TALLINN UNIVERSITY OF TECHNOLOGY
School of Information Technologies

Diana Vinogradova 212016YVEM

FINANCIAL ASSESSMENT OF THE DRUG-DRUG INTERACTION SYSTEM FOCUSING ON C-D CATEGORY IN THE ESTONIAN HEALTHCARE SYSTEM

Master thesis

Supervisor: Tanel Ross

MSc

Tallinn 2023

TALLINNA TEHNIKAÜLIKOOL
Infotehnoloogia teaduskond

Diana Vinogradova 212016YVEM

RAVIMITE KOOSTOIME HOIATUSSÜSTEEMI FINANTSHINNANG KESKENDUDES C-D KATEGOORIA KOOSTOIMETELE EESTI TERVISHOIUSÜSTEEMIS

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: Diana Vinogradova

11.05.2023

Abstract

Background: Drug-drug interactions are affecting the economic part of the Healthcare system, burdening the medical professionals and affecting the treatment process of the patient. The analysis of the DDI system together with the financial report will provide an incremental burden occurring as a result of ADE-DDI. **The aim of this thesis** was to investigate the potential financial estimates of C-D category interacting drugs, implementing international parameters and data from the Estonian DDI system, along with a comprehensive analysis of data from EHIF invoices over a five-year period. Two hypotheses were formulated, where the null hypothesis states that C-D category-related costs by health care system are lower in Estonia than in comparable countries, and the alternative hypothesis was that Estonia incurs a higher incremental cost. **Methods**: The study utilized data from the Prescription Centre and financial reports of the Estonian Health Insurance Fund to assess the additional costs associated with ADE-DDI. The cost estimation was based on the prevalent interactions and diagnoses observed. The calculation of costs was based on the average expenses associated with six disease codes that were linked to the probability of ADE-DDI. The analysis was based on the causal-comparative approach. **The results** indicate three main DDI with the relevant six disease codes. Based on the averaging method, the additional cost occurring from ADE-DDI was 378 Eur per patient and 809 072 Eur for the Estonian Healthcare system in 2022. The patient count did not change significantly within the five years, however the prices of the services became 84% more expensive compared to the 2018 data. The main expenditures of 50.1% are CVD related. **Conclusion:** The study concludes that Estonia has reported the lowest DDI cost compared to the countries observed. The highest costs are coming from the other medical care and stationary care service types.

This thesis is written in English and is 51 pages long, including 5 chapters, 4 figures, and 10 tables.

Annotatsioon

Ravimite koostoime hoiatussüsteemi finantshinnang keskendudes C-D kategooria koostoimele Eesti tervishoiusüsteemis

Taust: Ravimite koostoimed mõjutavad tervishoiusüsteemi majanduslikku osa, koormavad meditsiinitöötajaid ja mõjutavad patsiendi raviprotsessi. DDI süsteemi analüüs koos finantsaruandega annab ADE-DDI tulemusel tekkiva täiendava koormuse.. **Käesoleva magistritöö eesmärk** oli analüüsida C-D kategooria ravimite koostoimete võimalikke finantshinnanguid, rakendades rahvusvahelisi parameetreid ja Eesti DDI süsteemi andmeid. Viia läbi tervliklik analüüs Haigekassa raviarvetest viie aasta põhjal. Sellest tulenevalt on püstitatud kaks hüpoteesi: C-D kategooria DDI-ga seotud tervishoiusüsteemi kulud on Eestis väiksemad kui võrreldavates riikidesning alternatiivne: Eesti tervishoiusüsteemi kulud on kõrgemad. **Metoodika:** Uuringus kasutati ADE-DDI-ga kaasnevate lisakulude hindamiseks Retseptikeskuse andmeid ja Eesti Haigekassa finantsaruandeid. Kulude hinnang põhines levinud koostoimetel ja täheldatud diagnoosidel. Kulude arvutamisel võeti aluseks kuue haiguskoodiga seotud keskmised kulud, mis olid omakorda rakendatud ADE-DDI tõenäosusega. Analüüs põhines põhjus-võrdleval lähenemisel **Tulemused:** Tulemused näitavad kolme peamist DDI-d vastava kuue haiguskoodiga. ADE-DDI-st kaasnev lisakulu oli 2022. aastal keskmistamismeetodi põhjal 378 eurot patsiendi kohta ja kokku Eesti Tervishoiusüsteemile 809 072 eurot. Patsientide arv viie aasta jooksul oluliselt ei muutunud, kuid teenuste hinnad tõusid 84% võrreldes 2018. aasta andmetega. Peamised kulutused ehk 50,1% on seotud SVH-ga**. Järeldused:** Uuringus jõutakse järeldusele, et Eesti on teatanud madalaima DDI kulu võrreldes vaadeldud riikidega. Suurimad kulud tekivad kategoriseerimata arstiabi ja statsionaarse hoolduse teenuseliikidest.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 51 leheküljel, 5 peatükki, 4 joonist, 10 tabelit.

List of abbreviations and terms

EHIF	Estonian Health Insurance Fund
GDP	Gross Domestic Product
OOP	Out-of-Pocket
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
DDI	Drug-Drug Interaction
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
ICD	International Classification of Diseases
CVD	Cardiovascular disease

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Introduction

Drug-Drug interaction (DDI) is a significant concern in the healthcare industry. DDI refers to the interaction between two or more drugs, whereas the effectiveness of one drug is affected by the presence of the other drug [1]. The concept of the DDI between several medicines has been a challenging concept for many countries. An adverse drug event (ADE) as one of the possible consequences refers to the harmful effects that may occur in the body due to the use of medications [2]. Globally, around 1.3 million people require emergency visits annually due to ADE, with approximately 27% of these patients requiring hospitalisation [3]. The ADE frequency is higher in the older population as there is a positive correlation between the factor of age and medicine intake, while with rising age, the likelihood of having two or more prescribed drugs increases [4].

Estonia has implemented a unique e-prescription system, where DDI software is integrated that checks interactions within different drugs and sends a warning in the system itself, as well as in the web-portal of the application. This allows to see the full information about the patient, provider, medicine, etc [5] [6]. The DDI impact is not only limited to clinical effects in the face of prolonging of hospitalisation, emergency department visits, etc, but also affects the economical part of the treatment, such as costs of hospital admissions, change of the treatment plan, and extra medication purchase etc. [7].

The concept of the study is to provide an overview of the international researches that were analysing the impact of the ADE from the financial point of view and implement the theory into Estonian health care system for incremental cost occurring from DDI calculation. The idea is to find the approximate average cost for the DDI with a division of service type and relevant diagnose code as a representation of the incremental expenditure. Firstly, the author is evaluating TOP 3 most common C-D category DDI interactions observed during the specific period in the family medicine area. TOP3 DDI are later assigned with the relevant disease codes associated with the active substances involved in these interactions, based on relevant studies. Once the first analysis is made, the author requests medical invoice data based on the relevant ICD codes from Estonian Health Insurance Fund (EHIF). As a result, the author is evaluating the approximate average cost of ADE based on the most common outcomes. The structure for further cost calculation takes an example of Stark cost evaluation [8].

Secondly, the author evaluates the initial estimation of the potential number of ADEs resulting from DDIs based on three theories, which serves as the foundation for subsequent cost calculations, as the author is investigating the cost of ADE-DDI about to with concerning potential associated patients. The cost analysis is organized based on both outpatient and inpatient visits and is evaluated from the perspectives of family physicians and other healthcare professionals. Finally, the author is connecting both databases of potential patients with ADE-DDI and the medical invoices based on relevant ICD codes with the same amount of patients. As a result, the potential additional cost of ADE-DDI per patient is evaluated as well as the total Estonian Healthcare burden.

Due to the data limitations and no previous research on this topic, the author is using the parameters obtained from literature on DDI impact in health systems with similar characteristics as in Estonia. The main theory is taken from German studies due to the similar characteristics in the face of insurance coverage as well as geographical location [8] [9]. Other countries such as Sweden and Japan are taken as the comparison for ADE-DDI cost. For instance, Sweden has reported that approximately 5-6% of hospitalizations are attributed to drug-related incidents, leading to a financial burden of € 464.1 million for the Swedish government [10]. Whereas, Germany has reported a 1,26 Bln € annual cost resulting from ADEs, and Japan has claimed that the avoidance of ADE will lead to saving up to 6,796 Mln € per year [11] [8].

Currently, no investigations were made in Estonia, which leads to the problem statement that the Estonian DDI system has not been analysed from the financial angle. As a result, there is no financial proof of the effectiveness of the system. However, the current thesis applies heuristic comparative analysis to estimate C-D DDI costs in Estonia based on EHIF invoices, and may not represent the actual view of the situation.

