CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com Research Article

A PROSPECTIVE STUDY ON GASTRIC BLEEDING AND DRUG INTERACTIONS ASSOCIATED WITH ANTICOAGULANT THERAPY AT CARDIOLOGY DEPARTMENT OF A TERTIARY CARE HOSPITAL

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Abstract:

Background: *Anticoagulants are the class of drugs that are used to prevent thrombus extension and embolic complications by reducing the rate of fibrin formation. They do not dissolve already formed clot but prevent recurrences.*

Method: *A total of 200 patients were included in these prospective, uni-centric, observational studies who were suffering from Cardiovascular Diseases, from the cardiology inpatient department at a tertiary care hospital in Bangalore.*

Results: *It was observed that out of 200 patients included in the study, 122 (61%) patients were treated with anticoagulants and antiplatelets, 75(37.5%) were treated with anticoagulants only. Out of 200 prescriptions encountered, 198 (99%) prescriptions have rational use of anticoagulants and only 2 (1%) were irrational. It was also observed that only 0.5% was present with GI bleeding whereas 2% of the total population was present with other side effects like nasal bleeding, haematuria, etc. Among 200 prescriptions, 251 drug interactions were found with anticoagulants. where Heparin and Aspirin was the most frequently encountered (23.1%) interaction, The least (0.4%) seen drug interactions were Aspirin & Warfarin, Heparin & Eptifibatide, Enoxaparin & Eptifibatide, Heparin & Tirofiban, Heparin & Enoxaparin, Warfarin & Tramadol, Warfarin & Amoxicillin & Glipizide and Heparin.*

Keywords: *GI Bleeding, Anticoagulants*

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Please cite this article in press as Fereshteh Jaferi et al, ***A Prospective Study on Gastric Bleeding and Drug Interactions Associated With Anticoagulant Therapy at Cardiology Department of a Tertiary Care Hospital****, Indo Am. J. P. Sci, 2017; 4(11).*

INTRODUCTION:

