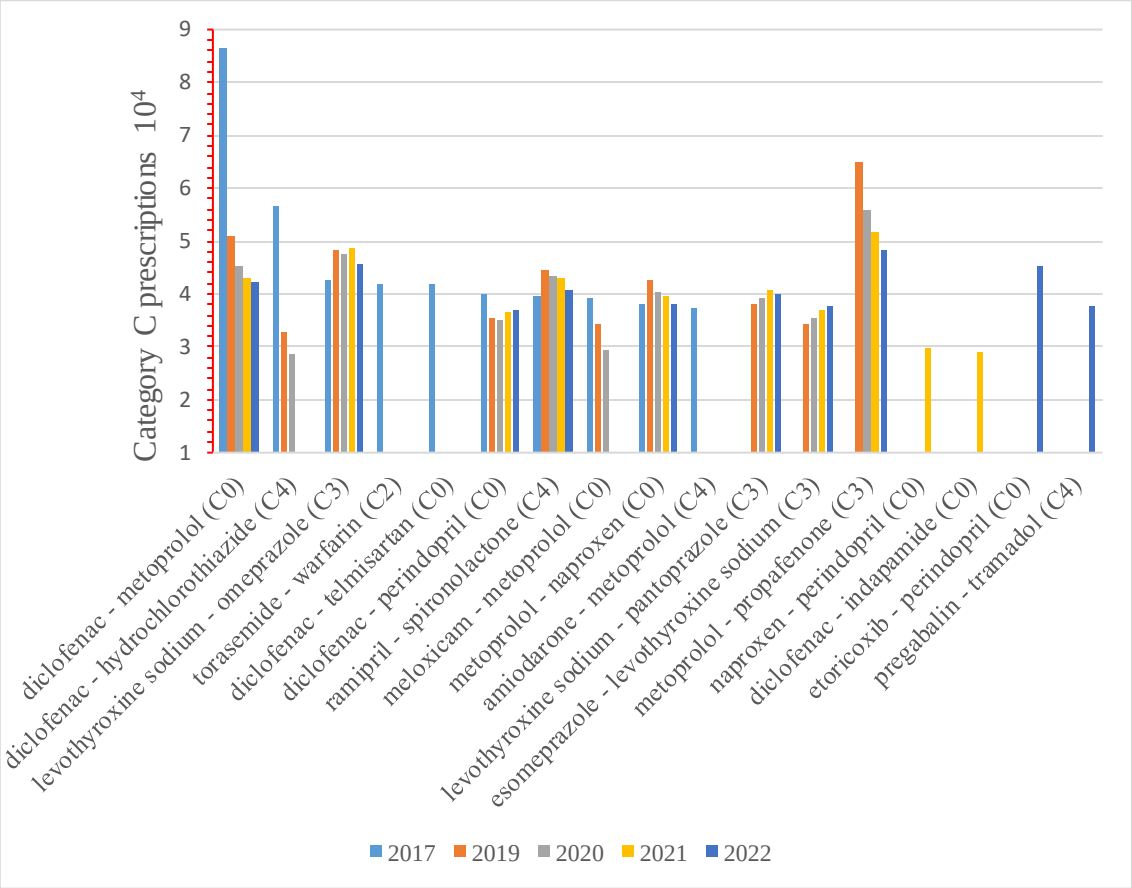

Figure 5. Significance level C top 10 drug DDIs (all prescriptions).

Figure 6 shows the top 10 drug pairs with a significance level of C, and is presented in ten thousands (10^4), which have remained largely stable over the years 2017, 2021, and 2022. For example, "diclofenac and metoprolol" was the most frequently prescribed drug pair in 2017 and has remained stable in relation to other drug pairs since 2019, with a 41.2% decrease. "Metoprolol and propafenone" has had a 13.4% decrease since 2019. While three drug pairs dropped out of the top 10, new pairs appeared in 2021-2022. Overall, there have been minimal changes in the drug pairs.

Figure 7 data is presented in ten thousands (10^4), and provides an analysis of CVD drug pairs.

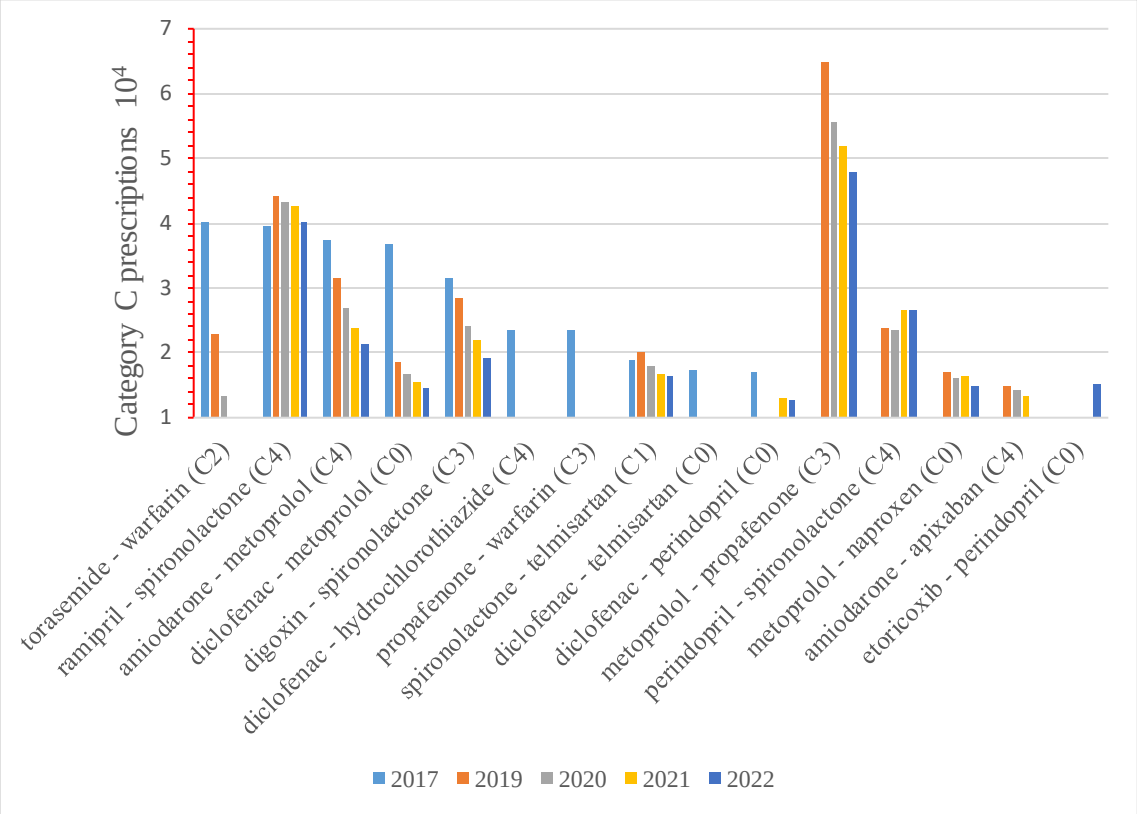

Figure 6. Significance level C top 10 drug-DDIs (CVD prescriptions).

