JIMMA UNIVERSITY
COLLEGE OF PUBLIC HEALTH AND MEDICAL SCIENCES
DEPATRTMENT OF PHARMACY

Assessment of potential drug-drug interactions among outpatients receiving cardiovascular medications at Jimma University Specialized Hospital, Jimma zone, Oromia region, South West Ethiopia

BY:
LEGESE CHELKEBA

THIS THESIS IS SUBMITTED TO GRADUATE STUDIES, DEPARTMENT OF PHARMACY, COLLEGE OF PUBLIC HEALTH AND MEDICAL SIENCES, JIMMA UNIVERSITY IN PARTIAL FULLFILLMENT OF THE REQUIREMENTS FOR DEGREE OF MASTER OF SCIENCES IN CLINICAL PHARMACY.

May, 2011
JIMMA, ETHIOPIA

JIMMA UNIVERSITY

COLLEGE OF PUBLIC HEALTH AND MEDICAL SCIENCES

DEPATRTMENT OF PHARMACY

Assessment of potential drug-drug interactions among outpatients receiving cardiovascular medications at Jimma University specialized hospital, Jimma zone, Oromia region, South West Ethiopia

By Legese Chelkeba

Advisors

1. Fessahaye Alemseged (MD, MPH)
2. Worku Bededa (B.pharm, MSc, phD student)
3. Ephrem Abebe (B.Pharm, MSc)

Abstract

Background: - The quality of pharmacotherapy is highly dependent on the process of choosing a drug in relation to nature of the disease. Several factors should be considered in choosing optimal pharmacotherapeutics strategy including efficacy, safety, availability, and cost of the drugs.

Objective: - To assess potential drug-drug interactions and risk factors in outpatients taking cardiovascular drugs at Jimma University specialized hospital

Methods: - A cross-sectional study was conducted to assess potential drug–drug interactions at Jimma University Specialized hospital from Feb. to April, 2011. All sampled outpatients (332) on cardiovascular medications and visiting the hospital during the study period were included. MicroMedex software was used to screen drug-drug interactions and binary logistic regression was made using spss window software versions-16 to assess the descriptive and association of variables

Results: - A total of 332 patients who were prescribed 1249 drugs (average, 3.76 drugs per prescription) were enrolled and the frequency of potential DDIs was found to be 241 (72.6%). It was found that 200 (67.3%) of the potential DDIs were of "moderate" severity, delayed in onset and good in documentation status. Cardiovascular drugs carried a risk of DDIs (676 drugs, or 77.5%). Patients who prescribed many drugs by medical intern had a higher risk of developing DDIs. The most common potential DDI observed was between enalapril and Furosemide (n = 59).

Conclusion: - patients with cardiovascular disorders are subjected to high risk of potential drug-drug interactions and the number of drugs prescribed and educational level of the prescribers has a high significantly associated with the occurrence of potential drug-drug interactions. Therefore, it is imperative that health care professional constantly alert to recognize this problem and provide appropriate mechanisms for management, thereby reducing adverse outcomes.

Key words: - drug-drug interactions, hospital, outpatients, prescriptions, southwest Ethiopia and risk factors

Acknowledgement

First and foremost, my heart-felt gratefulness goes to the Almighty God, the one who has no end for answering my questions in many ways and blessing me with the abilities that have enabled me to bring this thesis in its current shape.

I wish to express profound appreciation to my advisors Dr. Fessahye Alemseged Mr.Worku Bededa and Ephrem Abebe for their contribution to the preparation of this thesis by providing me with guidance, support, and constructive comments throughout my thesis preparations

Finally, my gratitude goes to my wife Shewaye Balata for her help in writing this thesis and for all help she provide me from the start up to the end and my daughters Hawi and Sena for their patience, prayers and support at home

Table of contents

Lists of Tables

Lists of figures

\

Acronyms

ACEIs- Angiotensin converting enzyme inhibitors

ADEs- Adverse drug events

ADRs- Adverse drug reactions

CCB- calcium channel blockers

CNS- central nervous system

DDIs- Drug-drug interactions

DIs- Drug interactions

ICU- intensive care unit

MAO_AIs- Monoamine oxidase A inhibitors

NSAID- nonsteroidal anti-inflammatory drug

OTC- over the counter

1. Introduction

1.1. Background

The quality of pharmacotherapy is highly dependent on the process of choosing a drug in relation to nature of the disease. In the process of choosing the optimal pharmacotherapeutics strategy, factors like route of administration, dose, contraindications, the potential for adverse drug reactions and costs play an important role. The possibility of a drug influencing the safety or efficacy of another drug (a drug-drug interaction) is an additional variable in making the optimal choice for pharmacotherapy (1).

An interaction is said to occur when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink or by some environmental chemical agent. The outcome of a drug interaction could be increased toxicity, reduced effectiveness or added effects of either of the drugs. For example, there is a considerable increase in risk of severe muscle damage if patients on statins start taking azole antifungals. Similarly, patients taking MAO_AIs may experience an acute and potentially life-threatening hypertensive crisis if they eat tyramine-rich foods such as 'cheese'. On the other hand, patients taking warfarin with rifampicin need more warfarin to maintain adequate and protective anticoagulation; in the same way patients taking tetracyclines or fluoroquinolones need to avoid antacids and dairy products to maintain the effectiveness of these drugs. These aforementioned outcomes of drug interactions are undesirable. However the outcomes of drug interactions can be beneficial to the patients. The deliberate co-prescription of different antihypertensive drugs and anti-TB drugs could be good examples here. The mechanisms of both types of interaction, whether the outcome is undesirable or beneficial, are often very similar, but the undesirable interactions are the main goals of our current investigation (2, 3).

1.1.1. Mechanisms of drug interaction

The mechanisms of drug-drug interactions can be subdivided into those that involve the pharmacokinetic process and those that involve pharmacodynamic course of action. A pharmacokinetic drug interaction is related to the body's effect on the drug; thus it can be caused by an alteration in absorption, distribution, metabolism, or excretion of a drug. An example can be an increase in the systemic concentration of a renally eliminated drug because of renal insufficiency. A pharmacodynamic drug interaction is related to the drug's effect on the body. It can be either beneficial or detrimental to patients. A beneficial example is the additive blood pressure–lowering effect ACE inhibitors and calcium channel blocker (CCB). The detrimental effect can be observed when alcohol and other CNS depressants are combined (4, 5).

1.2. Statement of the problems

Pharmacotherapy is the most common therapeutic procedure at any level of health care. However, it may also contribute to morbidity due to adverse drug effects. One important type of adverse drug effect is the adverse drug interaction, which has been defined as two or more drugs interacting in such a manner that the effectiveness or toxicity of one or more of the drugs is altered (6).

The incidence of ADRs has been estimated to be 2.2- 30% for hospitalized patients and 9.2- 70.3% for ambulatory patients. DDIs are estimated to account for 6-30% of all ADRs and 6% to 10% of ADEs. The cost of drug-related morbidity is substantial and may exceed $177 billion per year (4, 7). A review of nine studies of the epidemiology of DDIs in USA hospital admissions found that the reported incidence ranged from 0 - 2.8 %. In the Harvard Medical Practice study of ADEs, 20% of events in an acute hospital in-patient setting were drug related, of these, 8% were considered to be due to DDIs. The Boston Collaborative Drug Surveillance Program examined 83,200 drug exposures in 9,900 hospitalized patients and identified 3,600 ADRs. A total of 234 (6.5%) adverse drug reactions caused were attributed to DIs (7).