1 Theoretical background

1.1 Drug-Drug Interaction

1.1.1 Impact of Drug-Drug Interaction on the Health system

Drug prescription has been in place for decades and there are common solutions known to avoid unneeded pharmaceutical effects, like reducing alcohol consumption, smoking, or living a healthy lifestyle [12]. Unfortunately, not all these protect us from undesirable outcomes. Except for the lifestyle, people tend to have not only one disease to treat, which makes the treatment process more complicated. Therefore, we end up with an interaction within the therapy, more precisely DDI. The DDI itself is the interaction between two or more drugs, where the activity of one drug affects the efficiency of the other drug [1]. One of the possible impacts is ADE that is harming the body as a result of medicine intake [2]. There are different outcomes as a result of ADE that result from DDI and include treatment plan change, hospitalization, emergency visit as well as death [8].

The annual approximate emergency visit as a result of ADE counts 1.3 mln people, where roughly 27% of the patients need further hospitalisation [3]. Risk of ADE has a tight correlation, with the age of the patient because with rising age, the likelihood of having two or more prescribed drugs with potential interaction increases [4]. Based on the statistics from the Centers of Disease Control and Prevention, patients older than 65 years visit the emergency more than twice as often as the younger population [3]. Brahma et al. state in the medical review that patients above 65 years old are prescribed on average two to six drugs [13]. Due to the several medication the DDI concept is occuring, based on the Doan et. al each fifth prescribed drug is adding 12% of the likelihood of having a DDI [14]. As a result of interaction the harmful Adverse Drug Reaction (ADR) may occur [15]. ADR covers only the harm that is the result of normal dosage and normal use [16]. The likelihood, therefore, is 60% of ending up in hospital admission and 70% of requiring a long-term stay in the hospital [13]. In the present situation, two aspects are greatly impacted: the clinical and the economic.

The clinical aspect directly influences the severity of the toxicity and the treatment of the individual, while the economic aspect is related to the rise in cost [7]. In order to meet the goal of the thesis, the ADE-DDI cost is being analysed.

To reduce the impact of the ADE resulting from a medicine interaction, a few countries have integrated DDI systems. The system is operating to evaluate two main effects that are caused by the DDI: 1) Pharmacokinetic, where absorption, distribution or metabolism is retracted, or 2) Pharmacodynamic, where one drug modifies the biological effect of the other drug. Concerning the ideology of optimizing the therapeutic and economic outcomes, the DDI should be considered [17]. Databases with expanded DDI information are useful resources for prescription purposes, as they provide a timely warning to physicians and pharmacists about potential risks [17].

1.1.2 Estonian Healthcare system and Drug-Drug Interaction system

Estonia uses the universal insurance policy, where 95% of the population is insured through EHIF, therefore the country performs the same service quality for everyone [9]. Since the main part of the population is insured through EHIF, it could be considered as the main healthcare insurance provider. As a result, the datasets are reliable for conducting studies and analyses affecting the whole country or in particular the Healthcare system [9].

The major part of the Estonian healthcare funding comes through the payroll tax. Since 2017, the country has been a part of the health system financing reform, where each employer is obliged to pay 13% of the salary to health care [18]. Despite this figure, there is a governmental allocation of the budget, where a total of 7.5 % of the GDP is allocated to health care reported by Statista [19]. The figure 7.5 % shows that Estonian healthcare government spendings are below the EU average of 9.9%, which has a direct effect on the out-of-pocket(OOP) payments by the citizens. The proportion stays at 74.5% covered by EHIF and 23.9% for the OOP payment [18].

Despite that, EHIF acts as a mostly unique purchaser that is compensating all the contract providers under the payment system. The agreement should define the case and the following costs and quality requirements, such as waiting times. All the pricings are regulated by the governmental list with included payment methods, service rates, and benefit packages. The pricing is divided into four main parts: family physicians, specialist ambulatory care, rehabilitation care, and nursing care. Each of the pricing groups has its internal reimbursement plans and monthly prepayments [9].

All the medical invoices are transferred through the new channels that are built into the partner´s databases or through the web-portal application. In both cases, the data is transferred through X-road directly to EHIF [20]. As a result, EHIF has the full overview of the expenses coming from disease prevention as well as treatment. In addition, it is possible to see the history of the medical devices and products. This allows to see the breakdown of the services, providers and the medicine used [21].

In June 2016, Estonia implemented a unique DDI alert system, which was implemented as a unique program throughout the country [5] [6]. The system allows to view the full flow of the medicine that is prescribed for the patient excluding stationary prescribed drugs. It checks the interactions between different drugs and sends a warning in the system itself and in the web-portal of the application [5] [6]. Moreover, it allows to see the full information about the patient, provider, medicine, etc [6].

The system provides comprehensive information about patients, healthcare providers, medications, and more [6]. When a physician selects a medication for prescription, the system displays an overview of all active drugs and prescriptions from the previous six months. The prescriptions are organised based on the active substance, ATC code, and ICD code, grouping medications with the same ICD code. The medication details are available, including the active substance, dosage, and form of treatment. [22].

Digital solutions provide an information in a structured way that allows the user to see a short overview as well as the more complex explanation of the comments provided. In the case of a DDI, the system uses four classifications: 1) D – Clinical DDI that should be avoided; 2) C- Clinical DDI that could be managed through dosage adjustments; 3) B – Clinical DDI is not clear and could vary; 4) A – Not serious DDI. In order not to oversending the alerts, the system displays a red triangle (D – category) and yellow warning (C – category) to the user as the most serious alerts [23] [22]. Clicking on the warning sign reveals which treatments are interacting and provides additional information. As a result, the physician may be opt to switch to a better medication option that does not cause a DDI or continue with the treatment while considering the potential impact of the DDI on treatment efficacy [22].

Today, there are only two published master researches that analysed the DDI system in Estonia: 1) The most frequently occurring C, D level drug-drug interactions in Estonia: Pharmacists impact on occurring interactions [24], 2) Estonian family physicians usage and satisfaction with drug-drug interaction alert system [25]. In addition, there is another ongoing research made by Gerda Joa ,,Analysis of drug-drug interaction alert system: Prescription of cardiovascular drugs in outpatient care'', which is a supportive investigation of the current thesis. Currently, there is no financial assessment of the model, which leads to the importance and uniqueness of this thesis.

1.1.3 International research

DDI is the topic being highly discussed worldwide. As a consequence of the complexity of the current process due to the uncertainty of the ADE. There is a high difficulty in evaluating the negative impact of the DDI. The reason for that is the ambiguity of the patient path, as the clinical outcome could be the result of another factor that is not involved in DDI [26]. Despite the complexity of the calculation of the path, the DDI is the concept known worldwide and has unique characteristics. Nevertheless, there are studies available that were able to calculate the precise or estimated cost that will be the baseline for the current research. For the current thesis, the international researches were closely analysed based on similar characteristics or the matching calculation flow that would be interpreted into the Estonian Healthcare system.

The importance of the detection of DDI is laying in the clinical and economic burden of the treatment process [7]. Many countries have cooperation with the hospitals for the evaluation of the actual cost of the treatment as a result of an ADE-DDI. According to the Gyllesten et al. 5-6% of the hospitalisations are drug-related, where the reported ADEs have an impact on the 6% of the Swedish population that makes 632 961 people affected [27] [10]. The calculations were considering only self-reported ADRs with a need for hospitalisation or primary care visit that were extrapolated to 464,1 Mln € in annual direct cost for the Swedish government. The study covered 14 000 participants, where 2 320 people reported ADE&ADR. [10]. Another study compiled by Sultana et. al analysed the literature review on the ADE and conducted that there is a big gap in reporting the ADE due to the specificity of this topic. The research analysed the available studies and shows a range of 4.2-30% of the hospital admissions are accounted to ADEs in the USA and Canada. Just in the US, the annual ADE cost is 37,93 billion € additionally [7].

In some cases, the calculations of the costs are precise and concrete based on the ADE events from the DDI. As an example of Bates et. al, who made cross-check of the data collected from various sources using different models, stated an ADE cost of 1 billion € [28]. On the other hand, there were studies performed using hospital data that gave a better overview of the treatment process. However, they still involve assumptions for the ADE detection. In 2012, the German study was cooperating with three hospitals for a better evaluation of the ADE. In this case, they followed the logic by categorising possibilities with the ICD codes of the patients, stating the likely possibility of the ADE as 25%. In the research, 49 462 patients were taken as a total population for the study, and based on the algorithm, 1.14% or 564 patients with ADEs cause admissions. During the secondary diagnosis, the number increased to 2 049 patients with ADE. The total calculation assumed the total cost of 1.26 billion € per year nationwide [29]. Another German study takes however a baseline of 4.8% from the total amount of people taking a medication, which leads to the lower costs of 996,6 million € or the average cost of 465,32 € per case for the population of 2.14 Mln adults. The baseline for the calculation was the possible ICD codes (3 positions) and costs that are related to them [8].