Figure 7 showing that "metoprolol and propafenone" is the most commonly prescribed pair with a significance level C interaction since 2019, downgraded from significance level D in 2017. Despite its high frequency, there has been a notable decrease in its prescription, with a 4.5% decrease in 2019 and a 29.4% decrease in 2022 compared to 2017. Several drug pairs are no longer in the top 10 due to changes in drug regimens. While the overall frequency of drug prescription has remained stable, the occurrence of CVD DDIs has gradually decreased over the years, as reflected in the changing drug pairs.

Figure 8, data is presented in thousand (10^3), displays the top 10 drug pairs with the highest significance level D interactions.

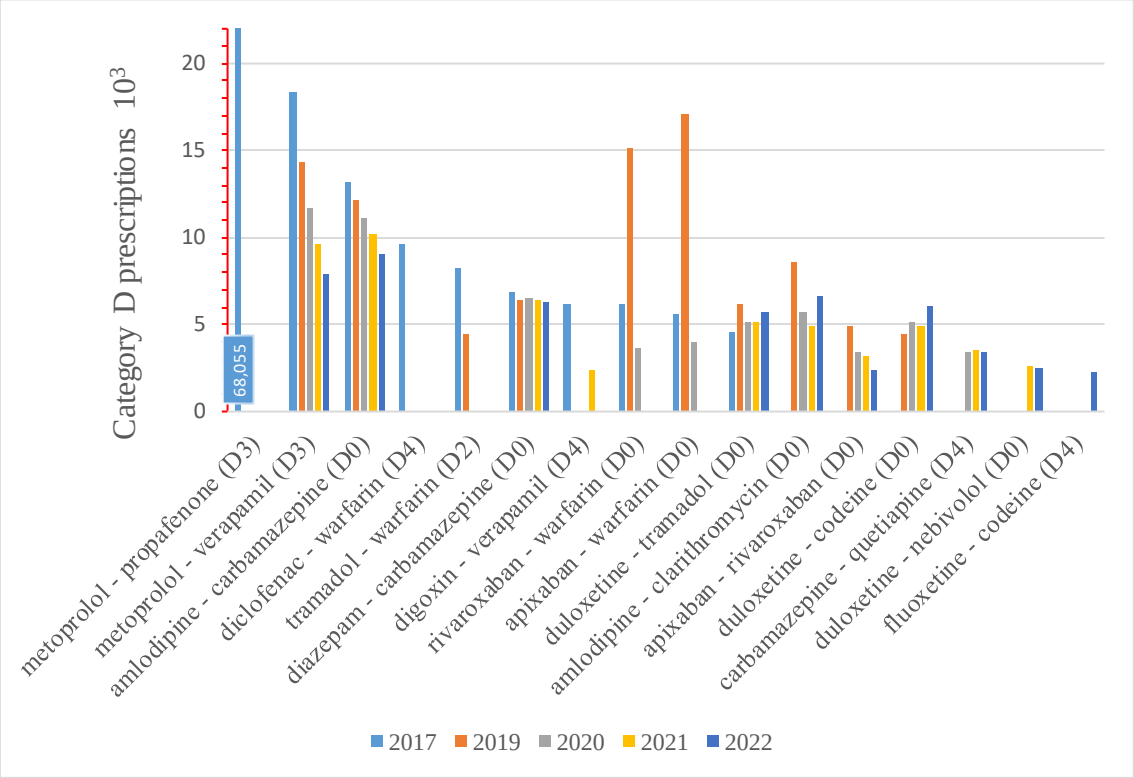

Figure 7. Significance level D top 10 DDIs (all prescriptions).

Figure 8: However, "metoprolol and propafenone," previously in the top 10, has been categorized as a significance level C interaction since 2019 and is now listed in Figure 6. While several drug pairs from 2017 are decreasing in prescription frequency, "diazepam and carbamazepine" remains consistent. In 2019, "rivaroxaban and warfarin" and "apixaban and warfarin" appeared in the top 10, but they have since declined and are no longer present. This may indicate a change in medication where patients were switched to a new treatment without canceling the previous one.

Figure 9 data is presented in thousand (10^3), and displays the top 10 drug pairs with the highest significance level D CVD DDIs.

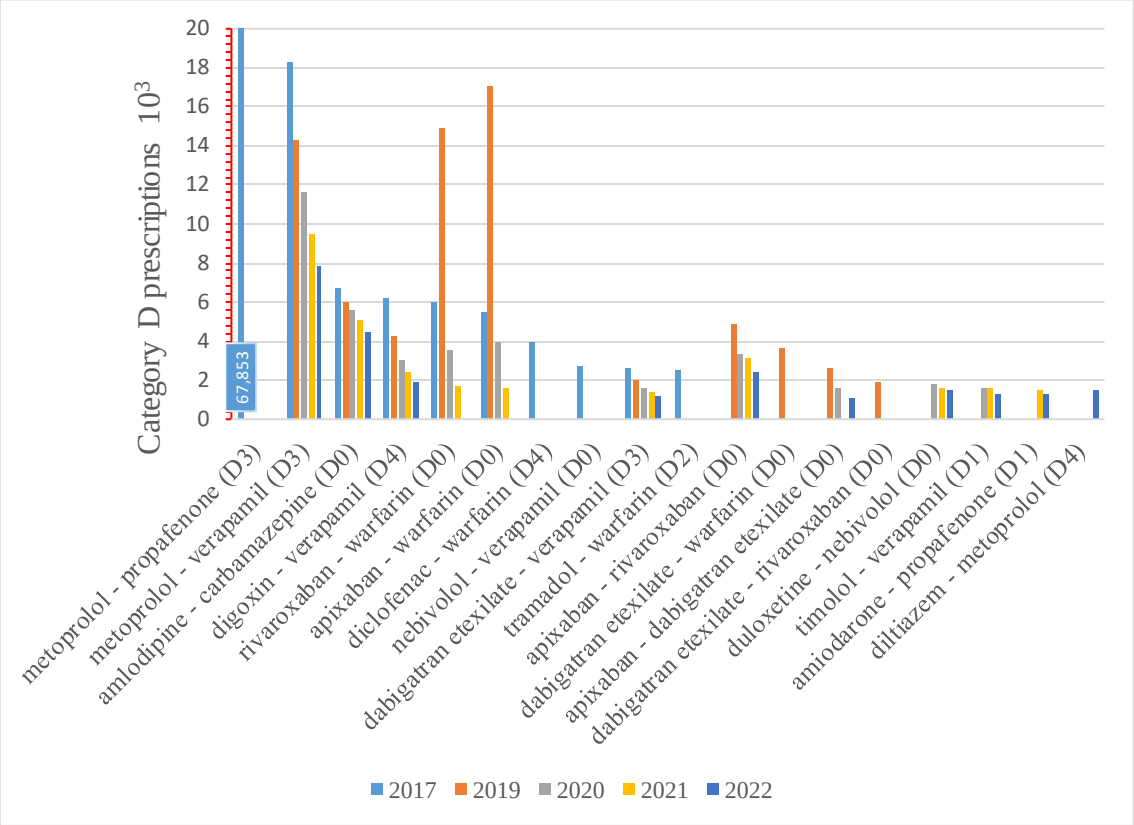

Figure 8. Significance level D top 10 DDI CVD prescriptions.