Anticoagulants are the drugs used to prevent thrombus extension and embolic complications by reducing the rate of fibrin formation. They do not dissolve already formed clot but prevent recurrences. In a hospital setting anticoagulants are mainly used for the following indications like deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), unstable angina, rheumatic heart disease, vascular surgery, prosthetic heart valve, retinal vessel thrombosis, extra corpuscular circulation, haemodialysis and defibrination syndrome[1]. Heparin, one of the oldest drugs still in widespread clinical use, is a naturally occurring glycosaminoglycan whose main function is to inhibit the coagulation of blood. It was discovered almost a century ago and took many years to move from the laboratory to the bedside [2]. Unfractionated heparin (UFH) binds to and increases the activity of antithrombin III by inducing a conformational change to factor Xa, which ultimately leads to inhibition at Xa and IIa in a1:1 ratio. Unfractionated heparin also has some inhibition on factors IXa, XIa, XIIa. Low molecular weight heparins (LMWs), which also bind AT3, are smaller and have a higher proportional impact on Xa, versus IIa, in a 3:1 or 2:1 ratio. Unlike warfarin, UFH is administered parenterally, both subcutaneous for its prophylaxis use and as a continuous intravenous infusion when used therapeutically. UFH has much faster onset of action as compared to warfarin; when used intravenously, while therapeutic efficacy is reached within 20-60 minutes when administered subcutaneously. The LMWH are parenterally-administered drugs, and include dalteparin, enoxaparin and tinzaparin. The LMWHs are administered at a fixed dose, based on total body weight. These drugs have near 100% bioavailability and reached peak levels 2-4 hours after subcutaneous administration. They have a half-life of 3-4 hours and are eliminated primarily (80%) via renal clearance, this necessitating dose reduction considerations in patients with renal insufficiency [3]. Vitamin K antagonists exert their anticoagulant effects by inhibiting hepatic production and depleting vitamin dependent clotting factors, especially clotting factor II (thrombin), VII, IX and X. The time to onset and offset of the anti-coagulant effect of warfarin is long because of the long half-lives of these vitamin K- dependent clotting factors, specially clotting factor II. Dabigatran directly inhibits activated clotting factor II (IIa), and rivaroxaban, apixaban and edoxaban directly inhibit activated clotting factor X (Xa) activity [4]. Throughout the world high morbidity and mortality is associated with cardiovascular diseases [5]. The risk factors for cardiovascular diseases are multiple such as elevated cholesterol and blood pressure levels, excessive smoking habits, diabetes, malnutrition and fatness, etc [6]. The treatment for coronary artery disease involves the use of various categories of drugs namely anti-platelet drugs, anticoagulants, anti-anginal drugs, beta-blockers, angiotensin converting enzyme inhibitors (ACEI)/ angiotensin II receptor blockers (ARBs), calcium channel blockers, diuretics, etc [7]. Drug utilization pattern study is a powerful exploratory tool which is a descriptive and analytical method of collection, quantification, understanding and evaluation of the prescription pattern, as well as dispensing and consumption for the advancement of existing therapy and enhancement of patient safety. Triad of right diagnosis, accurate prescription and excellent patient counselling leads to the effective and safe use of drug [8]. There is a need to record major bleeds in order to assess the safety of a new antithrombotic therapy. Especially prior to regulatory approval, counting major bleeds will allow detecting a signal for enhanced bleeding risk early during the course of clinical development of a new antithrombotic regime. Threatening bleeds, events that cause permanent organ damage and bleeds requiring acute intervention or operation to stabilize the patient, major bleeds also compromise asymptomatic haemoglobin drop of 2 or 3 gm/dl combined with a small access site or nasal bleed. The important risk factor for haemorrhage is the intensity of the anticoagulant effect. Studies indicate that with a target INR of >3.0 the incidence of major bleeding is two-fold greater compared to those with a target INR of 2.0-3.0. The combined use of VKAs and non-steroidal anti-inflammatory drugs may result in an 11-fold higher risk of hospitalization for gastro-intestinal bleeding as compared with the general population [9]. Moreover, practice guidelines by gastrointestinal professional societies only marginally address this topic as they mostly focus on management of anticoagulants in patients undergoing elective procedures. This paucity of data is even more relevant for direct oral anticoagulants [10]. Most of the haemorrhage risk schemes were developed from cohorts of patients newly prescribed or already taking anticoagulants, and as such reflects patients who were considered suitable for anticoagulation therapy. Several risk schemes were specifically developed in patients with atrial fibrillation and others in cohorts of venous thromboembolism and so some risk scores contain disease-specific risk factors. The Outpatient Bleeding Risk Index (OBRI) was the only one that had a mixed group of indications for anticoagulation and was primarily developed in a group of patient's newly starting warfarin for cardiac surgery/prosthetic heart valves [11]. In making a decision regarding whether to include new oral anticoagulant on the formulary, decision makers need to balance the benefit and the harm

associated with each therapeutic choice [12] the aim of this study was to evaluate the potential impact of the use of the new anticoagulants dabigatran and rivaroxaban in the local hospital setting for the prevention of venous thromboembolism (VTE) and stroke in patients with atrial fibrillation (SPAF), and subsequent estimate the costs involved [13].

METHODOLOGY:

STUDY SITE: a Tertiary Care Hospital in Bangalore

STUDY PERIOD: 6 months

STUDY DESIGN: Hospital based prospective study

SOURCES OF DATA:

a) Patient's case sheets
b) Medication charts
c) Lab reports
d) Patients'/ attendants' interview

STUDY CRITERIA

Inclusion Criteria

- All individuals of either sex above 18 years of age
- Diagnosed with cardiovascular complications
- Those who are on anticoagulant therapy

Exclusion criteria

- Patients on dialysis receiving Anticoagulants
- Patients with incomplete case records form

