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TO EVALUATE THE USE AND SAFETY OF BLOOD THINNING AGENTS IN TERTIARY CARE HOSPITAL

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Keywords:

Anticoagulant, Antiplatelet, Thrombolytic agents, Tertiary Care Hospital, Patient's safety

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ABSTRACT: Objective: To ensure the basic principles of drug utilization and the use and safety of blood thinning agents in tertiary care hospital. **Experimental design:** The study included 224 patients' and was conducted in a tertiary care hospital and we were focused on to find out the drug-drug interactions of anticoagulants, antiplatelet, and thrombolytic agents, to study the major area involvement for blood thinning agents. The newly admitted case charts to the medicine ward will randomly be selected on a daily basis and will be reviewed for the medication safety compliance. **Interpretation and Conclusion:** Appropriate use of anticoagulant therapy and any deviation from the guidelines to a large extent also depends on patient characteristics and concomitant therapy patient is receiving. Some major complications are seen with oral anticoagulants which emphasize the need for a constant monitor and patient education. The need for dosage adjustments in different diagnostic situations or specific populations is very crucial. To increase patient education, an alert was built to notify pharmacists to educate patients on these new oral anticoagulants before discharge. Further studies from time to time are required in drug utilization pattern and standard treatment guidelines to be circulated among practicing physicians. The therapy with these drugs needs to be cost-effective and reduce the complications associated with their use.

INTRODUCTION: The recent developments were introduced several new oral anticoagulants, and more drugs are currently under development. Among 2,518,064 patients, 808,897 (average age, 72 years) received at least one prescription for an antithrombotic agent over the study period (2002-2014).

Use of blood-thinning medications among older adults was significantly associated with higher rates of hematuria (the presence of blood in urine)-related complications, including emergency department visits, hospitalizations, and urologic procedures to manage visible hematuria, according to literature published.

The use of anticoagulants is a decision based on the risks and benefits of anticoagulation. The biggest risk of anticoagulation therapy is the increased risk of bleeding. Oral anticoagulants are used to prevent the progression or recurrence of acute deep vein thrombosis or pulmonary embolism following an initial course of heparin.

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They also are effective in preventing venous thromboembolism in patients undergoing orthopedic or gynecological surgery and in preventing systemic embolization in patients with acute myocardial infarction, prosthetic heart valves, or chronic atrial fibrillation [1]. For treatment of acute venous thromboembolism, heparin usually is continued for at least 4-5 days after oral anticoagulation is begun and until the INR is in the therapeutic range on 2 consecutive days. This overlap allows for adequate depletion of the vitamin K– dependent coagulation factors with long half-lives, especially factor II. Daily INR measurements are indicated at the onset of therapy to guard against excessive anticoagulation in the unusually sensitive patient. The testing interval can be lengthened gradually to weekly and then to monthly for patients on long-term therapy in that test results have been stable [2]. To improve the patient outcomes given drug prescription and intervention drug utilization evaluation want to study in the hospital. The World Health Organization (WHO) defines drug utilization research as "the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social, and economic consequences." In patients diagnosed with IHD, use of various cardiac acting drugs is more important to treat as first-line therapy. The following drugs like inotropes, vasopressors, antihypertensive, antiplatelet agents, lipid-lowering agents, and anticoagulants are frequently used in the hospital for the management of IHD [3]. The main approached behind this work was to ensure the basic principles of prevention and control to a wide range of healthcare settings office-based practice, long term care facilities. The overall descriptions presented in this study provide a baseline data which would be useful for any drug utilization study and may explore the strategies and or intervention that has been considering or use with the intention of encouraging patients.

Experimental Design: To study the evaluation of use and safety of blood thinning agents at Bangalore Baptist Hospital, India. This was a Prospective Observational Study and conducted in the Department of Surgery ward, Medicine ward, ICU, CCU a 500 bedded multi-specialty tertiary care teaching hospital. The first step in the study was to design a Data collection form and the patient data collection form was used to collect all the details like Inpatients number, Patient name, Age, Sex, Date of admission, Date of discharge, Chief complaints (c/o), History of Present Illness (HOPI), Past Medication history, Laboratory data, Culture sensitivity test, Diagnosis and Therapeutic management.