Figure 9 shows a decreasing trend in the prescription frequency of the top 10 CVD drug pairs, which may be due to the decrease in CVD prescriptions presented in Table 4. It's worth noting that 55% of the top 10 CVD drug pairs for interactions were also present in the top 10 for significance level D interactions. The selection of CVD drug pairs was based on diagnoses and filtered using ICD-10 codes I10-I89, without utilizing the Anatomical Therapeutic Chemical Classification System. The decline in the number of drug pairs in the top 10 suggests that medication regimens are being modified or updated. Moreover, the absence of any new drug pairs in the top 10 could indicate a more informed and cautious approach to prescribing medication.

As the strengths of drug-pair interactions may vary over time, Table 6 presents a comprehensive summary of all such changes.

Table 6. Drug pair interaction changes.

Interaction pair	2017	2019	2020	2021	2022
metoprolol - propafenone	D3 (68 055)	**C3 (65 115)**	C3 (55 712)	C3 (51 896)	C3 (48 180)
amlodipine - clarithromycin	C0 (10 022)	**D0** (8 560)	D0 (5 692)	D0 (4 903)	D0 (6 643)
diazepam - carbamazepine	C3 (239) + D0 (6853)	C3 (190) + D0 (6420)	C3 (100) + D0 (6491)	C3 (41) + D0 (6380)	C3 (47) + D0 (6308)
carbamazepine - tramadol	C3 (2 666)	**D3** (2 276)	D3 (1 838)	D3 (2 178)	D3 (2 050)
clarithromycin - simvastatin	C3 (1 570)	**D3** (992)	D3 (493)	D3 (385)	D3 (425)
apixaban - clarithromycin	D0 (418)	D0 (801)	D0 (630)	**C3 (541) + D0 (210)**	C3 (1 058)
budesonide - fluconazole	**C0** (195) + **D2** (649)	D2 (588)	D2 (626)	D2 (662)	D2 (625)
clarithromycin - triamcinolone	C0 (192)	**C0** (50) + **D0** (151)	C0 (8) + D0 (90)	**D0** (61)	D0 (113)
triamcinolone - verapamil	C0 (233)	**C0** (54)+ **D0** (66)	C0 (39)	**C0** (12) +**D0** (35)	D0 (41)
itraconazole - quetiapine	C0 (112)	C0 (82)	C0 (72)	**C0** (49) + **D0** (59)	D0 (78)
budesonide - itraconazole	**C3** (14) + **D3** (117)	D3 (73)	**C3** (5) + **D3** (96)	D3 (92)	D3 (53)
itraconazole - sildenafil	C0 (60)	C0 (63)	C0 (37)	C0 (63)	**C0** (5) + **D0** (36)
clozapine - ciprofloxacin	C4 (46)	**D2** (36)	D2 (48)	D2 (34)	D2 (34)
itraconazole - triamcinolone	**C0** (7) + **D0** (6)	C0 (33)	C0 (19)	D0 (16)	D0 (5)
carbamazepine - midazolam	C0 (42)	**D3** (23)	D3 (<5)	-	-
dapoxetine - clarithromycin	C0 (29)	C0 (18)	-	-	**D0** (12)
diltiazem - triamcinolone	C0 (16)	**D0** (19)	-	-	D0 (<5)
abiraterone - carbamazepine	C0 (13)		**D0** (15)	D0 (6)	D0 (<5)
tamoxifen - terbinafine	C0 (8)	**D0** (6)	D0 (<5)	D0 (<5)	
eplerenone - clarithromycin	C0 (<5)	-	-	-	**D0** (<5)
quetiapine - voriconazole	-	-	C0 (<5)	**D0** (<5)	D0 (<5)

Table 6 presents a detailed account of the changes in classification for all C-D drug pairs throughout the study period. Given the presence of metoprolol and propafenone among the top 10 drug pairs (Figure 9), it was essential to assess whether these changes could affect the overall decline of category D drug pairs. The table highlights the drug changes in bold and also indicates the number of prescribed prescriptions in parentheses. Among the 21 drug pairs that underwent a change in the strength of interaction category over time, 17 shifted from category C to category D. However, the overall impact on the decline of category D drugs was negligible as the total number of drug prescriptions was small.

In addition, data were collected on reasons for cancelling prescriptions. Table 7 provides an overview of all cancellation options that the prescription centre system offers.

Table 7. Reasons for cancellations.

AN01 Change in treatment plan: Unwanted side effect or interaction
AN02 Change in treatment plan: No expected treatment result
AN03 Change in treatment plan: Clarified diagnosis
AN04 Change in treatment plan: Treatment duplicative prescription
AN05 Change in treatment plan: Discontinuation of treatment/ recovery
AN06 Change in treatment plan: Incorrect registration
AN98 *Systemic annulment: invalidation
AN99 *Systemic cancellation: patient death

Table 7 gives an overview of all prescription cancellations (all specialties) with selected reasons AN01 (Change in treatment plan: Unwanted side effect or interaction) and AN98 (*Systemic annulment: invalidation), compared to all cancellations in family medicine and all cancellations in family medicine for CVD drugs.

Table 8. Cancelled prescriptions vs selected reason: AN01 “Change in treatment regimen: unwanted interaction or side effect” vs AN98 "*Systemic annulment: invalidation".

		ALL CANCELLED PRESCRIPTIONS		AN01 CHANGE IN TREATMENT REGIMEN: UNWANTED INTERACTION OR SIDE EFFECT		AN98 *SYSTEMIC ANNULMENT: INVALIDATION	
2017	All	2235107	100%	11815	1%	1950602	87%
	E300	1424623	64%	3664	0,3%	1226937	86%
	E300 CVD	578764	41%	1843	0,3%	497301	86%
2019	All	2336978	100%	14067	1%	2056245	88%
	E300	1468799	63%	3009	0,2%	1285907	88%
	E300 CVD	576021	39%	1500	0,3%	503041	87%
2020	All	2194282	100%	16475	1%	1929994	88%
	E300	1398828	64%	2803	0,2%	1226843	88%
	E300 CVD	556461	40%	1307	0,2%	487354	88%
2021	All	2247179	100%	15436	1%	1972766	88%
	E300	1408124	63%	2734	0,2%	1235653	88%
	E300 CVD	552773	39%	1276	0,2%	482942	87%
2022	All	1674236	100%	15170	1%	1394790	83%
	E300	1026595	61%	3495	0,3%	849809	83%
	E300 CVD	361585	35%	1550	0,4%	295060	82%

It is important to note that the AN01 reason for cancellation can indicate an adverse event as well as an interaction, making it an unreliable indicator of the number of prescriptions cancelled due to interactions. AN01 was selected very rarely, accounting for up to 1% of all cancellations. On the other hand, the AN98 reason, which represents prescription expiration or loss of validity and prompts the Prescription Centre to cancel the prescription, was relatively high. On average, 87.4% of cancellations were due to AN98 in 2017, 2019-2021. However, in 2022, this percentage decreased to an average of 83%. This could be because the data received included prescriptions that were prepared at the end of 2022 and were still active. Therefore, the author may not have a complete number of cancellations for 2022. As of today, it's possible that someone may have had a drug interaction that required the cancellation of the drug, or their physician may have changed their treatment regimen for some other reason, leading to a systemic cancellation that can occur 90+ days after the prescription of the drug. Considering that the patient have not bought out the medicine for some reason, this may mean all possible cancelling reasons including AN01.