Retrospective drug utilization review study done on incidence of clinically relevant potential drug-drug interactions in a large ambulatory population in USA on approximately 2.9 million patients with more than 30 million prescriptions dispensed in the 12-month period from September 2001 through August 2002 showed that a total of 244,703 cases of potential DDIs were identified (0.8% of total prescription claims) by simple automated screens. The combination of sophisticated DDI filters and clinical pharmacist review reduced the incidence of potentially serious DDIs by 94.3 % (8).

A large number of cardiovascular drugs are introduced every year and thus, new possible interactions between medications have increased the risk of hospitalization. Multiple drug regimens used for the treatment of complicated hypertension also carry the risk of adverse interactions (9). For example, a prospective observational study from Oct 2007 to Apr 2008 was carried out in ‘cardiology department’ of a hospital in South India on a

total of 812 patients to identify the incidence of potential drug-drug interaction showed that the incidence was 30.67 % (10).

There are various factors, contributing to the occurrence of DIs. This includes multiple pharmacological agents, multiple prescribers, use of non prescription drugs, drugs of abuse and patient nonadherence. Various patient variables are also implicated for drug interactions, i.e. age, genetic factors, disease states, renal function, hepatic function, alcohol consumption, smoking, diet, environmental factors, individual variations (11).

Furthermore, the health system in Ethiopia is totally dependent on the skills and knowledge of health professionals to identify and correct possible interactions. No software is utilized at any levels and types of health care system in Ethiopia to detect or monitor prescriptions for possible drug-drug interactions. Studies have suggested that medication use can be improved by better communication among patients, physicians, and pharmacists (4). This is also nearly absent in Ethiopian health care system. Health system is also loosely controlled, patients are buying drugs as OTC and if not identified through history, there is a high possibility for interaction between prescription and OTC drugs. Furthermore, due to economic problems, the probability of monitoring patients with concomitantly existing diseases using sophisticated instruments is not visible posing the patient to drug-disease interactions.

Despite these all serious consequences, drug-drug interactions in Ethiopia have never been considered as serious public health problem. Even in relatively better set up like JUSH, it was found that prevention of drug-drug interactions was far less than adequate and the figure was greater than what has been obtained in India. The purpose of this study was to assess potential drug-drug interactions and associated risk factors among adult patients receiving cardiovascular medications who have follow up in chronic care clinic of JUSH.

2. Literature review

A drug-drug interaction occurs if one drug (precipitant drug) alters the effect of another (object drug), and the outcome may be harmful if the interaction increases the toxicity or reduces the intended effect of the object drug. It has been estimated that between 10% and 20% of hospital admissions are caused by drug-related events, but only about 1% are caused by drug interactions. Between 2% and 3% of hospitalized patients in a medical ward experience adverse reactions caused by drug interactions (12).

A one-year outpatients' prescription data retrieved from the hospital computer records to estimate the rate of potential drug-drug interactions in outpatients of a typical Thai university, Thailand hospital and to identify risk factors for such interactions in Thai patients demonstrated that the overall rate of potential drug interactions was 27.9% with a maximal value of 57.8% at the Department of Psychiatry. The rate of the most potentially significant interactions was 2.6%, being the highest in the Department of Medicine (6.0%), with isoniazid vs. rifampin as the most common interacting combination. The rate increased with the patient's age and prescription size (P = 0.000). The odd's ratio of having at least one potential drug interaction was 1.8 (64.2%) when age increased by 20 years (P = 0.000) and 2.8 (165.7%) when another drug was added (P = 0.000). The rate of potential drug interactions was the same for both genders. The rate of potential drug interactions detected across prescriptions was higher than within prescriptions and was dependent on the time interval between prescriptions (13).

Retrospective database study of computer-based patient records to investigate the occurrence of potential *drug* interactions in primary health care from the perspective of the prescribing general practitioner analysis was carried out on approximately *55,000* drug prescriptions at *Linkciping University and Kronan Health Centre, Sundbyberg, Sweden reported that* a total of 1 074 *cases* of potential drug interactions were found, which corresponds to a rate of 1.9% of all *drug* prescriptions. The incidence rate of potential interactions was 12% for all patients at risk *(those* receiving two or more drugs) and 22% for elderly (> 65 years of age) patients at risk (6).

A study done in Mexico City on 624 ambulatory patients over 50 years of age with non-malignant pain syndrome, who made ambulatory visits to two IMSS family medicine clinics in Mexico City, showed that the average number of prescribed drugs was 5.9 ± 2.5. About 80.0% of patients had prescriptions implying one or more potential drug-drug interactions and 3.8% of patients were prescribed drug combinations with interactions that should be avoided. Also, 64.0% of patients had prescriptions implying one or more potential drug disease interactions. The factors significantly associated with having one or more potential interactions included: taking 5 or more medicines (adjusted Odds Ratio (OR): 4.34, 95%CI: 2.76–6.83), patient age 60 years or older (adjusted OR: 1.66, 95% CI: 1.01–2.74) and suffering from cardiovascular diseases (adjusted OR: 7.26, 95% CI: 4.61–11.44) *(14).*

A cross-sectional study that was conducted in Switzerland on age-related differences in the prevalence of potential drug-drug interactions in ambulatory dyslipidaemic patients treated with statins showed that 483 (17.6%) patients aged ≤54 years, 732 (26.7%) aged 55–64 years, 924 (33.7%) aged 65–74 years and 603 (22.0%) patients aged ≥75 years. In this study, patients ≥75 years had significantly more pharmacologically active substances prescribed than patients aged ≤54 years (mean 5.8 vs. 3.8, respectively; $p < 0.001$) and cardiovascular diseases such as coronary heart disease, heart failure or arrhythmias were also significantly more prevalent in patients aged ≥75 years than in younger patients *(15).*

According to study done in 2005 in Nablus, Palestine, extent of potential drug interactions among 876 patients with cardiovascular diseases who were receiving one or more antihypertensive medications was evaluated. The extent of drug interactions reported include 16 cases (3.7. %) leve1; 34 cases (7.8%) level 2; 116 case (26.6%) level 3; 136 cases (31.4%) level 4; and 131 (30.3%) level 5 interactions. The study also indicated that both age and number of drugs were significantly associated with the potential for significant interactions at all levels with a p value less than 0.025 (9).

A descriptive study conducted on 11280 regular, randomly sampled insured prescriptions issued by general physicians and specialists during the fist six months of the year 2000 in

eight drug stores of Sari Township to evaluate cardiovascular drug interactions showed that 50% of the prescriptions had drug interaction (16).

A study done in Japan on the extent of potential antihypertensive drug interactions in a medicaid population in 2002 on 1574 ambulatory patients reported that depending on age and sex, 23% to 48% of patients had a potential interaction of high significance and 55% to 84% had at least one potential interaction. Both increasing age (P = 0.0007, odds ratio [OR] 1.012 [1.005, 1.019]) and number of drugs (P <0.0001, OR 1.120 [1.092, 1.150]) were significantly associated with the potential for a highly significant drug interaction in the univariable models. Female sex was not significant (P = 0.56, OR 1.074 [0.845, 1.364]). The multivariable model found that there was a significant interaction between age and the number of drugs in the regimen (P < .0001) (4).

2.1. Significance of the Study

This study was designed to assess the prevalence of drug-drug interaction so that helps to facilitate decision making and quality improvement activities in health care delivery system. Without sound knowledge of potentially interacting drugs, it would be difficult to safeguard the public at large from the consequences of adverse drug interaction as result of multiple drug use. Patients having cardiovascular disease may take two or more potentially interacting drugs that can be detrimental to their health.