This is a prospective, unicentric, observational study conducted in 200 patients suffering from Cardiovascular Disease (CVD) at Cardiology Inpatient (IP) department of a tertiary care hospital. The study protocol was approved by the Institutional Ethics Committee Board (IECB). A suitable data collection form was designed (Annexure 1) to collect and document the data. Data collection form included the provision for collection of information related to socio-demographic details of the patients, pertaining to age, gender, family history, BMI, education status, place of stay, smoking status, daily alcohol consumption, assessment of diet were obtained and recorded. The prescription pattern of Anticoagulant drugs was assessed using WHO prescribing indicators. The prescribing indicators that were measured include: The average number of drugs prescribed per encounter was calculated to measure the degree of polypharmacy. It was calculated by dividing the total number of different drug products prescribed by the number of encounter surveyed. Combinations of drugs prescribed for one health problem were counted as one. Percentage of drugs prescribed by generic name is calculated to measure the tendency of prescribing by generic name. It was calculated by dividing the number of drugs prescribed by generic name by total number of drugs prescribed, multiplied by 100. Percentage of drugs from an essential drug list (EDL) was calculated to measure the degree to which practices conform to a national drug policy as indicated in the national drug list of WHO. Percentage is calculated by dividing number of products prescribed which are in essential drug list are by the total number of drugs prescribed multiplied by 100.

Statistical Analysis: Microsoft Excel software was used to analyse the data.

RESULTS:

I. Socio-Demographic Details

a) Age details

In our study, mean age was found to be 60.3±12.4years.The highest number of male (28.3%) were in the age group of 58-67 years. The highest numbers of female (26.9%) were in the age group of 58-67 years.

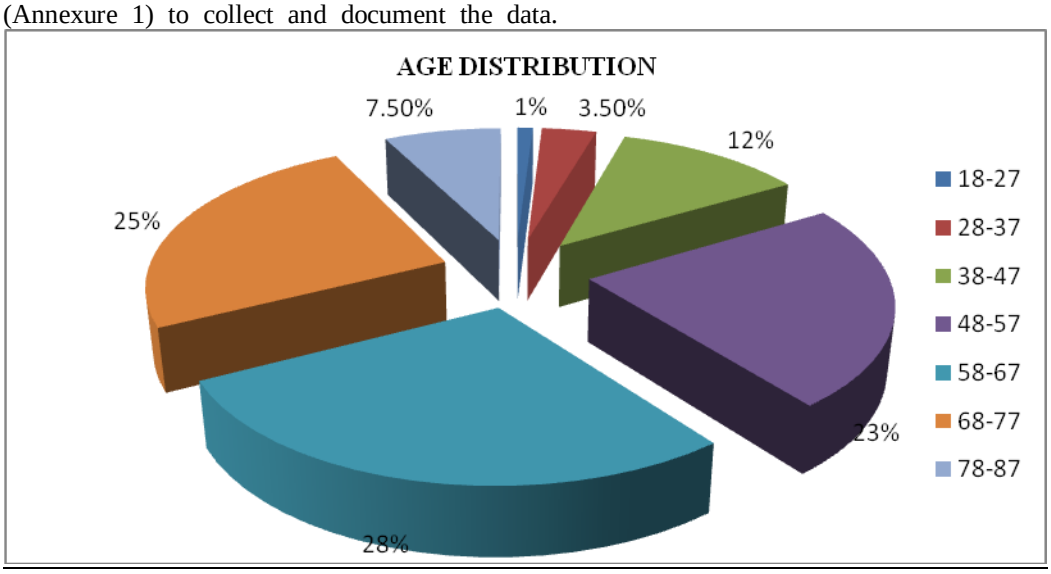


Fig 1: Pie chart representation of age distribution in our study population

b) Past medical history

In our study population, 33% of patients are present with HTN, 69% with IHD, 5% with CVA and 35.5% with MI.