Fabienne et. al found in their study that during a five month period, 28.7% or 284 patients were admitted due to the ADE. The study was conducted based on one University hospital and the ADE will result in additional 110.3 Mln Euros where 100.67 Mln will only come from the medical cost alone [30]. As for the Asian study, 11.1% (6 504 patients) were reporting a ADE related hospitalization. In total, Japan's burden of the ADE is reported to be 6. 796 Mln Euros per year [11].

The Table 1 shows the main studies that were analysed by the author in the current study [8] [29] [7] [10] [28] [30] [11]. The figures are later used as a comparison with the Estonian likely cost per patient, as well as the estimated average yearly cost. The inflation rate was used to update all of the values for 2022 to be comparable to each other. The Inflation tool was used to calculate the rates for the needed years [31].

Table 1 Overview of the cost of ADE international researches.

Source: Researches [8] [29] [7] [10] [28] [30] [11], modified by author.

Authors	**Year**	**Title**	**Journal**	**Country**	**ADE Cost in 2022 values, Eur**	**Average cost per patient, Eur**
Stark RG, John J, Leidl R.	2011	Health care use and costs of adverse drug events emerging from outpatient treatment in Germany: a modelling approach	BMC Health Serv Res. 2011 Jan 13;11:9.	Germany	996.6 Mln €	465,.32 €
Hasford, J., Rottenkolber, D. & Stausberg, J.	2012	Costs of Adverse Drug Events in German Hospitals—A Microcosting Study	Journal Value in Health 15 (2012) 868 – 875.	Germany	1.26 Bln €	2 425,72 €
Sultana J, Cutroneo P, Trifirò G.	2013	Clinical and economic burden of adverse drug reactions	J Pharmacol Pharmacother. 2013 Dec;4(Suppl 1) :S73-7.	The United States	37,93 Bln €	17.632,44 €
Gyllensten H, Rehnberg C, Jönsson AK, et al	2013	Cost of illness of patient-reported adverse drug events: a population-based cross-sectional survey	BMJ Open 2013;3:e002574.	Sweden	464.1 Mln €	803,72 €
Sarah P Slight, Diane L ,Seger, Calvin Franz, Adrian Wong, David W Bates,	2018	The national cost of adverse drug events resulting from inappropriate medication-related alert overrides in the United States	Journal of the American Medical Informatics Association, Volume 25, Issue 9, September 2018, Pages 1183–1188	The United States	1.08 Bln €	2 185,60 €
Fabienne J. H. Magdelijns, Patricia M. Stassen, Coen D. A. Stehouwer, Evelien Pijpers	2014	Direct health care costs of hospital admissions due to adverse events in the Netherlands	European Journal of Public Health, Volume 24, Issue 6, December 2014, Pages 1028–1033	Netherlands	110.3 Mln €	3 888,48 €
Aoyama, T., Goto, C., Katsuno, H., Matsuyama, T., Mizui, T., Noguchi, Y., Tachi, T., Teramachi, H., Sugioka, M. & Yasuda, M.	2021	Evaluation of the Direct Costs of Managing Adverse Drug Events in all Ages and of Avoidable Adverse Drug Events in Older Adults in Japan.	Journal Frontiers in Pharmacology.	Japan	6.796 Mln €	413,03 €

1.2 TOP 3 most common DDI C-D category for cost calculation

DDIs are a major problem for healthcare professionals, as they can lead to unexpected therapeutic outcomes or ADEs. Recognizing the significance of the progress and achieving efficiency, ADE is not only challenging the treatment process but additionally increasing the workload and leading to rising medication costs [7]. The idea of the medical cost was not analysed in the Estonian healthcare system and therefore has a huge potential in the financial assessment of the DDI system. The concept of DDI related costs is difficult, but it is crucial for countries to manage their expenses.

Since the research is made in two phases, the analysis of the data is necessary for further proceedings. The first phase is the evaluation of the TOP 3 most common C-D category DDI. To evaluate the approximate average cost of the potential ADE cases in the Estonian Healthcare system, the German example of Stark et. al was taken as an example due to the similar characteristics of the countries in terms of Insurance coverage and geographical position [9] [8]. For cost calculation, Stark. Et al. assigned possible ICD codes and 3 positions of the DDI as a base, related to the other performed study [8]. The same approach is taken in the Estonian calculation and the author is focusing on the most common DDI interaction as the main outcome of the ADE-DDI. Based on the relevant ICD codes, the author is requesting the medical invoice data from the EHIF. This will allow to see the average cost of the service type, which works as a representative of the incremental average expenditure occuring from ADE-DDI. Appropriately, the author calculates the likely cost of the ADE-DDI per person as well as the nationwide burden.

Therefore, the overview of the ICD codes based on the TOP 3 C-D DDI is visible under 4.1.1 TOP 3 DDI and the following diagnoses. For evaluation, the possible DDI related diagnoses, based on the Synbase database. The system is being used by medical professionals and the same warnings are visible to them [32].

Currently, there is no financial assessment available for the Estonian healthcare system. Appropriately two approaches can be taken to analyse the cost-effectiveness: one from the payer's perspective and the other from the perspective of the government insurance fund. Given that the majority of the Estonian population is insured by EHIF, this study focuses on analysing the situation from that perspective. As a result, the aim of the study is to investigate the potential financial estimates of C-D category interacting drugs, implementing international parameters and data from the Estonian DDI system, along with a comprehensive analysis of data from EHIF invoices over a five-year period.

Research questions:

1) What are the most common C-D category interactions and the relevant diseases in family medicine based on the EHIF invoices analysis of the DDI system in the period of 2017-2022?
2) What is the effect of clinically significant drug interactions on the cost of the treatment of patients in the Estonian healthcare system?

Correspondingly, the following hypothesis has been phrased:
Null hypothesis (H0): C-D category DDI related costs assumed by the health care system are lower in Estonia than in comparable countries.
Alternative hypothesis (H1): Estonia incurs a higher incremental cost related to C-D category DDI compared to comparable countries.

Due to research limitations, the author utilised an extrapolation method and a compilation of studies from other countries. Additionally, non-personal data collection influenced the study's flow, leading to an assessment based on the TOP 3 DDIs and their most likely associated diagnoses.

2 Data and Methods

2.1 Method

Study Philosophy

Current research relies on critical realism theory, where the author makes an assumption of the real-world scenario, how and why events occur. However, the theory also takes into account the social aspect, and as a result, it affects the perception of the study based on the independent reality of the author [33]. The research method is chosen as a secondary data analysis method due to the specificity of the topic. The current thesis analyses the data through the concrete research questions that were set. Based on the research questions, the author proceeded with the data collection and evaluation of the appropriate sources for the thesis. The advantage of the theory is the ability of a new angle and the discovery of new outcomes, which corresponds with the aim of the thesis as well as the explicity of the thesis for EHIF [34].

Study Design and Sample Size

A quantitative research design method was chosen for the thesis due to the data collection method and defined variables of the study. In order to determine a possible relationship and possible outcome, causal-comparative research is used for the deeper view. By using this method, the author clearly defines the independent variable, which in this case are the C-D category interactions [35]. However, the numbers are not manipulated during the study. In addition, the groups are chosen and prefiltered by EHIF based on the data following characteristics, and are divided into two steps:

1) The dataset pertains to C-D category interactions in the family medicine area during the years 2017, 2019-2022. This data includes comprehensive information on the total number of interactions in this category over a five-year period, including details on the number of patients, prescriptions, and total interactions observed.

2) The dataset on care volumes was obtained by requesting information on the Top 3 C-D category interactions observed in the first dataset, for the years 2017, 2019-2022. The corresponding ICD codes were assigned by the author based on relevant studies. This dataset provides information on the type of medical service provided, the medical

professional involved (family doctor or medical consultant), the pre-filtered division of the assigned ICD codes, the corresponding expenditures, and the number of patients involved.

As a result, the author evaluates the cause-effect relationship which is the additional cost for the EHIF as a result of ADE-DDI [36].

The sample size is collected from EHIF prescription data in two steps over a five year period, (full-year results, excluding 2018). The first dataset is based on the family medicine area and provides an overview of the C-D category DDI, with the following number of patients, the number of medicine prescribed, and the average drug intake per person. The data is grouped by half a year, age, and sex. The total number of 11 mln is being collected and analysed. Based on the data, the author is analysing the main DDI within the C-D category for the given period, later focusing on the TOP 3 DDI. The TOP 3 C-D category DDI are then assigned with the ICD codes based on the Synbase system, that is in use by the medical professionals [32]. As a result of the analysis, the author is retrieving the diagnoses that are associated with the DDI and makes a second data request from EHIF for the medical care volumes to calculate the average cost of DDI. This dataset includes the overview of the main divisions by specialty, service provided, patient count, and diagnoses, and is grouped on a yearly basis. The total care volume is therefore over 39 Mln Eur and covers 584 555 people for five year period.