Our country, Ethiopia, doesn't have any software that is used to alert the health professionals about these potential interactions and hence, health professionals use their own limited knowledge to detect clinically harmful interactions. However, it is not easy to know all drug-drug interactions that are potentially harmful. Therefore, this study can create awareness for health professional about drug-drug interactions; it will even point out the policy makers where the gap lies in public health improvement policy and the importance of health professionals that will suit to prevent these harmful effects. In addition, it will provide preliminary data to further investigate potential drug-drug interactions nation wide

2.2. Conceptual framework for this study

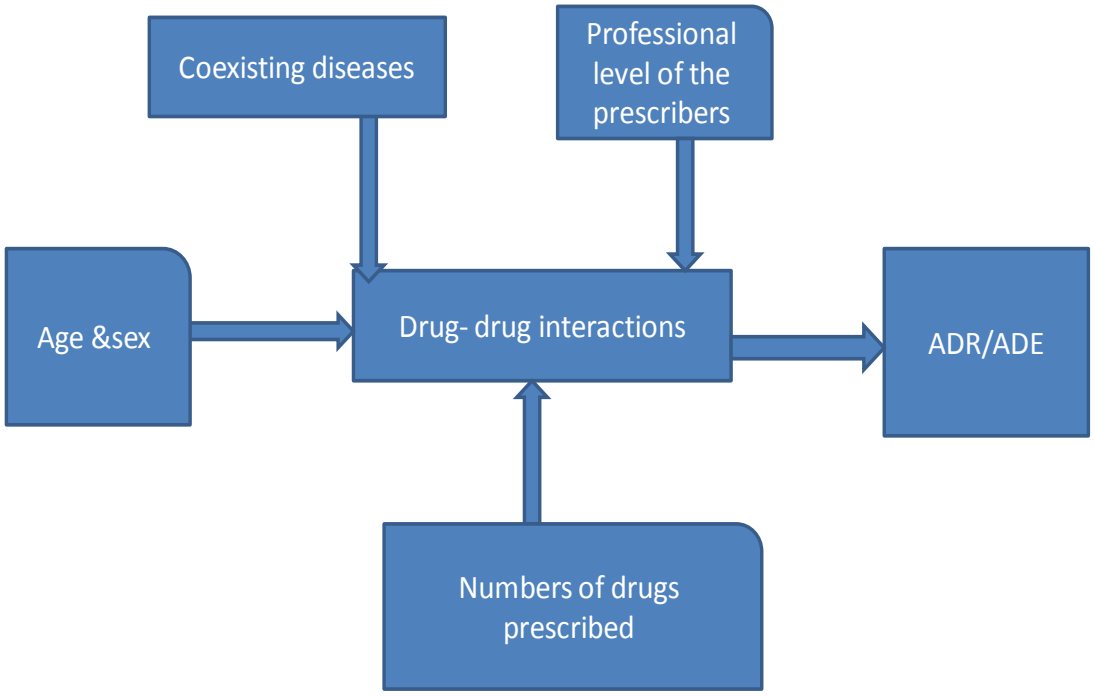

Figure 1:- Conceptual framework for this study at JUSH, Jimma, and May 2011

3. Objectives of the study

3.1. General objective

To assess potential drug-drug interactions and identification of associated risk factors in outpatients receiving cardiovascular medications at chronic care follow up clinic, Jimma University Specialized hospital, Jimma Zone, Oromia Region, Southwest Ethiopia.

3.2. Specific objects

1. To determine the frequency of potential drug-drug interactions
2. To assess the pattern of drug-drug interactions by clinical significance
3. To indentify the category of drugs with high risk of potential drug-drug interactions
4. To identify the high risk drugs responsible for potential drug-drug interactions
5. To identify the top 15 commonly interacting drugs pairs with their, clinical significance and possible adverse outcomes
6. To identify factors related to potential drug-drug interaction

3.3. Research Hypothesis

There are potential drug-drug interactions among outpatients receiving cardiovascular drugs and a strong relationship exists between ages, sex, number of drugs prescribed, presence of co morbidities, levels of education of prescribers and frequency of drug-drug interactions.

4. Methods and patients

4.1. Study area and Period

The study was conducted at Jimma university specialized hospital, Jimma zone, Oromia Region, Southwest Ethiopia from Feb. 1 to April 2011. Jimma town has a total population of 2,773,730 out of which 1,382,460 are males and 1,391,270 are females (*Ethiopian demographic and health survey, central statistical authority, 2007).*

.

Jimma University Specialized Hospital is found in Jimma town, which is located at 350km south west of Addis Ababa. Jimma University Specialized Hospital is one of the oldest public hospitals found in the country. Currently, it is the only teaching and referral hospital in the South Western of the country. It was established in 1937 G.C by Italian conquerors for the services of their soldiers. It provides specialized health services through its medical and other clinical and diagnostic departments for approximately 9,000 in-patients and 80,000outpatients each year with bed capacity of 450. It accommodates a total of more than 550 staffs out of which 395 are health professionals including 36 specialists, 77residents, 150 medical interns, 30 dental interns, around 10 pharmacists and the rest are nurses and medical laboratory technologists. Cardiovascular clinic is one of the chronic follow up clinics run twice weekly. The service is rendered by internists, medical residents, medical interns, and nurse. There are 2101 patients registered for follow up as to December 24, 2010.

4.2. Study Design

A cross-sectional study was conducted to assess potential drug-drug interaction among patients receiving cardiovascular medications and associated risk factors.

4.3. Population

4.3.1. Source Population

All out patients who visit the hospitals for cardiovascular problems during the study period

4.3.2. Study Population

All sampled adult outpatients with cardiovascular diseases who are attending the cardiovascular care clinic for follow up during data collection period were taken as study population

4. 3.2.1. Inclusion and exclusion criteria

Patients eligible were those who fulfill the following criteria:

1. The patient who were treated on outpatient basis
2. The medication profile contained at least two drugs of one belongs to drugs for cardiovascular diseases
3. The patient diagnosed with one or more cardiovascular diseases, such as heart failure, hypertension, ischemic heart diseases, or arrhythmias
4. The study involved only patients having three or less months follow up. Normally, adult cardiac follow up clinic appoints patients for one, two, three and six months. This study was not involve patients with six months appointment because these patients were patients that are receiving benzanthine penicillin prophylaxis and supposed to have less complicated cardiovascular problems.

Patients were excluded from the study if

1. It was impossible to obtain reliable information about drug therapy
2. The patient was pediatric. As to Jimma University Specialized hospital, the pediatric services were given to patients less than or equal to 14 year-old and the service for these patients group was given at separate clinic.
3. Pregnant women

4.3.3. Sample Size Determination

In order to determine sample size for quantitative method, formula for estimating single population proportion was used based on the following assumptions.

$$n = \frac{(z_{\alpha/2})^2\, p\,(1-p)}{d^2} = \frac{(1.96)^2 \times 0.5 \times 0.5}{(0.05)^2} = \frac{0.9604}{0.0025} = 384$$

Where n= the minimum sample size required

P= estimated prevalence rate of drug-drug interaction in outpatients taking cardiovascular medications. It is unknown in Ethiopia and an expected prevalence of 50 %(0.5) was used

d= the desired precision (marginal error) between sample size and population parameter was 5%.

$z\alpha/2$= standard normal score at 95% confidence interval

Therefore, the minimum sample size calculated was 327.

Since the source population is less than 10,000 the sample size was adjusted with the following correction formula.

$$nf = \frac{n}{1+\frac{n}{N}}$$

nf= 302, where n=384, N=1440 will be taken because this was the maximum number of patients that were appointed in three months. The rest patients were supposed to be those appointed for six months.