4.2 Interviews

Almost all of the physicians rated the drug interaction alert system positively, with only one exception. Before the system was introduced, physicians had to rely on their own knowledge to identify potential drug interactions, as there were no alert systems in place. This often meant having to memorize information or consult various sources such as drug registers, books, and leaflets. However, this information could be outdated, incomplete, or hard to find. As a novice physician, it was especially important to have access to reliable interaction knowledge. Now, the Inxbase and UptoDate databases are used separately, with the latter allowing physicians to include over-the-counter medicines and nutritional supplements in their treatment plans, providing a comprehensive overview of the entire treatment regimen.

The DDI alert system is a convenient and user-friendly tool that provides information on potential drug interactions without requiring separate research. The system is highly reliable, but does not force physicians to learn about interactions, but it doesn't interfere. System alerts them to potential interactions whenever a prescription is issued, allowing for quick checks to ensure patient safety. Initially, the number of interactions identified by the system was concerning, but the alerts have proven to be valuable in highlighting potential issues that might not have been considered otherwise. While one physician rated the system as satisfactory due to reliance on other sources but points out that the system has helped to avoid prescribing drugs that were not optimal for patient.

The number of alerts physicians encounter on a daily basis varies depending on the patient and the drugs being prescribed. Patients with two to three medications in their regimen will typically trigger alerts, as will some types of medications. Chronically ill patients tend to generate more alerts than healthy patients who only require antibiotics. In general, it is more common to receive alerts than not. While the alerts are specific to each patient, they are encountered on a daily basis by physicians.

Physicians are universally satisfied with the way alerts are displayed on the screen. The alerts are highly visible, featuring clear, colourful text that can be easily read by clicking on the alert. Importantly, the alerts do not interfere with the prescription view, making them highly convenient to use. While the alerts are generally effective, some physicians

have suggested that they could be more practical, such as providing recommended dosage adjustments or alternative drug options when changing a prescription.

Physicians agree that sometimes it is necessary to override a drug interaction alert, especially for short-term treatments or in situations where there are no other options. Yellow alerts, which typically involve a drug reducing the absorption of another drug, are the most commonly overridden alerts. Physicians monitor affected systems closely and have generally found that these interactions do not cause significant problems. Additional tools, such as cardiograms or blood pressure monitoring, may be used to mitigate potential risks for medications that affect blood pressure or heart function. When prescribing a new medication, physicians carefully consider its necessity and whether it should be added to the patient's current treatment regimen. However, physicians take red alerts very seriously and do not override them lightly.

Physicians may become accustomed to certain alerts and be aware of potential interactions, leading to additional time spent on prescription renewal to override alerts. However, physicians recognize this trade-off is necessary for patient safety. Improving the system to display a patient's entire treatment plan, including alerts for kidney function and allergies, could be helpful. For instance, prescribing an NSAID to a patient with a GFR of 20 would trigger a alert. Likewise, medications containing penicillin would be displayed in red for patients with penicillin allergies. Overall, physicians find the system useful, even with many yellow alerts, prompting them to carefully consider potential interactions and make informed decisions.

Physicians monitor medications prescribed by other healthcare providers, taking into account the possibility that the specialist may not have access to a drug interaction alert system or may have disregarded an alert. The newer generation of physicians document their awareness of potential interactions in the patient's medical record, and consider the clinical experience of specialists who have prescribed medications with potential interactions. If there is still uncertainty, physicians prioritize the patient's complaints or alert information and may adjust treatment accordingly. While efforts are made to avoid interactions, this is not always possible for chronically ill patients. Red interactions are taken seriously, but it is challenging to avoid yellow interactions. It is important to note that family physicians often monitor the general treatment plan and patient complaints after a specialist visit.

It was highlighted that the drug interaction alert system has some limitations in providing a complete overview of the treatment regimen. To make the system more patient-centred, it could take into account various factors, such as medical history, allergies, lab tests, and over-the-counter medications. It could also differentiate between topical and systemic drug interactions, as topical drug interactions are generally less significant. When the alert recommends changing the treatment dose or drug, it would be helpful to include alternative or recommended treatment options to save time. If there is no alternative, the drug can still be prescribed, taking into account the potential risks. Providing recommendations within the alert system would increase the likelihood of a drug change.

Additionally, a decision support feature could be incorporated into the alert system, such as reminding physicians to check the patient's kidney function if it has not been done in a while. For long-term use of psychotropic drugs, it could suggest reducing the treatment dose gradually. When prescribing a medicine, the alert could include recommendations on what to observe and how often, such as monitoring the patient's blood pressure or heart rate.

Overall, while the drug interaction alert system has some limitations, it is still a valuable tool for physicians to ensure patient safety. By incorporating patient-centred features and decision support, the system could be further improved to provide more comprehensive and tailored care.

Furthermore, it has been noted that the alert system considers medications prescribed within a certain time frame, but this could be improved by implementing filters to reduce unnecessary alerts. It is also important to mention that medications that have already been dispensed cannot be cancelled. For instance, if a patient had an adverse reaction to a medication and a different one was prescribed, the first medication will still trigger interaction alerts for a certain period, causing unnecessary noise.

Regarding the information system, it would be beneficial to have a centralized platform where allergies, interactions, physician comments, and cancelled prescriptions are documented in a standardized format. This would help ensure that all physicians have access to the most up-to-date and comprehensive information, ultimately leading to better patient care.

5 Discussion

This chapter presents the hypotheses that were established for the study, and provides a discussion of the findings. The results are compared with previous research studies, and an attempt is made to address the research questions that were formulated at the beginning of the study. Additionally, the limitations of the research are acknowledged and possible areas for future research are identified. Finally, the chapter concludes with a summary of the study findings.

5.1 Prescription centre data and interviews

The aim of this mixed methods study was to analyze the DDI alert system in primary health care in Estonia and better understand the relationship between C-D category DDIs and the CDSS system through both quantitative and qualitative data, it is important to note that the results of this study have provided valuable insights into the current state of the DDI alert system in Estonia. Therefore, it can be concluded that the aim of this thesis has been fulfilled.