Both datasets are prefiltered by EHIF based on the needed characteristics provided by the author. Additionally, due to the access to EHIF open prescription data, the parameters derived from the literature (e.g., percentage of patients potentially having an ADE-DDI) are applied to the overall Estonian population with prescriptions and compare the results with, e.g. actual number of people that have been prescribed C-D category DDIs. Due to the specificity of the study, the non-probability sampling method is being used. In this way, the author is narrowing the sample size to the concrete and needed version for further investigation. Moreover, for the better overview and calculation of the total EHIF additional costs, the results will be interpreted into full population reality [37].

Research Ethics and Permission

This study is conducted using anonymous data provided by EHIF for the period of 2017, with 2019-2022 focusing on the C-D category drug-drug interactions. Therefore, the data is secured and encrypted in the way it is impossible to evaluate, who are the patients. The study is therefore following the prescriptive ethics as it is aiming to evaluate the outcome in the face of valuable or not [38]. As a result, the author is willing to provide a financial assessment of the DDI prescription system to the EHIF that may increase the awareness of the costs associated with the ADE-DDI problem. Because of the specificity of health data to request information, an ethics committee request was made together with another ongoing study made by Gerda Joa ,,Analysis of drug-drug interaction alert system: Prescription of cardiovascular drugs in outpatient care''. The application is visible under Appendix 2.

Researches received an approval by Research Ethics Committee of the National Institute for Health Development on 1 November, 2022.

Research limitations

The main complication of the study is the non-personalised data that disables track precisely the path of the patient and calculate additional costs that are involved in the process. Another problem is to find the actual DDI incremental cost, as from a medical perspective it is hard to assume whether the complication is a consequence of the DDI or there is another factor involved. As a result, the author of the study is making the financial assessment based on the secondary data collected to calculate the assumption in the face of additional costs. Moreover, the data from EHIF excludes 2018 due to the technical reasons of their system, therefore the study involves the following years: 2017, 2019-2022. Another limitation of the study is the ADE marking as detecting the concrete reason why the patient ended up seeing a physician [39].

Data Collection

The data being collected from Estonian Health Insurance Fund (EHIF) and used a secondary data collection method [40]. The data is gathered for five years in a period of 2017, 2019-2022. The data is received by email in an Excel format and consists of several grouping. The internal validity concept is being used as the results are later interpreted as the true outcome of the study, which is the additional cost coming from ADE focusing on

C and D category drug-drug interactions for a full overview of the Estonian situation. Since the topic of the study is narrowed down to the three most common reactions based on the data provided, a deeper look is taken to analyse the results [41] [36].

The data request was done with two steps: 1) C-D category DDI data in family medicine specialty with overall grouped information; 2) Financial overview based on TOP 3 interactions and the most common diagnoses. The data collection was done as follows:

First data request:

1. C-D category drug-drug interactions involving all prescriptions, regardless of whether the prescription is unique or not, specialty family medicine.

2. The data for the period 2017, 2019-2022, data grouped by half a year.

3. Data based on the prescribed drugs divided by the age and by the number of drugs being prescribed and separately realised for one person (0-4, 5-9, 10-14, 15-... drugs).

4. The total amount of medicine prescribed within the given period.

Second data request:

1. The data for the period 2017, 2019-2022, data grouped by year, Specialty Family and all, and service type differentiable.

2. Data based on TOP 3 DDI and the possible ADE, in the current study the following ICD codes were being used [42] (For more details please follow the results and findings):

1) G47- Sleep disorder

2) I50.1 - Left ventricular failure

3) I10 -Hypertension

4) N17 – Acute renal failure

5) B96 – Bacterial agents

6) K21 – Gastro-oesophageal reflux disease

3. Service type: Ambulatory and Stationary. Divided by family physicians, and medical consultants.

4. Data includes: Number of treatment cases, service type, patient count and treatment cost.

There are several limitations of the data collection due to the non-personal data collection, which leads to the data being a lot dependent on the secondary data collection and the theory. As a result, the current research, there has to be more manipulation and adjustment of the data. The more precise calculation path can be found under the next two sections: Data and Statistical Analysis and Cost determination and calculation.

2.1.1 Data and Statistical Analysis

The aim of the research is to investigate the additional cost caused by ADE-DDI that is based on the financial calculation of the costs. To make a conclusion, the author is using descriptive statistics of numerical data to investigate the scores and drive takeaways. Due to the need of calculating the likelihood of ADE, the mean function is being used [43]. As a consequence of the difficulty of evaluation of ADE resulting from DDI, the author is presenting three theories and making a final assumption based on them. Based on the international research, the ADE occurence should stay within the range of 5-20% as a result of DDI [44].

The data is analysed from two viewpoints: Total and Top 3 interactions in the C-D category separately. This will allow to see how big is the part of the Top 3 from the total C-D category interactions. Due to the fact that the TOP 3 is the most common DDI, the author is assuming the ADE-DDI cost based on the average medical care cost for the relevant DDI and diagnoses assigned to them.

The decision flow is implemented for a better view and detection of steps for evaluation of the likely ADE-DDI within a different theories.

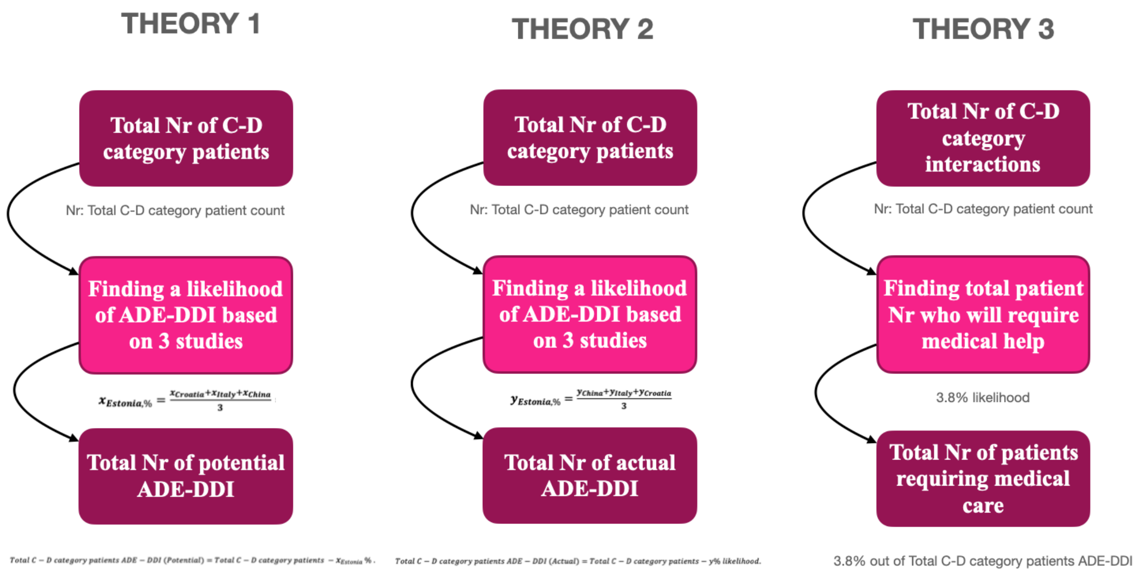

Figure 1 Decision flow to evaluate the additional cost for ADE-DDI different scenarios.

Source: Author's decision flow, 2023.

The evaluation of the possible ADE-DDI cases is divided into three main theories:

First Theory

In order to find the potential ADE-DDI cases that correspond to the Estonian Healthcare system, the author evaluated the $\boldsymbol{x_{Estonia}}$ (%) for the proper calculation of the actual potential cases of ADE-DDI. The author found three relevant studise, which estimated the potential ADE cases that were decided to be taken as a baseline. For the assumption, an average of the three studies performed was taken: Croatia of $\boldsymbol{x_{Croatia}} = \mathbf{20.8}\%$ [45], Italy of $\boldsymbol{x_{Italy}} = \mathbf{31.5}\%$ [46], and China reporting the lowest $\boldsymbol{x_{China}} = \mathbf{18.32}\%$ of ADE-DDI [47]. Since the DDI is a globally known issue and it is reported in the same way, the author takes into account three studies performed and this leads to the average calculation of the probabilities $\boldsymbol{x_{Estonia,\%}} = \frac{x_{Croatia}+x_{Italy}+x_{China}}{3} = \frac{(20.8+31.5+18.32)}{3} = \mathbf{23.54}\%$ of the cohort that were assumed to get a potential ADE-DDI. Appropriately the following formula is being used $Total\ C-D\ category\ patients\ ADE-DDI\ (Potential) = Total\ C-D\ category\ patients\ - x_{Estonia}\ \%$.