When a contingency of 10% was used for incomplete data where appropriate information was not available, the required total sample size was 302+30 = 332

4.3.4. Sampling Techniques

The sample technique that used to select patients was systemic random sampling method by considering both the inclusion and exclusion criteria. The data collection period was three months and the follow up service for adult patients with cardiovascular diseases was Friday. So, estimated daily load of patients with cardiovascular diseases was 120. This made of 120 adult outpatients with cardiovascular diseases visiting the cardiac follow up clinic per week and about 480 per month. To get sampling interval the expected patients with cardiovascular diseases was divided by the sample size (332) which was approximately 4. Therefore, information required from card of every four patient coming to the follow up clinic was recorded until the total of 332 patients obtained. In cases

where the patient have two or more follow up an appointments within a month, cross check was done from their card records/charts

4.4. Variables

4.4.1. Dependent Variables

- potential drug-drug interactions

4.2. Independent Variables

- Patient characters tics(age, sex)
- Number of drugs used
- Presence of Comorbidities
- Professional status of the prescribers

4.5. Data Collection

Data was collected using pretested, well structured format prepared by principal investigator. Data collection was carried out by 6 diploma nurses working in the cardiac clinic supervised by 4 medical interns working in the same roof after taking appropriate training.

4.6. Data Quality Control

The quality of data was assured through careful design; proper training of data collectors and supervisors and pretesting of the structural format made before the actual data collection time. Data clearing was done every day after data collectors finish collection by principal investigators to check for completeness of the questioner.

Pretest

A week before the actual data collection time, pretesting of the data collection format was undertaken in Jimma University specialized on 20 patients that were not included in actual study to determine the acceptability of the structural format, performance and adequacy of data collectors and supervisors and necessary modifications was made to the data.

4.7. Data Processing

Data clearing was done every day and formats with insufficient information were excluded from the study.

Tools

The MicroMedex electronic database was used to identify and analyses the pattern of potential DDIs. MicroMedex contains a separate section on DDIs known as the Drug-REAX System. On entering the drugs one by one, the program lists the possible DDIs and categorizes DDIs according to their severity, onset, and documentation status

DDI severity was classified as major, moderate, or minor.

- Major DDIs may be life-threatening, and medical intervention may be necessary to minimize or prevent serious adverse effects.
- Moderate DDIs may result in an exacerbation of the patient's condition and may require an alteration in therapy.
- Minor DDIs have limited clinical effects.

The onset of potential DDIs was classified as rapid, delayed, or not specified.

- Rapid-onset DDIs lead to the clinical "conflict" or adverse effects within 24 hours of drug administration.
- Delayed-onset DDIs did not lead to the onset of clinical conflict or adverse effects within the first 24 hours following drug administration.

The documentation status of the potential DDI was classified as excellent, good, fair, poor, or unlikely.

- Excellent: Controlled studies have clearly established the existence of the drug interaction.
- Good: The documentation strongly suggests that a drug interaction exists, but well-controlled studies are lacking.
- Fair: Available documentation is poor, but pharmacological considerations may lead clinicians to suspect the existence of a drug interaction; or documentation may be good for a pharmacologically similar drug.

- Poor: Documentation is scant, such as in limited case reports; however, the possibility of a clinical conflict exists.
- Unlikely: Documentation is poor, and a sound pharmacological basis is lacking.

4.8. Data Analysis

The data was analyzed using SPSS v 16 software windows versions , cross-tabulations was produced for the descriptive statistics and binary logistic regression was used to assess the relationship between different variables.

4.9. Ethical Consideration

Jimma University specialized hospital and then to chronic diseases follow up clinic. The names of the patients were excluded and only patients' ID was recorded.

The confidentiality of the patients was maintained through out the study period and only principal investigator, supervisors and data collectors were access to the patients' information

4.10. Dissemination of the Research Findings

The result of this study was summited to the department of pharmacy, college of public health and medical sciences, Jimma University specialized hospital. Further effort will be made to publish the findings on national and international peer reviewed journal

4.11. Scope and Limitations of the Study

This research was a cross-sectional study aiming to determine if there were potential drug-drug interactions among outpatients taking cardiovascular agents. The study population only consisted of all the outpatients taking cardiovascular drugs during the study period.

The limitations of the study should not be overlooked. First, the drug-drug interaction found were only potential (it is not clear whether they had resulted in any harm to the patients). No attempt was made in the study to find out if this was the case. Secondly, as a true measure of the occurrence and the risk of receiving drugs with potential interactions, the results in this study were probably slightly underestimated since only

prescribed medications were included and most illicit, OTC, and herbal medicines were not included. Third, potential DDIs may be highly dependent on the dose of the individual drugs administered. For example, in this study, aspirin was only prescribed as antiplatelet inhibitor in a daily dose of 100mg. None of these patients were prescribed a higher dose (e.g. 300mg/day) to inhibit platelet aggregation and non-were prescribed aspirin as analgesic. It is known that some potential DDIs with aspirin are clinically relevant if it is administered in analgesic doses (17). DRUG REAX used to evaluate the patient's medication regimen is not able to distinguish between the two different doses scheme. Therefore, potential DDIs involving aspirin that were regarded as clinically irrelevant if dosage of aspirin did not exceed 100mg/day (e.g. combination of low dose-aspirin with ACE inhibitors, which potentially results in a decreased ant-hypertensive effect) were not included in the analysis. Fourthly, only the contribution f medical interns and residents for drug-drug interaction were analyzed and that of internists and nurses are overlooked. This is due to the fact that nurses were not prescribing drugs in specific study place and there were less number of internists in our set up and their role was primarily supervision. Lastly but not least is that identification of potential DDIs was based mainly on the information obtained from the Micromedex database.

.

4.12. Operational definitions

Adverse drug events: - An *adverse drug event* is "an injury resulting from the use of a drug. Under this definition, the term ADE includes harm caused by the drug (adverse drug reactions and overdoses) and harm from the use of the drug (including dose reductions and discontinuations of drug therapy).

Adverse drug reactions: - drug effects that are unwanted, unpleasant, noxious, or potentially harmful which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function

Clinically significant drug interaction: - drug interactions that require monitoring therapy, modification of therapy or avoidance of therapy

Drug-drug interactions: - modification of the effect of a drug when administered with another drug

Frequency of drug interaction: - is the number of occurrences of drug interactions in specified period

Outpatient: - An outpatient is a patient who is not hospitalized for 24 hours or more but who visits a hospital, clinic, or associated facility for diagnosis or treatment.

Over the counter drugs: - Over-the-counter (OTC) drugs are medicines that may be sold directly to a consumer without a prescription from a health care professional

Potential drug interaction: - all possible drug interactions irrespective of the degree and consequences when two or more drugs taken together

Prescription drug: - prescription medication is a licensed medicine that is regulated by legislation to require a prescription before it can be obtained

5. Results

A total 0f 332 patients receiving cardiovascular medications were involved in the study and 100% response rate were given. There was no questioner excluded from the analysis since there was no incomplete information necessary for this study remained unfilled. **.**

Distribution of potential drug-drug interactions by sex, age, comorbidities and number of drugs prescribed.

A total of 332 patients who were prescribed 1249 drugs (average 3.76 drugs per prescription) were enrolled in this study. Of these, 51.5% were women and 48.5% were men. Among these patients, 72.6% (120 females and 121 males) were at risk of encountering 297 drug-drug interactions. Majority of the patients were in the age range of 40-70 years with mean age of 55 years indicated in **Table 1**.