A comparison of prescription burdens among different medical specialties suggests that family physicians have a significantly higher burden because they often prescribe medication for long-term or chronic diseases [12]. For instance, while a cardiologist may prescribe continuous medication for cardiovascular disease, it is the family physician who is extending the repeat prescription [12]. Depending on the patient's complaints, also changes the medications prescribed by the specialist. Given this responsibility, it is crucial for CDSS systems to provide accurate and relevant information. However, the DDI system used in Estonia only differentiates alerts by severity and colour [18], [27] and does not consider important factors such as the patient's entire treatment plan, allergies, and lab values that are essential for physicians to prescribe drugs accurately. As a result, physicians may receive repeated alerts when prescribing drugs, leading to alert fatigue [4], [20], [19].

This study primarily focused on evaluating the effectiveness of the DDI alert system and the prescribing patterns of category C-D drugs in general. Efforts are made to avoid interactions, but this is not always possible for chronically ill patients. If the alerts would

take into account the patient's characteristics and laboratory results, it would be possible to map the reasons for overriding [20]. Providing the exact reasons for overriding would help evaluate the prescriptions of drug pairs with interactions, contributing to analysis and improving the CDSS system. However, future research should conduct a more detailed analysis of the prescribing habits of family physicians.

Estonian DDI alert system effectively manages information overload by categorizing alerts with classification and importance indicators, including colour coding for classification clarity. However, the system does not offer a comprehensive view of regimens, lab analyses, demographics, or drug administration times which are important for patient safety [24], [22]. Interviews with physicians revealed that they would like the alert system to be more patient-centred, incorporating various factors such as medical history, allergies, lab tests, and over-the-counter medications. Therefore, an extension of the alert system may be necessary to meet the physicians needs.

In 2018, Metsla conducted a study over a three-month period that showed no significant decrease in DDIs, with the overall rate remaining around 35% of all interactions [10]. Similar study in 2020, showed decline with category C4 and D4 interactions but overall rate remained around 31,4% of all interactions [11]. Over the course of a five-year period, this study demonstrates a significant decrease of 45,8% in DDI rates for D category drugs, and with CVD D category drugs by 63,45% while C-D prescriptions remained steady at an average of 31.67%. The results indicate that the CDSS system has had a significant impact on reducing DDI rates for certain drug categories. While the C category drugs did not show a significant correlation with the use of the CDSS system, a strong negative correlation was observed for the D category drugs.

Additionally, the CDSS system appears to be more effective in preventing DDI rates for CVD prescriptions, especially for the D category drugs. These findings emphasize the crucial role of the CDSS system in improving patient safety by reducing the risk of potential drug interactions and guiding healthcare professionals in prescribing medication for their patients. CDSS system has a significant effect on the rate of C-D category DDIs over a five-year period in primary health care settings, as supported by alternative hypothesis (H1). The prescription centre data revealed a decreasing trend in both C and D category DDIs, while the interviews showed that family physicians perceived the CDSS system as a useful tool for preventing and managing DDIs. Furthermore, the CDSS

system was found to have a significant effect on the occurrence of DDIs in CVD prescriptions. These findings suggest that the implementation of CDSS systems can be an effective strategy for improving patient safety by reducing the risk of DDIs [4].

While the CDSS system has been shown to be effective in reducing DDI rates, it is important to note that many potential DDIs may not be clinically significant and can be appropriately monitored or adjusted through dose modifications [15]. Additionally, the data does not provide information on whether the potential DDI resulted in serious ADR or hospitalization.

The quantitative data collected did not provide any information on whether the physicians altered their prescribing decisions or made any adjustments to the dosage of the drug in response to the DDI alerts. Nevertheless, family physicians acknowledge that there may be situations where overriding the alerts may be necessary, but they make an effort to avoid doing so whenever possible. Typically, yellow alerts, which relate to one drug affecting the absorption of another, are more likely to be overridden, while red alerts are taken more seriously and are less likely to be ignored. The clinical significance classifications are colour distinguishable, with D level classification in red and C classification in yellow [28]. To increase interaction clinical relevance, it is recommended to optimize the types and frequencies of alerts based on patient-specific factors, review override alerts, reduce alert fatigue, and turn off alerts that are not clinically significant or of minor importance [20].

The study findings indicate an age-related increase in the number of drugs in the C-D category, including all prescriptions and those for CVD, which is consistent with Hanlon et alles observation that DDIs are prevalent among older adults and correlated with medication count and hospitalization [1]. The likelihood of at least one DDI is 50% for patients taking 5-9 drugs [13]. The average number of interacting drugs per patient remains constant at 7-8, but further in-depth analysis is necessary to evaluate the impact of DDIs on patients with a higher risk of drug interactions.

An analysis of the top 10 drug pairs with clinically significant interactions over the study period reveals that the main drug pairs remain relatively stable, with a few exceptions. One notable change is the drug pair "metoprolol and propafenone," which was a category D interaction in 2017 but changed to category C in 2019. While some drug pairs

prescribed in large numbers in 2017 have decreased, there has been no significant increase in interactions with other drug pairs, indicating the system's effectiveness. The top 10 D category DDIs include drug pairs with combinations of anticoagulants such as Warfarin and NOAC preparation (Rivaroxaban or Apixaban). Expert interviews conducted as part of the Metsla study suggest that there is a trend to go towards using NOACs due to their lesser side effects compared to Warfarin [10]. However, the system may display old prescriptions alongside new ones, and medications that have already been dispensed cannot be cancelled, which means that these DDI pairs continue to issue alerts for 90 days after the drugs are purchased [27]. In addition, there is a decline in the top 10 drug pairs prescribed in 2017, where Warfarin was one of the paired drugs.

The study examined changes in drug pair classifications and their impact on overall prescription rates for different drug categories. Although only a small percentage of drug pairs change classification over time, the trend is toward an increase in D-category drugs and a corresponding decrease in C-category drugs. The Estonian DDI alert system is updated four times per year [25], ensuring the database is constantly updated.

There is no clear overview of cancelled prescriptions, with drug interaction and side effects being categorized as one reason for cancellation. Prior to 2021, physicians were unable to cancel prescriptions issued by other physicians. If there was a need to change a prescribed drug, it could not be cancelled but had to expire. However, today it is possible for any prescription to be cancelled, regardless of who issued it. The significant number of systemic cancellations may indicate a range of reasons for treatment plan changes, including drug interactions. However, the quality of the data should also be considered, as drugs remain in the system until systemic cancellation and continue to trigger DDI alerts, leading to alert fatigue. It is worth noting that physicians can only cancel active prescriptions, meaning that prescriptions that have already been dispensed cannot be cancelled.

Sutton et alles suggest that to improve the system, critical alerts should be categorized, the system should be designed to avoid interfering with physician work, and alerts should be specific and concise. Each alert should provide information about what the alert relates to [24]. The study shows that the Estonian DDI alert system is a reliable, user-friendly tool that provides information on potential drug interactions without requiring separate search for the interactions and are distinguishable. The alerts are displayed in a highly

visible manner and do not interfere with the prescription view. In addition, interactions are displayed according to the classification of interaction [18] and are colour distinguishable [28].