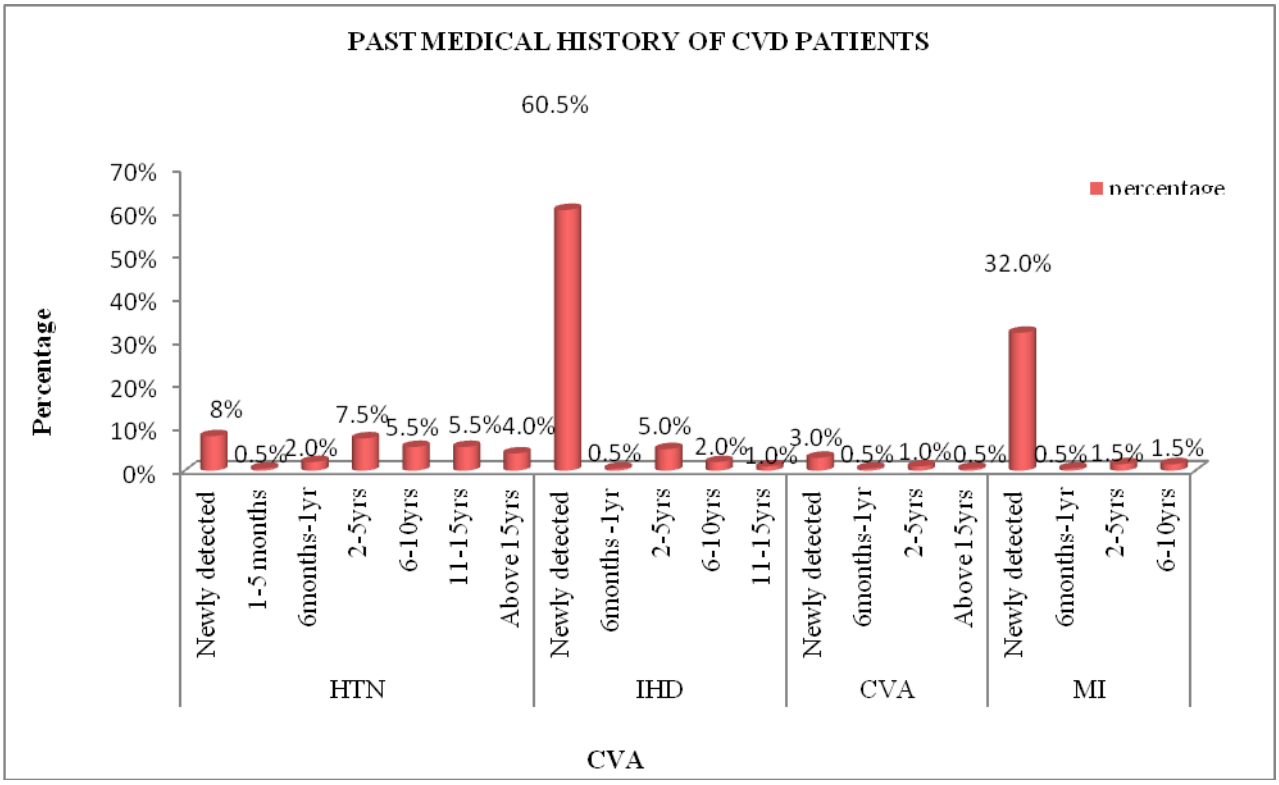


Fig 2: Bar chart representation of past medical history of CVD in our study population

II) Anticoagulant prescribing pattern: in our study population 37.5% were prescribed with monotherapy and 61% were prescribed as combination with antiplatelets .