Out of the 28 (8.4%) patients for which two drugs prescribed, the potential DDIs was observed in 11(39.3%) and of 117(35.2%) patients prescribed with three drugs 70(59.8%) were observed to have potential DDIs. Among 85 (25.6) patients taking four drugs, 60(70.6%) had potential DDIs and those for whom five or more drugs prescribed, 97.5% had DDIs indicated in **Table 1**.

The most commonly existing co-morbidity with cardiovascular disorders in the current study was peptic ulcer (61, 40.1%) followed by infectious disease (35, 23%), specifically community acquired pneumonia for which macrolides or doxycycline were prescribed and urinary tract infections for which norfloxacin was prescribed as indicated in **Table 1.**

Table 1: The distribution of DDIs by patients' demographics and clinical characteristics (n=332) at JUSH, Jimma, May 2011

Variables	Patients without DDIs on their	Patients with DDIs on their prescription
Gender		
Male	40 (24.8%)	121 (75.2%)
Female	51 (29.8%)	120 (70.2%)
Age range (years)		
15-25	9 (42.9%)	12 (67.1%)
26-36	11 (44%)	14 (56%)
37-47	20 (27%)	54(73%)
48-58	26 (30.2%)	60 (68.8%)
59-69	25 (27.2%)	67 (72.8%)
≥70	13 (27.7%)	34 (72.3%)
Diseases		
Peptic ulcers	16 (26.2%)	45 (73.8%)
Diabetes mellitus	1 (11%)	8 (89%)
Headache and back pain	1 (3%)	33(97%)
Infectious	6 (17%)	29 (83%)
Epilepsy	1 (16.7%)	5 (83.3%)
Asthma	1 (14.3%)	6 (85.7%)
Number of drugs used		
Two	17 (60.7%)	11 (39.3%)
three	47 (40%)	70 (60%)
Four	25 (29.4%)	60 (70.6%)
Five or greater	2 (2.4%)	80 (97.6%)

Professional status of the prescribers

There was a direct relationship between the professional status of the prescribers and the frequency of potential DDIs (r=0.245, p<0.00), as illustrated by **Figure 2**.

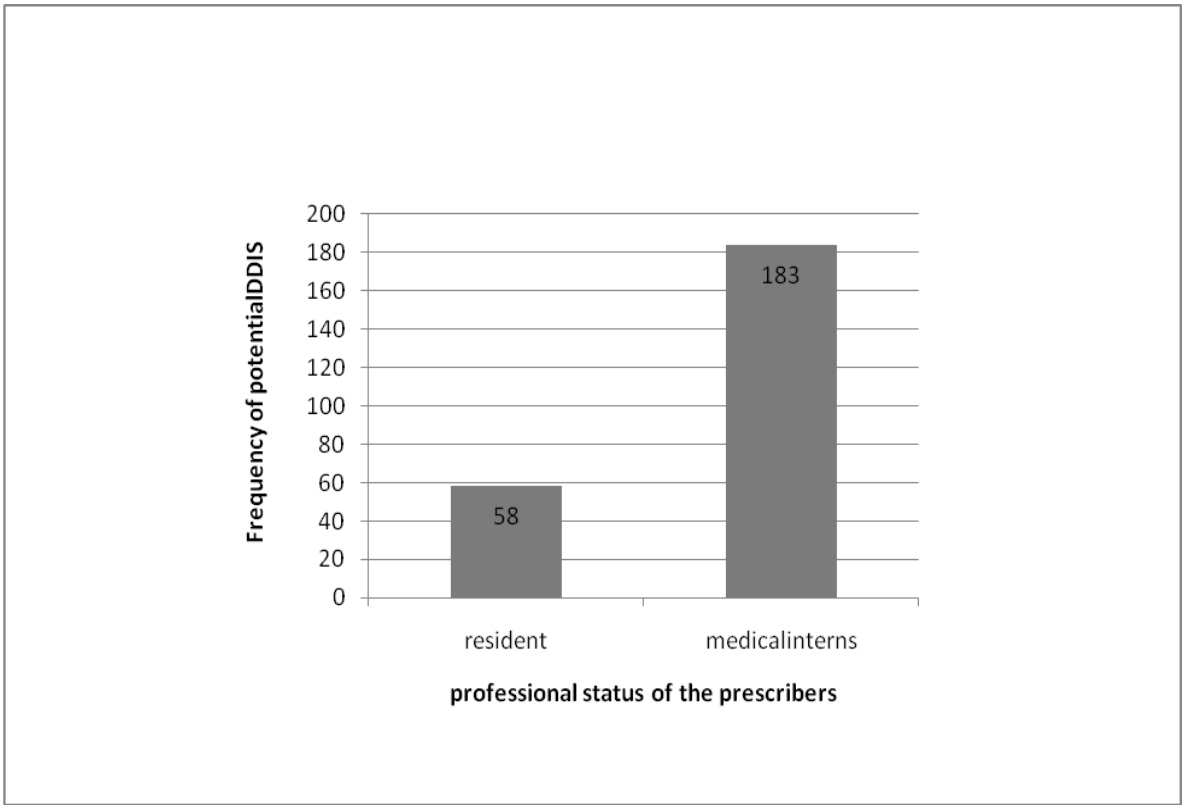

Figure 2: Relationship between frequency of DDIs and professional status of the prescribers at JUSH, Jimma, and May 2011 (P<0.000)

DDIs by clinical significance

From the severity point of view, 88 (29.6%) of the potential DDIs were major, 200 (67.3%) were moderate and 10 (3%) were considered minor. Similarly, among the potential DDIs, 123(41.4%) were delayed onset, 164 (55.2%) were rapid onset and 10 (3.4%) were not specified. Among the potential DDIs, 43 (14.5%) were with excellent documentation status, 224 (75.4%) good status and 30 (10.1%) fair status. Patters of potential DDIs in terms of severity, onset and documentation status are described in **table 2**

Table 2: Patterns of potential DDIs by clinical significance (n = 297) at JUSH, Jimma, May 2011

Pattern	Frequency	Percent (%)
Severity		
Major	88	29.6
Moderate	200	67.3
Minor	9	3.1
Onset		
Rapid	123	41.4
Delayed	164	55.2
Not Specified	10	3.4
Documentation		
Excellent	43	14.5
Good	224	75.4
Fair	30	10.1

Class category of drugs with high potential DDIs

Altogether, 297 potential DDIs were observed and involved 872 drugs. The therapeutic classification of drugs with a potential risk for producing DDIs is listed in **Table 3**.

Table 3: Classification of category of drug associated with a high risk of potential DDIs (n=872) at JUSH, Jimma, may 2011

Rank	Therapeutic category	Frequency	Percent (%)
1	Cardiovascular drugs	676	77.5
2	NSAIDS***	66	7.7
3	Antimicrobials	61	7
4	Antacids	26	3
5	Anti diabetics	24	2.8
6	Proton pump inhibitors	12	1.4
7	Anti epileptics	2	0.03
8	glucocorticoids	2	0.03
9	H_2-antagonists*	2	0.0
10	β_2- agonists**	1	0.01

*includes Cimetidine **Albuterol *** Non-steroidal anti-inflammatory drugs

Individual drugs with high probability of causing potential DDIs

The high risk drugs responsible for DDIs are listed in **Table 4.** Enalapril was found to be the cardiovascular drug with the highest risk of carrying potential DDI; among the non-cardiovascular drugs, diclofenac was associated with a high number of potential DDIs

Table 4: Drugs with a high probability of causing DDIs at JUSH, Jimma, May 2011

Rank	Drug	Frequency	Percent (%)
1	Enalapril	200	23.5
2	Furosemide	120	14.1
3	Hydrochlorothiazide	84	9.9
4	Spironolactone	78	9.2
5	Diogxin	60	7
6	Atenolol	50	5.9
7	Captopril	40	4.7
8	Diclofenac	26	3
9	Antacid	23	2.7
10	Ibuprofen	20	2.3
11	Amlodipine	16	1.9
19	Lovastatin	16	1.9
13	Indomethacn	12	1.4
14	Clarithromycin	12	1.4
15	Erythromycin	12	1.4
12	Aspirin	10	1.2
16	Omeprazole	10	1.2
17	Glybuide	10	1.2
18	Nifedipne	8	0.94
20	Propranolol	8	0.94
24	Insulin	8	0.94
23	Metformin	6	0.7
21	Doxycycline	5	0.6
22	Cimetidine	4	0.5
25	Prednisolone	4	0.5
29	Norfloxacin	4	0.5
26	Albuterol	2	0.2
27	Phenobarbital	2	0.2
28	Phenytoin	2	0.2

Highly interacting drug pairs

The top 15 drug pairs with the potential for interacting are listed below in **Table 5** with their clinical significance and possible outcomes. The most common DDI observed was between enalapril and furosemide having moderate severity with the possibility of causing first dose hypotension.