The study identifies some limitations of the drug interaction alert system in providing a comprehensive overview of the treatment regimen. Tannenbaum et alles note that the system, which only evaluates two drug profiles at a time, cannot evaluate multidrug combinations, leaving physicians to rely on incomplete information [3]. Physicians are required to refer to other databases, such as INXBASE (online, not integrated to prescription centre) and UpToDate, in order to view overview of treatment regimen plans, resulting in additional time consumption as they have to search for information from external sources.

Physicians points out that to make the system more patient-centred, it could take into account various factors, such as medical history, allergies, lab tests, and over-the-counter medications. Incorporating decision support features, such as reminding physicians to check the patient's kidney function if it has not been done in a while or suggesting gradual reduction of treatment dose for long-term use of psychotropic drugs, could also be helpful. Overall, there is room for further improvement to provide more comprehensive and tailored care.

To improve the user experience, the INXBASE advertises providing practical recommendations for dealing with each possible DDI [18]. In interviews, it was found that the alerts often recommend changing the treatment dose or drug without offering alternative options, which can have a negative impact on the user experience [24]. By providing more comprehensive guidance and alternative options, the INXBASE could help users make informed decisions and avoid potential drug interactions.

5.2 Main contribution

The main contribution of the study is to highlight the importance of DDI alert systems in preventing ADR and improving patient safety. The study provides an evaluation of the effectiveness of the DDI alert system in Estonian primary health care settings and identifies areas for improvement, such as the need for more personalized and patient-centred information, and the importance of categorizing critical alerts.

The core audience should learn about the benefits and limitations of DDI alert systems, how physicians use them in practice, and what improvements could be made to better support clinical decision making. They should also gain an understanding of the prevalence and severity of drug interactions, and the potential impact on patient outcomes. The study provides practical recommendations for how to improve the effectiveness and usability of DDI alert systems, which can inform future research and development in the field. Overall, the readers should come away with a greater appreciation for the role of CDSS systems in improving patient safety and optimizing medication management.

5.3 Main limitations

There are several limitations to this study that should be considered when interpreting the results. Firstly, the study only included depersonalized prescription centre data, which limited the ability to analyze patient-specific factors that could affect the occurrence of DDIs. Future studies could benefit from using personalized data, which could provide more detailed information on the patient's medication history, medical conditions, and other relevant factors that could affect the occurrence of DDIs.

Secondly, the author did not have information about the indication and duration of the treatment, about the dosage. Therefore, there were several shortcomings that do not account for different dosages, treatment changes. Aim of the study was to investigate whether CDSS is effective in the C-D category rate of DDI, more closely with CVD drugs. Therefore, this study intention was not to use a method that included patient age, sex, and concomitant therapy, which would have allowed us to learn about risk factors associated with DDI.

Another limitation of this study is that the data do not provide information on how often physicians changed their prescribing behaviour due to alerts. As a result, it is possible that some alerts were ignored or overridden, while less severe interactions were preferred. This aspect of the study could be further explored by conducting surveys or interviews with physicians to gain a deeper understanding of their decision-making processes when it comes to prescribing medications and responding to DDI alerts. Additionally, future studies could incorporate data from electronic health records or prescription centre database to track changes in prescribing behaviour following DDI alerts.

5.4 Future research

In the future, it would be beneficial to conduct research on personalized data to monitor the quality of treatment and medication habits of patients. This could provide insights into whether patients are regularly consuming medication and whether their treatment regimen is being monitored. Furthermore, analysing personalized data detailing a patient's diagnoses and when they were added could aid in tracking whether medical conditions may be due to drug interactions.

Additionally, a study could be conducted on the frequency of medication prescriptions and whether drug pairs with interactions are prescribed too often or ignored. This study could provide an overview of the frequency of prescribing medications, prevalence, and trends in prescribing and usage patterns. It could also analyze whether changes in prescribing practices are related to the physician or healthcare institution.

Timely monitoring of treatment plans and changes could also be researched to provide an overall picture of the risk of drug interaction for patients and the impact on their health plan. Clinical trials with patients taking 10-14 medications could investigate whether patients are aware of potential drug interactions and the effectiveness of interaction-based alerts. Overall, future research should focus on improving personalized care and treatment plans to reduce the risk of drug interactions and improve patient outcomes.

Develop patient-specific DDI alert systems: DDI alerts could be tailored to each patient's medical history, lab results, and medication history. Future research could explore the feasibility and effectiveness of such patient-specific DDI alert systems.

6 Summary

This thesis studied the impact of a CDSS on DDIs in primary health care in Estonia from 2017-2022. Prescription data and end-user surveys were used to measure the system's effect on C-D category DDIs and DDIs in patients with CVD. Two hypotheses were tested, showing that the CDSS had a significant impact on reducing both types of DDIs. The analysis indicates a declining trend in drug-drug interactions between 2017 and 2022. The study found that the use of the CDSS system was associated with a significant decrease in DDI rates for D category drugs, with a reduction of 45,8% compared to the 2017. However, the impact on reducing DDI rates for CVD D category drugs was even more significant, with a reduction of 63,45%.

The decrease in the number of drug pairs in the top 10 suggests a more informed and cautious approach to prescribing medication, as healthcare professionals may be more aware of potential interactions and are taking steps to avoid them.

The study found that older patients, particularly those aged 70-84, are at a higher risk of receiving a prescription with a clinically significant interaction. The proportion of interacting drugs prescribed by age is similar for all C-D and CVD interacting drugs, indicating that these types of interactions are not more prevalent in any particular age group.

The drug interaction alert system is highly rated by physicians, except for one. It eliminates the need for physicians to rely on their own knowledge and research for potential drug interactions, which can be outdated, incomplete, or hard to find. The DDI alert system is user-friendly and displays clear, colourful text alerts on the screen, which physicians take seriously, especially for category D alerts. The system prompts physicians to consider potential interactions carefully and make informed decisions, even with many category C alerts. The drug interaction alert system has limitations, but incorporating patient-centred features and decision support could improve it further. Overall, the system is a valuable and effective tool for physicians to ensure patient safety.

References

[1] J. T. Hanlon, S. Perera, A. B. Newman, J. M. Thorpe, J. M. Donohue, E. M. Simonsick, R. I. Shorr, D. C. Bauer and Z. A. Marcum, "Potential Drug-Drug and Drug-Disease Interactions in Well Functioning Community Dwelling Older Adults," *Journal of Clinical Pharmacy and Therapeutics,* vol. 42, no. 2, pp. 228-233, 2017.

[2] T. J. Geng, R. Madonna, R. C. Hermida and M. H. Smolensky, "Pharmacogenomics and circadian rhythms as mediators of cardiovascular drug-drug interactions," *Current Research in Pharmacology and Drug Discovery,* vol. 2, 2021.

[3] C. Tannenbaum and N. L. Sheehan, "Understanding and preventing drug-drug and drug-gene interactions," *Expert Review of Clinical Pharmacology,* vol. 7, no. 4, pp. 533-544, 2014.