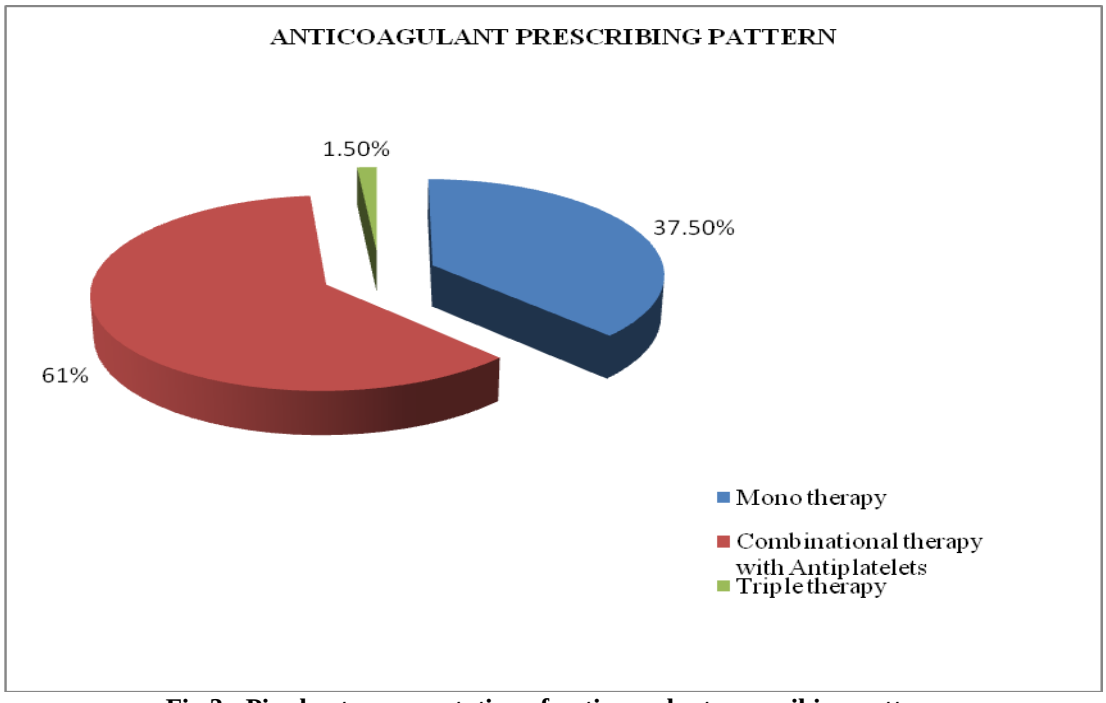


Fig 3: Pie chart representation of anticoagulant prescribing pattern

III) Various classes of drugs

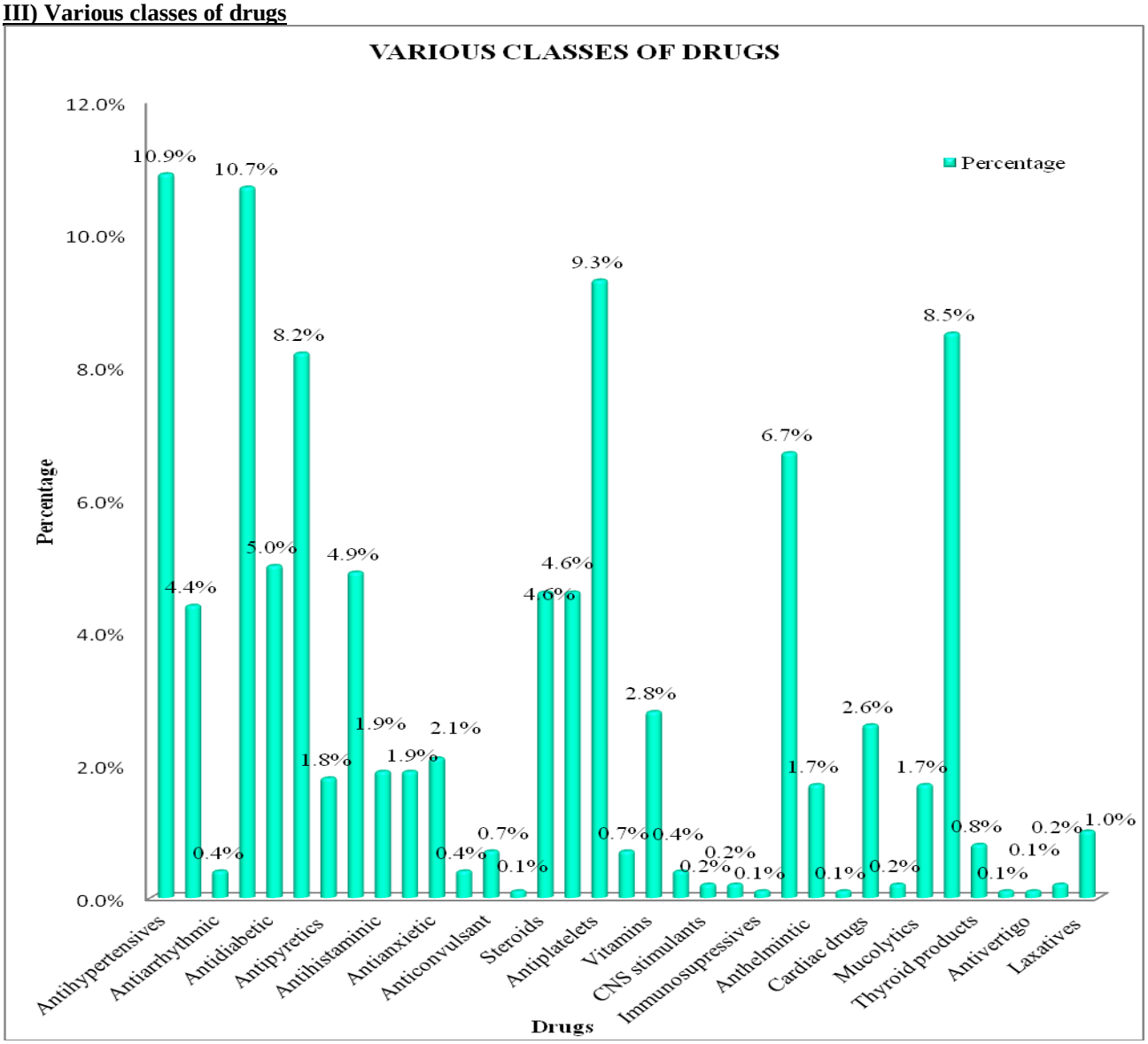
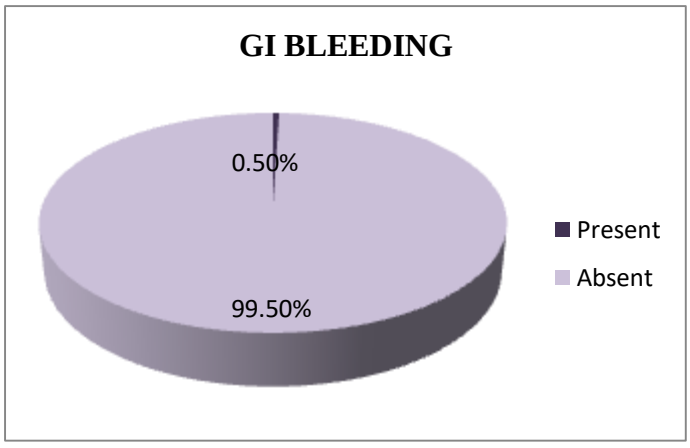


Fig 4: presentation of different classes of drugs

IV) SIDE EFFECTS

i) GI bleeding: In our study population, it is observed that only 0.5% were present with GI bleeding.



population

Fig 5: Pie chart representation incidences of GI bleeding in the study

ii) Other side effects : In our study population, 2% of the total population was present with other side effects like nasal bleeding, haematuria, etc.