Table 5: Distribution of 15 potentially interacting drug pairs with their clinical significance and possible adverse outcomes at JUSH, Jimma, and May 2011

Rank	Drug Pairs	Frequency	Clinical significance	Possible adverse out come
1	Enalapril -Furosemide	59	Moderate	Postural hypotension (first dose)
2	Enalapril-HCT**	57	Moderate	Postural hypotension (first dose)
3	Enalapril-Spironolactone	39	Major	Hyperkalemia
4	Digxin-Furosemide	31	Moderate	Hypokalemia
5	Digoxin-Spironolactone	30	Major	Digoxin toxicity (nausea, vomiting, cardiac arrhythmias)
6	Digoxin- Atenolol	15	Moderate	AV block and possible digoxin toxicity
7	Digoxin-Macrolides* and Doxycycline	13	Major	Digoxin toxicity(nausea, vomiting and arrhythmias)
8	HCT**- Diclofenac	13	Moderate	Decreased diuretic and antihypertensive efficacy
9	Lovastatin-Macrolides*	12	Major	Increased risk of myopathy or rhabdomyolysis
10	Captopril-Spironolactone	12	Major	Hyperkalemia
11	Captopril-Furosemide	11	Moderate	Postural hypotension (first dose)
12	Atenolol-Amlodipine	9	Moderate	Hypotension and / or bradycardia
13	Digoxin-HCT**	8	Moderate	hyperkalemia
14	Atenolol-Diclofenac	8	Moderate	Decreased antihypertensive effect
15	HCT-Ibuprofen	6	Moderate	Decreased diuretic and antihypertensive efficacy

*clarithromycin/erythromycin **hydrochlorothiazide

Factors related to potential drug-drug interaction

In binary logistic regression analysis, a number of parameters such as advanced age, sex, number of drugs prescribed, coexisting diseases and professional status of the prescribers have been linked for their association with the frequency of potential drug-drug interactions. The overall number of prescribed drugs and the level of education of prescribers were identified as predictors of potential DDISs in this work. Age (p=0.496), sex (p= 0.310) and co-morbidities (p= 1.00) were not strongly associated with the occurrence of potential DDIs in this study **table 6.**

Table 6: Binary logistic regression analysis for factors associated with DDIs at JUSH, Jimma, and May 2011

Variables	**Adjusted Odds ratio***	**± 95%CI**	**P-value**
Age	0.96	0.308-2.33	0.496
Sex	1.286	0.792-2.088	0.310
Number of drugs prescribed**	4.09	3.940- 5.391	0.000
Co morbidities	0.966	0.678- 5.146	1.000
Professional status**	4.566	0.146-4.10	0.000

CL= confidence interval *standardized regression coefficient

** Factors having statistical significance with potential drug interactions

Table 7: Estimates of the logistic regression for variables those were statistically significant at JUSH, Jimma, and May 2011

Number of drugs prescribed	**Crude O.R (95.0% C.I.)**	**Educational status of the prescribers**	**Crude O.R (95.0% C.I.)**
Two	4.02 (3.499- 32.157)	Residents	0.25 (0.166-0.842)
Three	3.578 (3.95-13.4837)	Medical interns	1
four	1.48(3.083-5.857)		
≥ five drugs	1		

6. Discussion

Medication safety is a growing area of interest and concern, not only in the inpatient setting but also in the outpatient setting. One way in which medication use can be risky is via the concomitant use of medications known to have potential detrimental clinical interactions. Prior efforts are documented the use of potentially interacting medication pairs as well as adverse events associated with their use. Despite these findings, an understanding of potentially interacting medication use is only beginning to be gained especially in the outpatient setting (18).

The present study demonstrated that 72.6% of patients with cardiovascular disorders have at least one potential DDIs. Many studies tried to reveal the frequency of potential DDIs. For instance, study done by Janchawee and colleagues revealed that the rate of potential drug-drug interactions in outpatients was 27.9%, which is far below the value obtained in this study. In fact such value cannot be directly compared with this study because of the differences in the study design (retrospective) (13). Other explanations for this difference could be the differences in the level of understanding about drug-drug interactions by prescribers in the two studies and the presence of clinical pharmacists in those settings reduce the probability of potential drug-drug interactions.

In other studies on the incidence of potential DDIs in elderly patients with arterial hypertension in Crotia and on ambulatory patients over 55 years of age in Mexico city were found to be 90.6% and 80% respectively which are far greater than the value obtained in this study (14, 19) . These differences in the incidences of interactions are perhaps a consequence of the enrollment of younger patients in this study (average age 55 years) compared to their studies which enrolled elderly patients with mean age of 73 years and 69 years respectively (9). The other possible explanation for the discrepancy is that the hospital in which this study was conducted uses none of the cardiovascular drugs that are highly interacting such as warfarin, quinine, amiodarone, and veramapil perhaps due to the inaccessibility of these drugs to the hospital or fear of their adverse outcomes in the set up with limited infrastructures to monitor the patients or unfamiliarity of the physicians with these drugs.

The rate of occurrence of potential DDIs incase where residents prescribed the drugs were found to be less likely than when prescribed by the medical interns perhaps due to knowledge gaps between the two levels of training. Gender, sex and concomitantly existing diseases were not identified as predictors of potential DDIs. This is similar to the work done by Vrca and colleagues (19).

In this study most potential DDIs were moderate (67.3%). These potential DDIs suggest that there is a need for modification or alteration of therapy such as dosage adjustment. In order to prevent these DDIs, health care providers should have adequate information about DDIs not only via drug information center which can provide evidence-based information to health care professionals but also through encouraging the empowerment of clinical pharmacists that can provide evidence based approach to drugs and thereby prevent drug therapy problems of which DDIs is one. This study also found that 55.2% of the potential DDIs were of delayed type. For example, the DDI between enalapril and Spironolactone is known to have delayed hyperkalemic effect. This suggests the need for counseling the patients who are at risk for experiencing these DDIs, such as elderly and patients with renal insufficiency.

The documentation status of most of the potential DDIs was good (75.4%), suggesting that these potential DDIs may be prevented by evidence-based approach. Perhaps, better approaches are to obtain data on drugs from drug information center or information on drugs from clinical pharmacists during prescribing, thus ideally avoiding DDIs in the patients. These results were slightly lower than study done by Souza and Thomas on the epidemiology of drug interactions and Egger and colleages in terms of severity, onset and documentation status (15, 20). These differences might be arising from differences in sample size and study design; their sample size (1089) was much greater than the sample size in this study. Another explanation could be awareness of prescribers about major drug-drug interactions and presence of drug information center and Clinical pharmacists in their study.