[4] P. A. Glassman, B. Simon, P. Belperio and A. Lanto, "Improving Recognition of Drug Interactions: Benefits and Barriers to Using Automated Drug Alerts," *MEDICAL CARE,* vol. 40, no. 12, pp. 1161-1171, 2002.

[5] World Health Organization, "Cardiovascular diseases (CVDs)," 11 June 2021. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). [Accessed 5 March 2023].

[6] World Health Organization, "Medicines safety week," 26 November 2019. [Online]. Available: https://www.who.int/news/item/26-11-2019-medicines-safety-week. [Accessed 5 March 2023].

[7] Eurostat, "Cardiovascular diseases statistics," September 2022. [Online]. Available: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Cardiovascular_diseases_statistics. [Accessed 5 March 2023].

[8] Eesti Tervisekassa, "Krooniliste haiguste ennetamine," [Online]. Available: https://www.haigekassa.ee/inimesele/haiguste-ennetus/krooniliste-haiguste-ennetamine. [Accessed 6 March 2023].

[9] L. Ilves, "Digiretsepti uus teenus: ravimite koostoime kontroll," *Eesti Arst* , vol. 95, no. 5, p. 282–284, 2016.

[10] K. Metsla, "Master's theses: Estonian Family Physicians Usage and Satisfaction With Drug-Drug Interaction alert System," Tallinn University of Tehnology, 31 May 2018. [Online]. Available: https://digikogu.taltech.ee/en/Item/b7f719e9-d530-4f6c-9283-ae6092993cf8.

[11] A. Kurbatova, "Master's theses: The Most Frequently Occurring C, D Level Drug-drug Interactions in Estonia: Pharmacists Impact on Occurring Interactions," Tallinn University of Tehnology, 20 June 2020. [Online]. Available: https://digikogu.taltech.ee/et/Item/a25b0fdc-7e3e-4de0-a0cf-ebf20f212c86.

[12] Eesti Tervisekassa, "Retsept arstile," [Online]. Available: https://www.haigekassa.ee/partnerile/raviasutusele/retsept-arstile. [Accessed 6 March 2023].

[13] J. Doan, H. Zakrzewski-Jakubiak, J. Roy, J. Turgeon and C. Tannenbaum, "Prevalence and Risk of Potential Cytochrome P450-Mediated Druh-DrugInteractions in Older Hospitalized Patients with Polypharmacy," *Annals of Pharmacotherapy,* vol. 47, no. 3, pp. 324-332, 2013.

[14] R. M. Turner, E. M. de Koning, V. Fontana, A. Thompson and M. Pirmohamed, "Multimorbidity, polypharmacy, and drug-drug-gene interactions following a non-ST elevation acute coronary syndrome: analysis of a multicentre observational study," *BMC Medicine,* vol. 18, no. 1, 2020.

[15] P. D. Hansten, "Drug interaction management," *Pharm World Sci,* vol. 25, no. 3, p. 94–97., 2003.

[16] Y. Rochlani, N. V. Pothineni, S. Kovelamudi and J. L. Mehta, "Metabolic syndrome: Pathophysiology, management, and modulation by natural compounds," *Therapeutic Advances in Cardiovascular Disease,* vol. 11, no. 8, pp. 215-225, 2017.

[17] R. Kalda, M. Oona, H.-I. Maaroos, P. Rospu, K. Suija, A. Rätsep, P. Ööpik, E. Merilind and H. Tähepõld, Peremeditsiin, Tartu: Tartu Ülikooli Kirjastus, 2020.

[18] Y. Böttiger, K. Laine, M. L. Andersson, T. Korhonen, B. Molin, M. L. Ovesjö, T. Tirkkonen, A. Rane, L. L. Gustafsson and B. Eiermann, "SFINX - A drug-drug interaction database designed for clinical decision support systems," *European Journal of Clinical Pharmacology,* vol. 65, no. 6, pp. 627-633, 2009.

[19] A. Wright, D. S. McEvoy, S. Aaron, A. B. McCoy, M. G. Amato, H. Kim, A. Ai, J. J. Cimino, B. R. Desai, R. El-Kareh, W. Galanter, C. A. Longhurst, S. Malhotra, R. P. Radecki, L. Samal, R. Schreiber, E. Shelov, A. M. Sirajuddin and D. Sittig, "Structured override reasons for drug-drug interaction alerts in electronic health records," *Journal of the American Medical Informatics Association,* vol. 26, no. 10, pp. 934-942, 2019.

[20] T. N. Poly, H. C. Yang, Y. C. J. Li and M. Islam, "Appropriateness of overridden alerts in computerized physician order entry: Systematic review," *JMIR Medical Informatics,* vol. 8, no. 7, 2020.

[21] J. S. Ancker, A. Edwards, S. Nosal, D. Hauser, E. Mauer and R. Kaushal, "Effects of workload, work complexity, and repeated alerts on alert fatigue in a clinical decision support system," *BMC Medical Informatics and Decision Making,* vol. 17, no. 1, 2018.

[22] M. Heringa, A. van der Heide , A. Floor-Schreudering, P. A. De and M. L. Bouvy , "Better specification of triggers to reduce the number of drug interaction alerts in primary care," *International Journal of Medical Informatics,* vol. 109, pp. 96-102, 2018.

[23] K. M. Muylle, K. Gentens, A. G. Dupont and P. Cornu, "Evaluation of an optimized context-aware clinical decision support system for drug-drug interaction screening," *International Journal of Medical Informatics,* vol. 148, 2021.

[24] R. T. Sutton, D. Pincock, D. C. Baumgart, D. C. Sadowski, R. N. Fedorak and K. I. Kroeker, "An overview of clinical decision support systems: benefits, risks, and strategies for success," *npj Digital Medicine,* vol. 3, no. 1, 2020.

[25] Duodecim, "Terveysportin SFINX-PHARAO on nyt Lääkeinteraktiot ja -haitat," 20 March 2017. [Online]. Available: https://terveysportti.mobi/kotisivut/uutismaailma.duodecimapi.uutisarkisto?p_arkisto=1&p_palsta=23&p_artikkeli=uux21492. [Accessed 5 March 2023].

[26] Eesti Tervisekassa, "Koostoimete loetelu teenus," 17 August 2017. [Online]. Available: https://www.haigekassa.ee/sites/default/files/IT_juhised/xtee_rets.koostoime_list.pdf. [Accessed 5 March 2023].

[27] Eesti Tervisekassa, "Retseptikeskuse teenused ja liidestumise juhend," 2018. [Online]. Available: https://www.haigekassa.ee/sites/default/files/IT_juhised/dr_liidestamise_juhend_3.9.pdf. [Accessed 5 October 2022].

[28] Eesti Tervisekassa, "Ravimite koostoimete e-teenus: koostoime teadete kuvamine haigla või perearsti infosüsteemis," 2018. [Online]. Available: https://www.haigekassa.ee/sites/default/files/IT_juhised/koostoimete_kuvamine_infosusteemis.pdf. [Accessed 2022 October 9].

[29] J. W. Creswell, Research design. Qualitative, Quantitative, and Mixed Methods Approaches, United States of America: SAGE Publications, 2009.