Second theory

Next step was the evaluation of the actual possible ADE-DDI cases. In order to make a calculation, the author is considering the probability of DDI occurring depending on three studies performed. All of the studies were evaluating the likelihood of experiencing the actual ADE-DDI. Therefore, the author is finding an average to implement it to an Estonian probability of $\boldsymbol{y_{Estonia}}$ (%). The calculation is based on the Chinese $\boldsymbol{y_{China} = 11,3}$% [47], Italian study of $\boldsymbol{y_{Italy} = 9}$% [48] and Croatian study of $\boldsymbol{y_{Croatia} = 7,8}$% [45]. This way allows author to estimate the actual ADE-DDI cases, the formula stays as follows $\boldsymbol{y_{Estonia,\%} = \frac{y_{China}+y_{Italy}+y_{Croatia}}{3} = \frac{(11,3+9+7,8)}{3} = 9,37\%}$**.** As for the further step, the author is integrating the new Estonian likelihood into the total C-D category patient group. As a result, the following formula is being used for evaluating the Total C-D category patients ADE-DDI (Actual) : $Total\ C-D\ category\ patients\ ADE-DDI\ (Actual) = Total\ C-D\ category\ patients - y\%\ likelihood.$

Third theory

The author evaluated the number of people who would require medical care due to ADE-DDI, considering that some cases may not present any symptoms. To find the number of people, it was decided to take a theory from the German study performed by Stark, et al [8]. The basepoint of the implementation of the theory is the similarities of the countries. In both cases, the cost evaluated is happening from the perspective of their respective national health insurance funds. In both Estonia and Germany, a high percentage of the population (95% and 90%, respectively) is insured by the government, making the two countries similar [9] [8]. Another common point is that both countries are located in Europe. As a result, the following results would be taken into the Estonian case. The overall probability of experiencing an ADE-DDI with a needed medical consultant visit was 3.8%, with 3% requiring ambulatory care, 0,3% needing a hospitalisation, 0.494% facing another medical outcome, and a minority facing death 0.006% [8].

The main outcome of the extrapolation is the potential amount of people that require a medical care as a result of ADE-DDI.

Cost determination and calculation

The direct cost of ADE-DDI is calculated in an example of previous studies and from the EHIF point of view. The outcome of the calculation is the evaluation of the additional cost occurring from potential ADE-DDI for EHIF. Cost calculation is based on the actual invoices for the care provided to the patients and takes the values delivered from the data. For increased accuracy and better comparison with the literature, the „patient'' is taken as a base cost unit. All values are marked in the monetary value in Euro currency, in the case of other currencies current exchange rate of 2022 was used.

The bottom-up approach is used for the current thesis, firstly author is calculating the cost on the microlevel, and in this case that is each group´s (Service type division) monetary value, and then moves to the total amount that will be an additional burden of EHIF occurring from ADE-DDI [49]. The data consists of information on the total cost of services provided for the patient with an additional sub-division of each service. It is prefiltered based on the characteristics and grouped in the desired way. The direct cost is calculated by the approximate average treatment cost that was associated with the diagnoses class. To calculate the possible cost for five years, the study was assigned with possible ICD codes (6 positions) [42]. The ICD codes were chosen by the main interactions and were linked to the main possible health consequences based on the Synbase database [32].

As a result, the author received data from EHIF for cost structure based on the five years of data and six ICD codes, which are therefore divided by the service type, healthcare provider (family physician/medical consultant) as well as ICD code.

In order to connect two databases and make the relevant assumption, the author is taking the actual potential cases of people having an ADE-DDI that were evaluated from the first dataset. Based on the results, the probability of experiencing an ADE under the care of a healthcare professional was determined to be 3.8%, with 3.0% resulting in the need for outpatient medical attention, 0.3% leading to hospitalization, and 0.006% resulting in mortality [8]. Afterward extracting and implementing potential ADE-DDI cases into the invoice datasets. The codes are being implemented to find the total cost of the ADE-DDI based on the following codes: G47, I50.1, K21, I50, N17, I10 [42]. Based on the characteristics above, the author is able to get the total amount of expenditures for each category. The data consists of the service provided as well as the patient count, in this case, the average cost per patient for each service type/category is being retrieved in the following way: $Cost\ per\ patient, Eur = \frac{Total\ sum\ per\ year, Eur}{Total\ patient\ count, Nr}$. The same formula is integrated in every category and on a yearly basis.

For the next proceedings, the average Cost per patient, Eur is being implemented into the percentages for the probabilities of different outcomes (Ambulatory care, Stationary, Death and Other medical care). This way allows to see how much additional cost brings each sector separately. Once each group cost is evaluated, the author is summarizing the total and achieves the total expenditure as a result of a potential ADE-DDI. Since the base point of the study is the „patient'' , additional division by the total patient count ADE-DDI on a yearly basis is needed $Cost\ per\ patient\ ADE - DDI, Eur = \frac{Total\ sum\ of\ ADE-DDI\ per\ year, Eur}{Total\ patient\ count\ of\ ADE-DDI, Nr}$.

Finally, the Cost per patient ADE-DDI is implemented into the Estonian population size for each year. This allows to evaluate the potential annual burden from the total population point of view. The table 2 represents the population by year [50].

Table 2 Estonian population within five years.

Source: Macrotrends [50], modified by the author.

Estonian population	2017	2019	2020	2021	2022
Number of people	1.317.549	1.327.039	1.329.444	1.328.701	1.326.062

To be able to compare the prices the healthcare price index is taken as a base of the comparison [51]. With the simple manipulation of the ratio, it is possible to calculate different scenarios [52]. The author evaluates the new price for each country in comparison to Estonia. This allows to see the real prices on the country level. The healthcare price index and ratio overview are visible in Table 3.

Table 3 Healthcare price index and ratio.

Source: The global economy 2017 [51], modified by the author.

Country	Healthcare price index	Ratio to Estonia
Japan	122.84	1.71:1
Germany	112.67	1.567:1
Sweden	189.48	2.639:1
Estonia	71.8	1:1

3 Results and main findings

3.1 Reflection and main findings

The data for C-D category DDI and financial overview based on the TOP 3 C-D category DDI was collected from EHIF for the period of 2017, 2019-2022. The data for 2018 is missing due to the technical error of EHIF. It was sent through email in Excel format and later analysed through Excel Analyse Toolkit and Pivot functions.

3.1.1 TOP 3 DDI and the following diagnoses

Analysis of the data from EHIF shows that there were over 11 Mln prescriptions with interactions. To evaluate the cost of an ADE, the author is evaluating the TOP 3 interactions. Figure 2 represents the three most significant and commonly encountered DDIs:

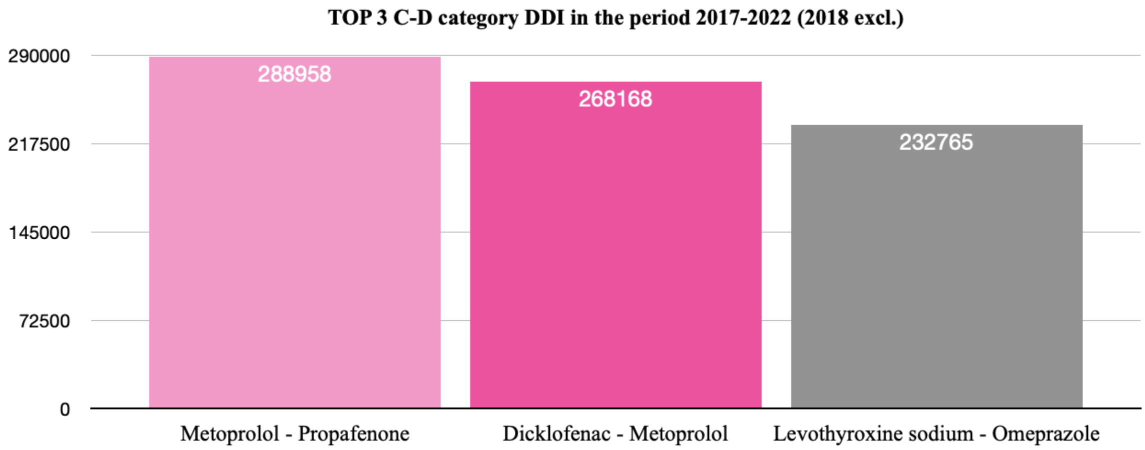

Figure 2 TOP 3 C-D category DDI in the period 2017-2022 (2018 excl.).

Source: EHIF data C-D category DDI, 2017, 2019-2022, modified by the author.

1. Metoprolol - Propafenone

This combination is the most common C-D category interaction in the Estonian Healthcare system within the last five years (2017, 2019-2022). For the given period, a total number of 288 958 interactions were reported. Both drugs fall into the category of antiarrhythmic drugs that work as a blocking agent. The consolidation of these two treatments has a high risk of ADE occurrence. The main common ADE is reported to be:

severe nightmare (ICD code: G47- Sleep disorder [42]) and left ventricular failure (ICD code: I50.1 - Left ventricular failure [42]). The symptoms are reported to happen in 50% of the cases, where two drugs are being prescribed. That is making the treatment process more complex and requires better dosage monitoring and follow-ups [53].