In this study, cardiovascular drugs posed the maximum risk for potential DDIs followed by NSAIDs (6, 21and22). Among the various drugs implicated for the potential DDIs, Enalapril ranked first, followed by Furosemide and hydrochlorothiazide. In study done in Italia (Margo et al, 2007), digoxin was the most frequently involved drugs followed by hydrochlorothiazide which was different from this study probably due to the change in the therapy of heart failure.

The non-cardiac drug that frequently involved in potential DDIs in this study was Diclofenac (NSADs), antacids and antimicrobials such as clarithromycin and erythromycin. NSAIDs were commonly prescribed for the treatment of headache and back pain where as antacids were prescribed for peptic ulcer relief. Antacids and drugs used here to relief peptic ulcer diseases are non-specifically prescribed for the dyspepsia patients complaining that could be due to gastrointestinal effects cardiovascular or other drugs taken by the patients or may be due to the actual diagnosis of peptic ulcer that remain to be confirmed.

The three combinations with DDI that were found most frequently in this study were among reported by Vrca and colleagues (19). In these drug interactions, two of them were moderate severity and without dose adjustment and patient monitoring. Such reactions may result in postural hypotension (Enalapril-Furosemide and Enalapril-HCT). Other frequent potential DDIs was major in severity (Enalapril-Spironolactone) and result in life threatening hyperkalemia and need medical intervention according to DRUG REAX system. Other relatively less frequent major DDIs that were found in this study were Digoxin-Spironolactone, Digoxin-Clarithromycin/Erythromycin/Doxycycline and Lovastatin-Macrolides. These DDIs were potentially resulted in an increase in digoxin toxicity such as nausea, vomiting and arrhythmia. The mechanisms were supposed to be inhibiting digoxin clearance by Spironolactone and by increasing the bioavailability of digoxin through inhibiting gastrointestinal micro flora that are responsible for degradation of digoxin by Clarithromycin/Erythromycin and Doxycycline. The interaction between lovastatin and macrolides is inhibition of metabolism of Lovastatin by macrolides which result in myopathy and rhabdomyolysis according to DRUG REAX system.

In binary logistic regression analysis, a number of parameters such as advanced age, sex, number of drugs prescribed, coexisting diseases and professional status of the prescribers have been linked for their association with the frequency of potential DDIs. The overall number of prescribed drugs (p= 0.000) and the level of education of prescribers (p= 0.000) were identified as predictors of potential DDISs in this study. Advanced age (p= 0.496), sex (p= 0.310) and co-morbidities (p= 1.000) were not found to be the key factors for adverse drug reactions and potential DDIs in this study in contrast to the study done by Sweileh (9) where these all factors were associated with the frequency of potential drug-drug interaction. These differences might result from the fact that this study involved relatively younger patients in which co morbidities were less likely and therefore, polypharmacy is less compared to their work.

The odds of having potential drug-drug interactions in patients taking five or more drugs is 4 times more likely than those patients taking two drugs. Similarly, the odds of having potential drug-drug interactions in patients taking five or more drugs 3.6 times more likely than those patients taking three drugs and it is 1.5 times more likely than those patients taking four drugs. This is similar to the study done by Doubova and colleagues *(*14*).* The odds of having potential drug-drug interactions in cases where medical interns prescribed drugs to the patients is 4 times more likely that when prescribed by residents

7. Conclusion and recommendation

7.1 Conclusion

This study was successful in identifying the frequency and pattern of potential DDIS in outpatient cardiovascular chronic care clinic, JUSH. The frequency of potential DDIs was found to be 72.6% and majority of the DDIs were moderate in severity, delayed in onset and good in documentation status. Enalapril and Furosemide were the high-risk drugs for DDIs. Moreover, medical professionals' level of training is inversely related to the risk of potential DDIs.

7.2 Recommendation

The following recommendation forwarded to health care professionals, school of pharmacy, Jimma University and federal ministry of health, Ethiopia.

1. Proper emphasis should be given to drug information center and training of clinical pharmacy at JUSH which can play an important role in minimizing DDIs in cardiovascular patients by providing DDI-related information to prescribers.
2. It also forwards the need to develop a collaborative, patient centered approach in the education of pharmacy professionals to deliver effective drug therapy
3. The finding of this study warms the health professionals to educate patients about drugs, adverse effects and how to report on time
4. Based on this study results, conducting large study for better analysis is highly recommended.

8. References

1. Van Roon E. Drug-Drug Interactions: a Structured Assessment Procedure. Drug Safety 2005; 28 (12): 1131-11.
2. Scheen A. Drug Interactions of Clinical Importance with antihyperglycaemic agents. Drug Safety 2005; 28 (7): 601-631.
3. Baxter K. Stockley's Drug Interactions. Eighth edition, the Pharmaceutical Press, London; (2008); 10.
4. Carter BL, Lund BC, Hayase N, and Chrischilles E. The extent of potential antihypertensive drug interactions in a Medicaid population. AJH 2002; 15:953–957.
5. Triplitt C. Drug Interactions of Medications Commonly Used in Diabetes. Diabetes2006; 19 (4): 202-211.
6. Linnarsson R. Drug interactions in primary health care; a retrospective database study and its implications for the design of a computerized decision support system. Scand J Prim Health Care1993; 11: 181-186.
7. Bista D, PalaianS AND Shankar P. Understanding the essentials of drug interactions: A potential need for safe and effective use of drugs. Kathmandu University Medical Journal, 2006: 4(15):421-430.
8. Peng CC, Glassman PA, Marks IR, Fowler C, Castiglione B, and Good CB. Retrospective Drug Utilization Review: Incidence of clinically relevant potential drug-drug interactions in a large ambulatory population. J Managed Care Pharm. 2003; 9(6):513-22.
9. Sweileh W. Extent of potential interactions among patients receiving anti-hypertensive medications. Saudi Med J 2005; 26(4):548-552.
10. Patel VK, Acharya LD, Rajakannan T, Surulivelrajan M, Guddattu V, Padmakumar R. Potential drug interactions in patients admitted to cardiology wards of a south Indian teaching hospital. Australasian Medical Journal 2011; 4(1): 9-14.
11. Hussar DA. Drug interaction. In: GennaroL, Marderosian A, Hanson G et al. Remington The science and practice of pharmacy. Philadelphia: seventh edition: Lippincott Williams and Willinks 2007; 1746-61.

12. Bjerrum L, Andersen M, Petersen G and KragstrupJ. Exposure to potential drug interactions in primary health care. Scand J Prim Health Care 2003; 21:153-158.
13. Janchawee B, Wongpoowarak W, Owatranporn T and Chongsuvivatwong V. Pharmacoepidemiology study of potential drug interactions in outpatients of a university hospital in Thailand. Journal of Clinical Pharmacy and Therapeutics 2005; 30:13–20.
14. Doubova (Dubova) SV, Morales HR, Arreola LT and Ortega MS. Potential drug-drug and drug-disease interactions in prescriptions for ambulatory patients over 50 years of age in family medicine clinics in Mexico City. BMC Health Services Research 2007, 7:147.
15. Egger SS, R¨atz Bravo AE, Hess L, Schlienger RG and Kr¨ahen¨uhl S. Age-related differences in the prevalence of potential drug-drug interactions in ambulatory dyslipidaemic patients treated with statins. Drugs Aging 2007; 24 (5): 429-440.
16. Morteza S, Saeidi M, Gharipour O. Evaluation of cardiovascular drug interactions in insured prescription in Sari. Journal of Mazandaran University of medical sciences 2001; 11(32):37-44.
17. Straubhaar B, Krahenbuhl S, Schlienger RG. Prevalence of potential drug interaction in patients with heart failure at hospital discharge. Drug safety 2006; 29(1):79-90.
18. Lafata JE, Schultz L, Simpkins J, Chan KA, Horn JR, and Long C. Potential drug-drug interactions in outpatient setting. Medical care 2006; 44(6):534-41.
19. Vrca VB , Marusic S , Erdeljic V, Falamic S, Tomic NG and Rahelic D. The incidence of potential DDIs in elderly patients with arterial hypertension. Pharm world sci 2010; 4(1): 1-7.
20. Souza JM and Thomson JC. Pharmacoepidemiology study of DIs in a Brazil teaching hospital. Clinics 2006; 61(6):515-20.
21. Buurma H, Smet PA and Egberts AC. Clinical Risk Management in Dutch Community Pharmacies; the Case of Drug-Drug Interactions. Drug Safety 2006; 29 (8): 723-732.