[30] L. Doyle, A. M. Brady and G. Byrne, "An overview of mixed methods research," *Journal of Research in Nursing,* vol. 14, no. 2, pp. 175-185, 2009.

[31] M. Tavako and A. Zeinaloo, "Medical Research Paradigms: Positivistic Inquiry Paradigm versus Naturalistic Inquiry Paradigm," *Journal of Medical Education,* vol. 5, no. 2, pp. 75-80, 2004.

[32] V. Braun and V. Clarke, "Using thematic analysis in psychology," *Qualitative Research in Psychology,* vol. 3, no. 2, pp. 77-101, 2006.

[33] M. DeJonckheere and L. M. Vaughn, "Semistructured interviewing in primary care research: a balance of relationship and rigour," *BMJ journals,* vol. 7, no. 2, 2019.

[34] Tallinn University of Tehnology, "Veebipõhine kõnetuvastus," [Online]. Available: http://bark.phon.ioc.ee/webtrans/.

Appendix 1 – Non-exclusive licence for reproduction and publication of a graduation thesis[1]

I Gerda Joa

1. grant Tallinn University of Technology free licence (non-exclusive licence) for my thesis

"Analysis of drug-drug interaction alert system: prescription of cardiovascular drugs in primary health care", supervised by Tanel Ross, to be

1.1. reproduced for the purposes of preservation and electronic publication, incl. to be entered in the digital collection of TUT library until expiry of the term of copyright;

1.2. published via the web of Tallinn University of Technology, incl. to be entered in the digital collection of TUT library until expiry of the term of copyright.

2. I am aware that the author also retains the rights specified in clause 1.

3. I confirm that granting the non-exclusive licence does not infringe third persons' intellectual property rights, the rights arising from the Personal Data Protection Act or rights arising from other legislation.

06.05.2023

1 The non-exclusive licence is not valid during the validity of access restriction indicated in the student's application for restriction on access to the graduation thesis that has been signed by the school's dean, except in case of the university's right to reproduce the thesis for preservation purposes only. If a graduation thesis is based on the joint creative activity of two or more persons and the co-author(s) has/have not granted, by the set deadline, the student defending his/her graduation thesis consent to reproduce and publish the graduation thesis in compliance with clauses 1.1 and 1.2 of the non-exclusive licence, the non-exclusive license shall not be valid for the period.

Appendix 2 – Cover letter

„Analysis of drug-drug interaction alert system: prescription of cardiovascular drugs in primary health care“

I am Gerda Joa, a masters student in E-health at Tallinn University of Technology, and I invite you to participate in the study „Analysis of drug-drug interaction alert system: prescription of cardiovascular drugs in primary health care“.

Drug-related errors account for half of all medication errors worldwide, which can arise at various stages of drug use. One significant risk factor is the occurrence of drug-drug interactions, which can escalate the chances of adverse drug reactions, functional impairments, healthcare utilization, and even mortality. To minimize such risks, clinical decision support systems have been developed to enhance drug interaction recognition and bolster patient safety. By automatically alerting healthcare providers of potential drug interactions, such systems can effectively reduce the incidence of clinically significant interactions caused by specific drug combinations.

This study aims to analyze the drug interaction alert system in family medicine from 2017 to 2022, using a mixed methods approach. By examining data from the prescription centre, the study will measure the relationship between drug pairs and the alert system. Additionally, the study will investigate the satisfaction and usability of the system among family physicians. Through this analysis, the study seeks to provide insights into the effectiveness and practicality of the drug interaction alert system in the specialty of family medicine.

Despite being in use since 2016, the clinical decision support system lacks a comprehensive overview of its alert system's operation and long-term effectiveness. Data analyses in 2018 and 2020 were limited to only 1-3 months, providing inadequate insight into the system's performance. Given that patients with chronic diseases can purchase prescriptions for up to six months, and package sizes may exceed 100 tablets, a more in-depth analysis is needed to fully understand the system's effectiveness.

Participation in this study is voluntary and involves an individual interview, which will be recorded and lasts approximately 30 minutes. During the interview, we will ask you to share your evaluation of the drug interaction alert system, including the factors that influence your decisions and the system's bottlenecks. The interview is confidential, and no personal data will be used or disclosed. The results will be published in a non-identifiable form in a master's thesis.

Appendix 3 – Semi structured interview questions

1. Could you please share your thoughts on the drug interaction alert system? In your experience, what aspects of the system have been helpful, and what aspects could be improved?

2. On an average day, how often do you encounter drug interaction alerts, and do you feel that the number of alerts is appropriate or overwhelming?

3. Can you describe a situation where you have decided to override a drug interaction alert? What factors influenced your decision, and what was the outcome of that decision? Based on your experience, what do you think are the most common reasons for overriding drug interaction alerts?

4. Can you describe your experience with the drug interaction alerts as presented on screen? Are the alerts easy to read and understand? Have you ever encountered an alert that was difficult to interpret or that you felt was unclear?

5. How do you perceive the usefulness and effectiveness of the interaction alerts, and to what extent do they impact your workflow and decision-making process?

6. How do you take into account the drug interaction alerts when developing a treatment plan for your patients, and what factors influence your decision to accept or override an alert?

7. Before the implementation of the automated drug interaction alert system, how did you typically check for potential drug interactions?

8. Can you describe a recent instance when you had to modify a prescription based on an interaction alert, and what were the factors that led to your decision to change the prescription?

9. How do you think the current system could be improved? What limitations have you encountered while using the current system to identify drug interactions?

10. Is there anything else you would like to add about your experience with the drug interaction alert system?

Appendix 4 – Research Ethics Committee of the National Institute for Health Development approval

Tervise Arengu Instituudi inimuuringute eetikakomitee

Otsus nr 1130

Tervise Arengu Instituudi inimuuringute eetikakomitee (TAIEK) koosseisus K.Innos, C.Murd, A.Kull, A-R. Tereping, M.Tammaru, T.Pruunsild, M.Liibek arutas oma koosolekul 20. oktoobril 2022 ja otsustas lugeda kooskõlastatuks uuringu „**Ravimite koosmõju hoiatussüsteemi teadete kuvamise analüüs perearsti infosüsteemis ja kuidas käsitlevad perearstid ravimite koostoimete hoiatusi“, mille v**astutav uurija on **Tanel Ross** (TTÜ Tervishoiutehnoloogiate instituut) ja põhitäitja on **Gerda Joa** (TTÜ magistrant) ning kaastöötaja on **Diana Vinogradova** (TTÜ)

Uuring nr 23404, TAIEK koosoleku protokoll nr 45.

Otsus nr 1130 on väljastatud 01.11.2022

Kaire Innos
TAIEK aseesimees /allkirjastatud digitaalselt/

Marje Liibek
TAIEK sekretär /allkirjastatud digitaalselt/

Tervise Arengu Instituudi inimuuringute
eetikakomitee
Tervise Arengu Instituut, Hiiu 42, 11619 Tallinn
tel 659 3924
eetikakomitee@tai.ee
www.tai.ee