2. Dicklofenac – Metoprolol

The second most common interaction is Dicklofenac with Metoprolol, which resulted in the amount of 268 168 interactions. This combination is commonly used to manage hypertension as well as acute renal failure patients. Combining these two treatments has a high risk of ADEs. The most serious reported ADE is hypertension (ICD code: I10 - Hypertension [42]) and Acute renal failure (ICD Code: N17 – Acute renal failure) [54] [55]. The intake of the two drugs has an effect on renal prostaglandin synthesis, which has an impact on blood pressure. In order to minimize or exclude the effect, dosage adjustment and continuous monitoring are needed [56].

3. Levothyroxine sodium – Omeprazole

The third treatment set is Levothyroxine sodium in combination with Omeprazole that is used for treating patients with Gastro-oesophageal reflux disease. The frequency of prescribing the combination is almost a third of the total TOP 3 group. Total 42 017 patients were prescribed with the combination, and it results in 232 765 prescriptions. The main ADE is Helicobacter pylori-related gastritis (ICD code: B96 – Bacterial agents [42]) or Gastro-oesophageal reflux disease (ICD code: K21 – Gastro-oesophageal reflux disease [42]). The correct dosage and continuous monitoring help to prevent the loss of clinical efficiency of the drugs [57].

According to the results, the most prevalent ADEs are associated with cardiovascular conditions, such as hypertension and left ventricular failure. During the study period, a total of 789 981 interacting drugs were reported. The biggest share of 37% is the combination of Metoprolol and Propafenone, and the least 29% is the combination of Levothyroxine sodium - Omeprazole. In total, 133 512 patients were having a C-D category DDI. In comparison with the abroad examples, Hafizi reports that in a Switzerland study, more than half of the patients (51.1%) had an effect on the cardiovascular system by DDI with the most common symptom of Hypotension (12.6%), followed by the Hypertension, Hyperkalemia, etc [58].

3.1.2 Statistics of prescriptions reports of EHIF for a specific period

The EHIF provided the data for the period of five years with reported 1 091 649 patients, who were prescribed with C-D category DDI. The data provided consists of how many interactions the drugs have, patient count as well as the total number of receipts prescribed. By using Excel Analysis Tool-kit and descriptive statistics.

For checking the first theory the Estonian probability was assigned to likelihood of $\boldsymbol{x_{Estonia}} = \mathbf{23.54}\%$, that was implemented as the average of three studies made abroad. This leads to the following calculation of 23.54% out of total C-D category patients, $Patients\ with\ ADE - DDI\ (potential) = \frac{23{,}54*1.091.649}{100} = 256\ 974$ patients with ADE-DDI. The data shows that almost a quarter of the total C-D category patients will experience an ADE-DDI. Below in Table 4, the division on a yearly base is visible.

Table 4 Patients with ADE-DDI (potential) per year.

Source: Calculations by the author.

	2017	2019	2020	2021	2022	TOTAL
Patients with ADE	220 535	209 758	201 353	220 969	239 034	1 091 649
Probability, %	23,54%	23,54%	23,54%	23,54%	23,54%	23,54%
Patients with ADE-DDI	51 914	49 377	47 398	52 016	56 269	256 974

The next step of the evaluation was to estimate the results of probability based on the second theory of an actual ADE-DDI patient count evaluation. In this case, the likelihood of $\boldsymbol{y_{Estonia}} = \mathbf{9,37}\%$ is integrated to the total cohort of 1 091 649 patients. Accordingly the following formula is being used: $Patients\ with\ ADE - DDI\ (actual) = \frac{9{,}37*1.091.649}{100} = 102\ 254$. The new actual ADE-DDI shows that every tenth person would experience an ADE-DDI. Table 5 represents the yearly view on the actual ADE-DDI occurrence in Estonian Healthcare for the C-D category DDI patients, yearly.

Table 5 Patients with ADE-DDI (actual) per year.

Source: Calculations by the author.

	2017	2019	2020	2021	2022	TOTAL
Total patients count, nr	220 535	209 758	201 353	220 969	239 034	1 091 649
Probability, %	9,37%	9,37%	9,37%	9,37%	9,37%	9,37%
Patients with ADE-DDI	20 657	19 648	18 861	20 698	22 390	102 254

The following step is to evaluate, how many people need medical consultation help for ADE-DDI as a result of third theory. The author calculates different probabilities based on the Stark theory [8]. The table shows, what is the patients count for each category and then converts the number into a full value as the people count cannot be with the digits. In this case, the total number of 9 765 patients will require medical expertise based on the theory stated earlier. Also, a significant minority of the total ADE-DDI needs additional medical help or adjustments to the treatment. In comparison to the total amount of patients from the first theory, the patients who need a medical care is 3,8% and comparing to the second one it is 9,5%. Table 6 represents the probabilities of medical interaction as a result of ADE-DDI.

Table 6 Probabilities of medical interaction as a result of ADE-DDI.
Source: Author Calculation, 2023.

Medical visit needs	Probability %	2017	2019	2020	2021	2022	TOTAL
Ambulatory medical care, Nr	3%	1 557	1 481	1 422	1 560	1 688	7 709
Hospitalisation, Nr	0,30%	156	148	142	156	169	771
Death, Nr	0,006%	3	3	3	3	3	15
Other, Nr	0,494%	256	244	234	257	278	1 269
TOTAL, Nr	3,80%	1 973	1 876	1 801	1 977	2 138	9 765

3.1.3 Statistics of financial reports of EHIF for a specific period

The financial report from EHIF covers the view of the expenditures based on the six ICD codes and the division by age, specialty, diagnosis, and service & service type provided. In this way, the author can evaluate the percentage of overall spending compared to the ADE-DDI part as well with the differentiable specilialty. As the first part of the calculation was considering the family medicine area data, the percentage of it will be evaluated in further steps.

Figure 3 represents the EHIF expenditures in 2017, 2019-2022 for the ICD codes: I10, G47, K21, N17, I50.1, and B96. The figure shows the percentage and the value of all specialties and Family medicine (E300) separately. In this case, almost a quarter of the costs are coming from the family medicine area which makes 23% or 12 163 277 Eur from the total of 39 902 416 Eur for all areas.

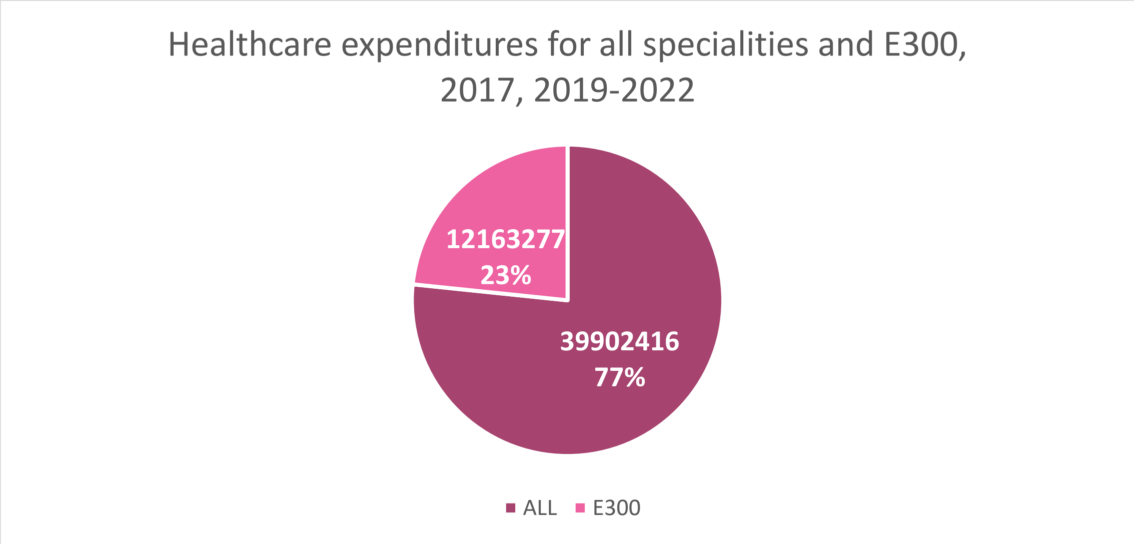

Figure 3 Healthcare expenditures based on 6 ICD codes for all specialties and E300, 2017-2022 2018 excl.).

Source: EHIF data for healthcare expenditures, 2017, 2019-2022.