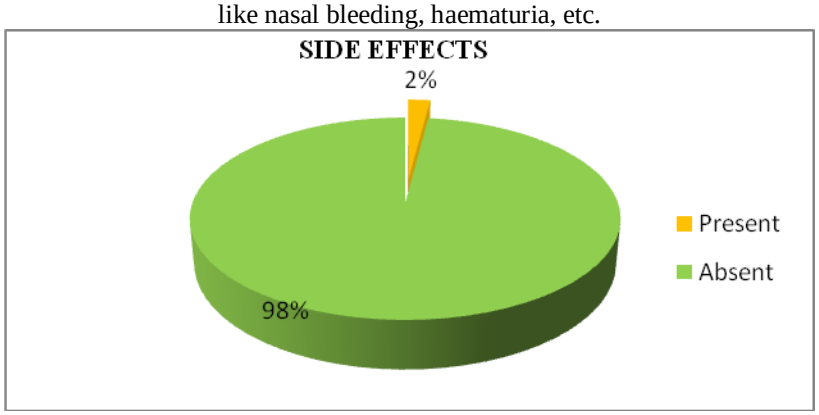


Fig 6: Pie chart representation of side effects observed in study population

V. PHARMACIST INTERVENTION

Drug-drug interaction

Among 200 prescriptions, 251 drug interactions were found. Heparin and Aspirin were most frequently encountered (23.1%) drug interaction. The least (0.4%) seen drug interactions were Aspirin and Warfarin, Heparin and Eptifibatide, Enoxaparin and Eptifibatide, Heparin and Tirofiban, Heparin+ Enoxaparin, Warfarin and Tramadol, Warfarin and Amoxicillin and Glipizide and Heparin.