22. Magro L, Conforti A, Del Zotti F, Leone R, Iorio ML Meneghelli I et al. Identification of severe potential drug-drug interactions using an Italian general-practitioner database. Eur J Clin Pharmacol 2007; 1: 1-8.

9. Appendix

Training Guideline for data collectors on recoding information on Evaluation of potential drug-drug interactions and associated risk factors

First of all, we would like to thank you for your interest and willingness to participate as a data collector in this study.

In order to accomplish the data/sample collection properly you are expected to follow the training attentively and participate in the practical activities which will be carried out in JUSH.

Objectives of the training:

- To orient data collectors on the protocol of the study
- To orient data collectors on their standard operating procedures
- To familiarize data/sample collectors with the data collection instrument; and
- To enable data collectors, investigators work under the same frame of reference.
- To facilitate the ease of data collection and ensure reliability of data collection

The training will be given in the form of discussion and practical exercise in training rooms and in JUSH. The practical part will be helpful to familiarize trainees with the data collection approach.

Guideline for record review (abstracting data from records)

1. Approach the person who is expected to provide patient cards /unit ART register in a friendly, polite manner and try to create a welcoming atmosphere.
2. Discuss the objectives of the study (if necessary) with patient card/unit ART register holder (person responsible to authorize data access) and inform him/her that it is not to report how they did rather it is used for the study purpose only.
3. Care should be taken when you abstract data from the main document, be sure that you are looking to the required information before writing on the form.
4. Be sure that you are completing all important information from the patient card before looking for the next sample.
5. When you use the recorded data (if in the form of hard copy) try to keep it as it is and take care not to damage since it is an important record; and don't write anything on it nor delete from it.
6. Data abstraction form should be completed on all patient cards/unit ART register selected for the study. But if the selected sample was incomplete &/or was not complete for at least a period of one treatment cycle, use the next sample.
7. Write only what is available there on patient information sheet, do not guess or try to fill data which was not initially recorded in the PIS.
8. Thank the person (s) who provides (s) you the patient Information sheet

Informed Consent

A. For patients to get access to their card

1. Dear participant, I'm clinical pharmacy student in Jimma university college of public health and medical sciences and currently conducting my thesis on: potential drug-drug interactions and associated risk factors in cardiac chronic follow up clinic of JUSH. The study will be conducted by reviewing your cards. Your card is only accessed if you are voluntary and you have the right not to give your card in the study or to take your card at any time you feel uncomfortable. The output of this research will be greatly helpful to the patient, community and health professionals by creating awareness and recommending possible solutions. The information obtained from your card will be kept confidential by avoiding using of your names and securing from access to others other than principal investigator. After the research is over, the information obtained from your card will be discarded. Thank you in advance for your cooperation.
2. Shall I use your card? Yes----------No ---------
3. **በመጀመሪያ እንደምን አደሩ/ዋሉ የተከበሩ የጥናታችን ተሳታፊ።እኔ በጅማ ዩኒቨርስቲ የህብረተሰብ ጤናና የህክምና ኮሌጅ የድህረ ምረቃ ት/ቤት የክሊኒካል ፋርማሲ ተማሪ ስሆን በአሁኑ ጊዜ የምረቃ ፁህፈን የመጼሃኒት ስህተትና ምክንያቱ በሚል ርዕስ እየሰራሁ ነዉ።ስለሆነም ለጥናቱ መሳካት ካርድዎ ስለሚያስፈልገን ካርድዎን እንዲፈቅዱልን ስል የእርስዎን ትብብር በትህትና እጠይቃለሁ። ካርድዎን መዉሰድ የምንችለዉ በእርስዎ ፈቃድ ብቻ ነዉ። ካርድዎን የመስጠትም ሆነ ያለመስጠት መብት የእርስዉ ነዉ።እንዲሁም በማንኛዉም ሰዓት ካርድዎን የመዉሰድም ሆነ የማስቆም መብትዎ የተጠበቀ ነዉ።በዚህ ጥናት ተገኛ ዉጤት ለበሽተኛ፤ ለህብረተሰብ እንዲሁም ለጤና ባለሙያዎች ይጠቅማል።ከእርስዎ ካርድ የተገኘ መረጃ ሚስጥራዊነቱ የተጠበቀ ነዉ።ለዚህም ሲባል ስምዎ አይጠቀስም፤ መረጃዉ በሌላ አካል እንዳይገኝ አስፈላጊዉ ጥንቃቄ ይደረጋል።ጥናቱ ካለቀ በሆላ መረጃዉ ይወገዳል።ስለትብብርዎ ከልብ እናመሰግናለን!**
4. **ካርድዎን መጠቀም እችላለሁ? አዎ----------አይቻልም----------**
5. Duraan dursee kabajamoo hirmaatota qu'annoo keenyaa akkam bultan/oltanii? Ani Legese Chelkeba kanan sedhamu uniiveersitii jimmaatti kuta barnootaa kiliniikaal faarmaasii tii,barnoota digirii lammaffaa warkaa eebaa koo mata duree walitti bu;u qorichootaaf sababa ka'umsa isaa jedhu irratti hojiiechu irrati argama. kanaaafuu galma gahuu qo'annoo kanaaf kaardiin yaalaa keesan babaachisaa waanta'eef nuti agarsiisuun akka nugargaartan kabajaan isin qaafadha.kaardii keessan eeyama keesan yoo ta'l qofadha kan faya dammu dardeenyu. Kanaafuu kaardii kardii keesan nutli aqarsiisuufista'ee, dhorkachuuf mirqa qabdu. Qo'annoo kanaan firiin argamu yaalamtootaaf, uummataa fi beektota yaalaattif baay'ee barbaachisaadha. Firiin kardii keessanii icitiin niqabama. Kanafis maqaan keessan asirratt, hinbarreeffamu,firiin kardii kessanii qaamni biroon akka itti hin fayyada mni ofeeqanoon cimaan ni qodhama.qu'annoo kun erqa raawatee booda firiin kardii kessanii ni dhabamsiifama.
6. Harqarsa nuuf qootaniif qudda isin qaala teefana
7. Kardii kessan itti fayyadamuu nau dada'aa? Eyyeen_____lakkii_____

Structural formats for data collection

1. *Patient's ID*----------
2. *Age of patient (in years)* ----------

3. Sex of the patient
   a. M
   b. F

4. Lists of drugs currently prescribed for the patient including name of the drug, indication, dose, and dosing frequency

Drug name	**Indication**	**dose**	**Dosing frequency**	**remark**

5. Lists of current diagnosis

   ----

6. Professional status of the prescribers

   A. Medical intern

   B. Resident