Figure 4 shows the division of the cost based on the year and diagnosis code in a family medicine area. There is a clear visible uplift trend, that shows that over time, the family physicians are dealing more with the patients of the ICD groups (I10, G47, K21, N17, I50.1, B96). On average, the spending for the following diagnoses increased by 20%. Since 2018 is missing and it is impossible to evaluate the growth from 2017-2019 yearly, the biggest yearly growth happened in 2022 where expenditures grew by 27% compared to 2021.

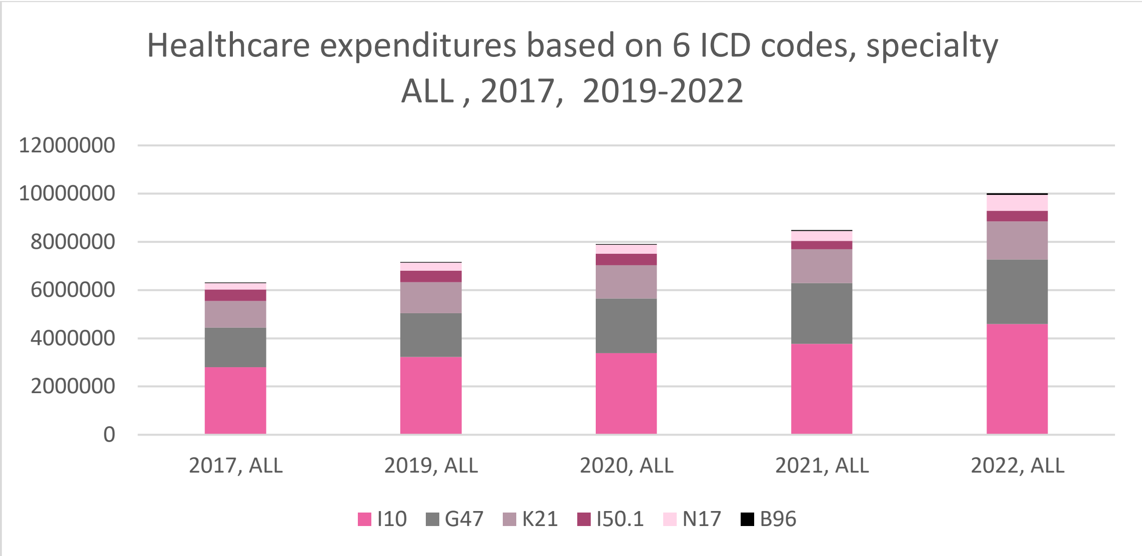

Figure 4 Healthcare expenditures based on 6 ICD codes for all specialties, 2017-2022 2018 excl.).

Source: EHIF data for healthcare expenditures, 2017, 2019-2022.

The present study includes a cost evaluation analysis for each patient group, performed on an annual basis. The calculation process is presented in Table 7, with each division being assessed separately based on the type of medical service provided. This approach enables the determination of the cost per patient for each group. Notably, the costs of death and stationary medical care were combined, as the cost of death is based on the stationary services price list and cannot be differentiated using the available data. In the final step, each patient group was multiplied by the number of patients obtained in the first calculation, using the corresponding cost per patient/group. The total cost was then divided by the number of patients, leading to total cost per patient, visible under Table 7.

Table 7 Medical care cost calculation based on the division, yearly.

Source: Author Calculation, 2023.

Medical visit needs	**2017**	**2019**	**2020**	**2021**	**2022**	**TOTAL**
Ambulatory medical care, Nr	1 557	1 481	1 422	1 560	1 688	7 709
Hospitalisation, Nr	156	148	142	156	169	771
Death, Nr	3	3	3	3	3	15
Other, Nr	256	244	234	257	278	1 269
Total patients C-D category ADE-DDI, Nr	1 973	1 876	1 801	1 977	2 138	9 765
Ambulatory medical care - Cost calculation						
Sum of Invoices, Ambulatory Eur	4 513 224 €	5 301 533 €	5 869 261 €	6 530 523 €	7 491 508 €	29 706 049 €
Count of Patient, Ambulatory Nr	170 672	175 764	74 664	73 291	81 263	575 654
Cost per Patient, Eur	26 €	30 €	79 €	89 €	92 €	317 €
Stationary medical care (Death included) - Cost calculation						
Sum of Invoices, Stationary Eur	1 305 591 €	1 404 218 €	1 472 884 €	1 447 069 €	1 816 845 €	7 446 607 €
Count of Patient, Stationary Nr	1 473	1 388	1 173	1 228	1.230	6 492
Cost per Patient, Eur	886 €	1 012 €	1 256 €	1 178 €	1 477 €	5 809 €
Other medical care - Cost calculation						
Sum of Invoices, Other Eur	495 905 €	458 320 €	563 577 €	518 337 €	713 621 €	2 749 760 €
Count of Patient, Other Eur	492	470	481	469	497	2 409
Cost per Patient, Eur	1 008 €	975 €	1 172 €	1 105 €	1 436 €	5 696 €
Medical care - Cost calculation for each division						
Ambulatory medical care, Eur	41 184 €	44 680 €	111 778 €	139 045 €	155 619 €	492 308 €
Hospitalisation, Eur	138 041 €	149 862 €	178 549 €	183 887 €	249 345 €	899 683 €
Death, Eur	2 761 €	2 997 €	3 571 €	3 678 €	4 987 €	17 994 €
Other, Eur	258 490 €	237 861 €	274 347 €	283 991 €	399 121 €	1 453 809 €
Total cost C-D category ADE-DDI, Eur	440 477 €	435 400 €	568 245 €	610 600 €	809 072 €	2 863 794€
TOTAL per patient, Eur	**223 €**	**232 €**	**315 €**	**309 €**	**378 €**	**1 458 €**

The result is therefore implemented into other theories to view the different scenarios of cost in case of all ADE-DDI will result in medical care need. The third theory costs work as a base. The cost calculation in case of all patients with ADE-DDI require a medical help is visible in Table 8.

Table 8 ADE-DDI cost calculation for different scenarios.

Source: Author Calculation, 2023.

Theory	Cost calculation for each theory	2017	2018	2020	2021	2022	TOTAL
1	Total patients C-D category ADE-DDI, Nr (Potential)	51 914	49 377	47 398	52 016	56 269	256 974
1	Total cost C-D category ADE-DDI, Eur	11 576 822 €	11 455 464 €	14 930 370 €	16 072 944 €	21 269 682 €	75 305 282 €
2	Total patients C-D category ADE-DDI, Nr (Actual)	20 657	19 648	18 861	20 698	22 390	102 254
2	Total cost C-D category ADE-DDI, Eur	4 606 511 €	4 558 336	5 941 215	6 395 682	8 463 420	29 965 164 €
3	Total patients C-D category ADE-DDI, Nr (Medical only)	1 973	1 876	1 801	1 977	2 138	9 765
3	Total cost C-D category ADE-DDI, Eur	440 477 €	435 400 €	568 245 €	610 600 €	809 072 €	2 863 794€
	TOTAL per patient, Eur	**223 €**	**232 €**	**315 €**	**309 €**	**378 €**	**1 458 €**

In order to make a better comparison the healthcare price index is being used. Table 9 represents the healthcare price index based on the country ranking [51]. The ratios were applied to equalize the data, the actual prices were then divided by the ratio to be comparable with Estonian level.

Table 9 Healthcare price index and ratio.

Source: The global economy 2017 [51], modified by the author.

Country	Healthcare price index	Ratio to Estonia	ADE-DDI cost per patient, Eur	Applied ratios based on Estonian cost, Eur	Difference Estonian cost VS Ratio adjusted, Eur
Japan	122.84	1.71:1	413 €	242 €	136 €
Germany	112.67	1.567:1	465 €	297 €	81 €
Sweden	189.48	2.639:1	804 €	304 €	74 €
Estonia	**71.8**	**1:1**	**378 €**	**378 €**	**- €**

As the final step of the calculation, the author is calculating the annual estimated burden for the Estonian Healthcare system. Table 10 shows the expenditure within five years using the cost retrieved from Table7.

Table 10 Total medical care cost, yearly.

Source: Author Calculation, 2023

Estonian population	**2017**	**2019**	**2020**	**2021**	**2022**	**TOTAL**
People, Nr	1 317 549	1 327 039	1 329 444	1 328 701	1 326 062	**6 628 795**
Total cost per patient, Eur	223 €	232 €	315 €	309 €	378 €	**1 458 €**
Annual cost for Estonia, Eur	**293 813 427 €**	**307 873 048 €**	**418 774 860 €**	**410 568 609 €**	**501 251 436 €**	**1 932 281 380€**

4 Discussion

4.1 C-D category DDI

Based on the analysis of the C-D category interaction in the family medicine area, the total amount of 1 091 649 patients was reported in a five year period. To evaluate the potential amount of people suffering from ADE-DDI, three calculations were made. The first theory evaluated the possibility of a potential ADE based on the the averaging method of three studies, that lead to 23,54% probability of ADE-DDI in the Estonian healthcare. Based on Estonian results, 256 974 of the total amount of patients experienced ADE-DDI in a five year period. The result stays almost within the range of probable likelihood of ADE-DDI that is 5-20% [44]. While looking at the division of the slight fluctuation of the patient count per year is visible. The relatively small down lift of patients happened in COVID time 2019-2020. Starting in 2021, the patient count started rising by 9%.