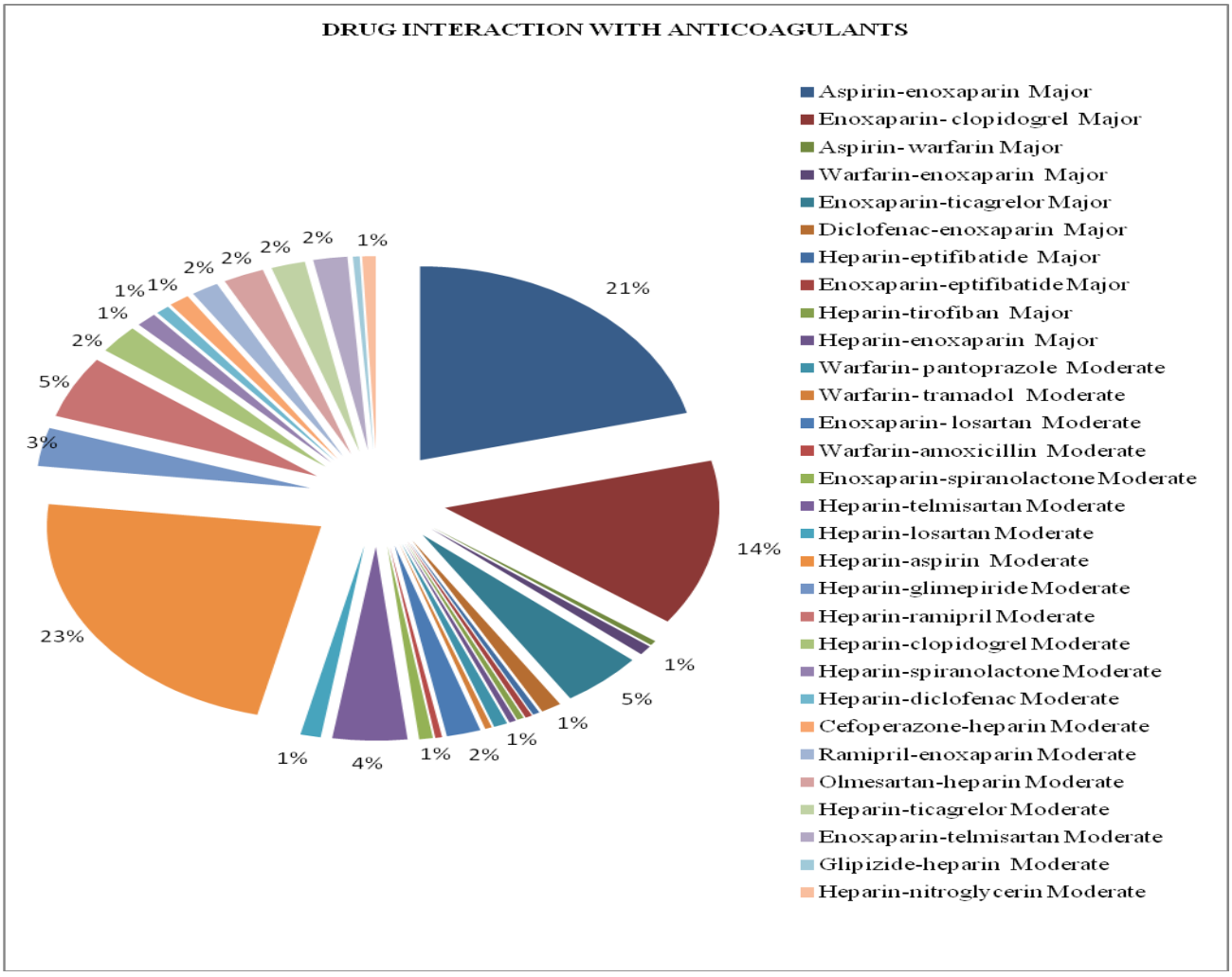


Fig 7: Pie chart representation of drug interaction with other drugs

Out of 296 drug interactions the highest (7.8%) was found between Aspirin and Clopidogrel, the second highest (4.4%) drug interaction was found between Furosemide and Metoprolol.

DISCUSSION:

The mean age of the patients with Cardiovascular Disease (CVD) in our study population were found to be 60.3±12.4 years (Figure 1). Among 200 patients studied, 58(52.5%) patients presented with hypertension, 138(69%) presented with ischaemic heart disease, 10(5%) patients presented with CVA, 71(35.5%) patients were suffering from myocardial infarction. (Figure2). Earlier studies reported that among 112 patients enrolled, 84.82% had hyperlipidemia followed by hypertension (80.35%) and ischaemic heart disease(66.69%).[12] It was also reported that 105(46.46%) were on anticoagulants among which 96(40.26%) received enoxaparin sodium, 5(2.21%) received Heparin and 4(1.76%) received Acenocoumarol. The details of the prescribing pattern of anticoagulants when assessed showed 75(37.5%) were prescribed with anticoagulant as monotherapy, 122(61%) were prescribed anticoagulant along with an antiplatelet.[12] 3(5.8%) females were prescribed with triple therapy in combination of two anticoagulants and one antiplatelet drug. (Figure 3). In a similar study it was found that 63(84%) patients received only one anticoagulant during their hospitalization. 21(16%) patients received more than one anticoagulant. This combination therapy included parental and oral drugs or combination of two or more drugs administered orally. Most common combination therapy was Acenocoumarol and Enoxaparin, Acenocoumarol and Heparin followed by Enoxaparin and Heparin and Warfarin, Enoxaparin and Acenocoumarol and Heparin, Enoxaparin and Warfarin, Enoxaparin and Heparin was used in hospital. [1] it was observed the distribution pattern of various drugs along with anticoagulant drug therapy. among these the most commonly prescribed were Antihypertensive 147(10.9%) followed by Antihyperlipidemics 144(10.7%).it was also observed Hepatoprotectants and Immunosuppressants 1(0.1%) were least prescribed. (Figure 4).In a similar study, among 170 patients, it was seen that Antiplatelets (99.41%) were most commonly given, followed by Antihyperlipidemics (95.29%) and Antihypertensives (64.71%).[13] In our study population, it was observed that only 1(0.5%) of the total study population presented with GI bleeding as a side effects whereas it was absent in the 199 (99.5%) of the remaining population.(Figure 5). 4(2%) of the total study population presented with other side effects like bleeding, haematuria whereas it was absent in rest of the 196(98%) of the study population (Figure 6). When overall interaction of the drug in the prescription were assessed, 296 drug interactions were found where the highest occurring major interaction was Aspirin and Clopidogrel 20(9.1%) followed by Furosemide and Metoprolol with highest occurring moderate interaction effect accounting 12(5.5%)and 1(1.3%) in male and female (Fig7).

CONCLUSION:

In the present study, the prevalence of CVD was high with increasing age. The male patients with an age group of 58-67years were most affected. The use of AC and antiplatelet combination was seen in most of the patients which adds a value in the effective treatment as well as prevention of IHD. Various potential drug interactions were encountered in the prescription.

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