The second theory was an estimation of the actual ADE-DDI cases relying on the average of three international researches. The new probability of an actual ADE-DDI was 9,37% for Estonia. As a result, the average yearly actual cases would be reported at 20 451 cases, and in five year total 102 254 patients. It is worth of highlighting that the difference between the first two approaches are roughly half. This means that the potential estimation is highly increased to the maximum possible probability. Whereas, in reality the ADE-DDI actual cases are twice likely to happen.

Due to the reason that not all ADE-DDI requires a medical visit, the probabilities were used to evaluate the patient amount in different scenarios. Since both of the countries have similar characteristics in terms of insurance and geographical location, German study probabiltities for the medical professional need were implemented accordingly [8]. The 3.8% likelihood reported a final patient count as 9 765 patients of the total patients being reported in C-D category DDI. The annual average patient count stayed for 1 953 patients per year in the period of five years.

Another interesting finding is the proportion of patients in both ADE only and ADE-DDI cases, as the patient count has almost no fluctuation over the years. The slight down lift is visible in 2020, when the Corona crisis was evolving. From 2021, the uplift tendency is visible from the trend perspective. The biggest proportion covers the ambulatory medical care need, whereas the last ones go to death and hospitalisation. This shows that even though the class of C-D category DDI is among the most serious ones, where adjustment or avoiding is necessary, the amount of serious consequences is really low. The reason for that might be in the doctor´s decision-making flow, as the system is warning the user of the adjustments. Therefore, the doctors may change the treatment plan according to the system warnings.

For calculation reasons, the TOP 3 DDI was analysed and assigned with the relevant ICD code based on the SynBase system. The most common interactions were: 1) Metoprolol – Propafenone; 2) Dicklofenac – Metoprolol; 3) Levothyroxine sodium – Omeprazole. All of the DDI groups were divided relatively stable on average 33% of the group. The DDI reported had six main ADE as a result of an interaction, the ADE in this case is the diagnosis that results from the DDI. Diagnoses were assigned with the ICD codes that are: 1) G47- Sleep disorder; 2) I50.1 - Left ventricular failure; 3) I10 -Hypertension; 4) N17 – Acute renal failure; 5) B96 – Bacterial agents; 6) K21 – Gastro-oesophageal reflux disease.

Upon data retrieval, the author of the study assessed the proportion of family physicians to specialists, which was determined to be 23% and 77%, respectively. To provide a comprehensive evaluation of patients seeking care from different healthcare providers, the analysis included all medical specialties. The subsequent step involved analyzing different scenarios resulting from ADE and DDI. Based on the provided DDI, six ICD codes were assessed to inform further research. The analysis indicated that the majority of healthcare spending was attributed to the CVD group, with I50.1 and I10 accounting for 50.1% of the total spending and representing the highest cost area. In addition, it is worth mentioning that the biggest proportion is coming from cardiovascular diseases which correlates with the Hafizi study, where he reported 51.1% of the DDI occurring from CVD [58].

The next step was the evaluation of the total cost per patient as a result of ADE-DDI. Firstly, the author evaluated each group’s cost per patient that later summed together to find out the total cost per patient for the ADE-DDI. The biggest proportion is covered by ambulatory care. Each year, on average 5.9 Mln Eur is spent on the medical care, however, the average cost is 63 Eur per patient, which makes it the lowest within the cohort study group. The highest cost per patient is coming from „Other medical care'', which takes an average of 1 139 Eur. Based on each category, it is clearly visible that the cost has been rising on a yearly basis. The only down lift is visible within the Other medical care in 2019, where costs decreased by 1,2%. The highest spending among all groups is recorded in 2022, where in total, the expenditures raised by 84% on average within all years compared to 2018.

In total for a five year period, the ADE-DDI brought an additional 2 863 794 Eur cost for the EHIF. The trend is showing the rising cost as well as the amount of people in need for medical expert visits. Based on the 2022 data, the average cost per patient ADE-DDI is 378 Eur. The cost is the lowest among the researches being analysed, which proves the author´s hypothesis (H0) C-D category DDI related costs assumed by the health care system are lower in Estonia than in comparable countries. The closest ADE-DDI patient costs are recorded in Japan and Germany, 413 Eur and 465 Eur [11] [8]. That is followed by Sweden, where patient the cost is 804 Eur, which is more than twice as high as in Estonia [10].

The research contains of three different scenarios of ADE-DDI cases evaluation, where two calculate only the cases and the third one the outcome in the face of medical care need. The first averaging method shows a probability of 23,54% and a burden of 75,3 Mln Eur. In the second scenario in the face of actual ADE-DDI cases probability of 9,37%, the burden is almost three times less comparing to the potential cases. The incremental cost of EHIF would result of 29,9 Mln Eur. Both of the scenarios are aligned with the international parameters as the results stay within the range of 5-20% [44]. All of the values are based on the calculation resulting from Stark probabilities of 3.8% [8].

For a better overview of healthcare prices, it is needed to implement the index with the following ratios. Among the four countries observed, Estonia has reported the lowest healthcare price index of 71.8 [51]. It means that on average Estonian healthcare prices are almost twice lower compared to the other countries. As a result of ratio implementation, the author evaluates new prices that can be compared to Estonian ones. The closest pricing occurs in Sweden, where the new adjusted price is equal to 304 Eur, which is 74 Eur less expensive healthcare per person. The biggest difference compared to Healthcare prices of Estonia is in Japan, where the new price is expected to be 242 Eur per person.

In order to evaluate the additional annual burden for the whole population of Estonia, the author was multiplying the Cost per patient by the total population. In total for five years, Estonia would have gotten a burden of 1.9 Bln Euros. The highest population count of 1.33 Mln people was reported in 2020 and would cost 418 Mln Euros. Whereas, due to the higher cost occurring in 2022, the peak cost was assumed to be 501 Mln Euros. Due to the high difference in population size, the data cannot be compared to other researches.

4.2 Areas for further research

For further research, the author is recommending to use personalised data to be more specific and track the possible outcomes based on real-world numbers. Since this was the main limitation of the study, it did not allow the author to evaluate the actual situation and make more accurate conclusions. This way will allow to see the flow of the patients and differentiate the main ADE and costs evolving from the DDI. Later comparing the data with the current and international studies.

Another interesting aspect would be the cost determination for the hospitals due to the better transparency, as well as bigger comparison points with international researches. The idea would be to show the full path of the patient who experienced ADE-DDI and calculate the costs occurring due to the event. Hospital calculation could be done using two approaches the patient specific as well as the hospital burden in the face of working hours of medical personnel, etc. Due to the uniqueness of financial assumptions, the author believes that there are many aspects that could and should be analysed.

5 Summary

DDI as a global concern is being analysed from different angles. There are two main outcomes that are being affected by the DDI concept: clinical and economical. Both sides have a direct impact in the face of the treatment process and the cost occurring from it. The current thesis evaluated the financial impact of DDI on the Estonian Healthcare system within the period of five years. Prescription data as well as financial reports were used to calculate additional costs occurring as a result of ADE-DDI. The study aimed to answer two main questions, indicating that the most common C-D category interactions in the family medicine which are: 1) Metoprolol – Propafenone; 2) Dicklofenac – Metoprolol; 3) Levothyroxine sodium – Omeprazole. The total 789 981 interactions were reported with the main ADE falling into CVD. Another finding is the financial burden of the Estonian healthcare system as a result of DDI. The single patient reports an additional cost of 378 Eur (2022), whereas in the period of five years the C-D category patients brought an additional 2 863 794 Eur worth of costs for EHIF. However, the actual burden is likely to be higher as the cohort was narrowed to C-D category DDI. In case if all population will be affected, the burden of the country will be 501 Mln Eur in 2022.

The study found out that Estonia has the lowest spend of 378 Eur occurring from ADE-DDI. That proves the hypothesis that was tested by the author. The closest expenditures were shown in Japan and Germany, 413 Eur and 465 Eur respectively. The highest spending is coming from the stationary and other medical need services bringing an incremental 2 353 493 Eur. Whereas the most used service type by the patients is recorded to be ambulatory care.

Based on the calculations Estonian patient count suffering from ADE-DDI is 9 765 from the total amount of C-D category patients. The author assumes that the doctors are checking widely the warnings and changing the treatment plan when the alert is shown. This directly affects the number of patients who experience an ADE-DDI with a need for medical care.

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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)

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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