Study Procedure: The patient demographics and all medically relevant information will be noted in a predefined data collection form. Alternatively, these case charts will be reviewed for prescription legibility and completeness, unaccepted abbreviations, the capture of relevant information in case sheet, contraindication, drug interactions, and adverse drug events and dose calculations based on their weight and BSA. The changes and the daily notes in the case sheets will be followed until the patient is discharged or shift to other wards. The prescription guidelines, Lexicomp, Medscape and references books will be used as tools to review the prescription and case charts. During the study patient's medication chart was also monitored for any drug-drug interaction involving the anticoagulants used and any adverse drug reactions experienced by the patients on anticoagulant treatment. The data will be stored confidentially and will be subjected to further analysis using the appropriate software. In our study, we have generated a questionnaire to assess nursing department HODs regarding blood thinning agents, later on, we had validated.

RESULTS:

Gender Categorization with Interactions: The study patients were 224 in our study, out of them 149 (66.52%) were male, and 75 (33.48%) were female. The interactions found in our study were 65 out of 224 patients. Among them, 37 (56.93%) interactions were from male and 28 (43.07%) interactions were from the female category. **Table 1** and **Fig. 1** showed the details of categorization and **Fig. 2** total interaction, the proportion of male patients was more compared to the female patients.

TABLE 1: GENDER CATEGORIZATION WITH INTERACTIONS

Gender	Study Population n=224	Study Population (%)	Total Interaction n=65	Total Interaction (%)
Male	149	66.52	37	56.93
Female	75	33.48	28	43.07

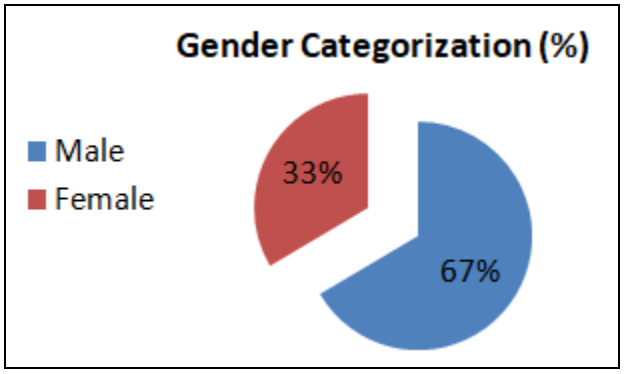

FIG. 1: GENDER CATEGORIZATION WITH RESPECT TO TOTAL POPULATION

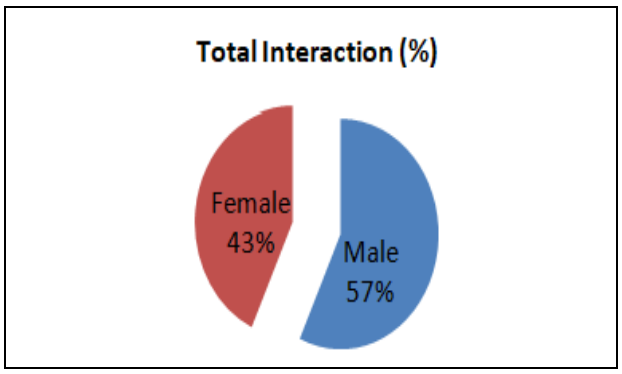

FIG. 2: TOTAL INTERACTION WITH RESPECT TO PATIENT'S DEMOGRAPHIC

Age Wise Categorization with Interaction: In our study, most of the patients having interactions were from the age group 60-69 years (21.42%) followed by 70-79 years (18.75%), 50-59 years (14.28%) and 20-29 years group (12.94%). **Table 2** and **Fig. 3** showed the details of patient's age-wise categorization and interaction.

TABLE 2: AGE GROUP CATEGORIZATION WITH INTERACTIONS IN THE STUDY PATIENTS

Age (Years)	Study Population %	Total Interactions %
20-29	12.94	4.62
30-39	9.37	9.23
40-49	11.62	16.9
50-59	14.28	18.46
60-69	21.42	20.1
70-79	18.75	18.46
80-89	11.62	12.32

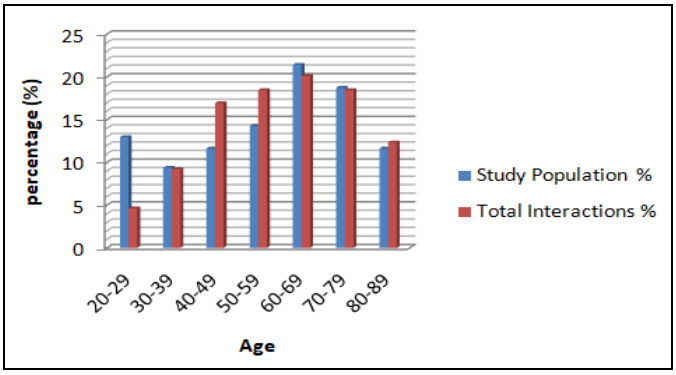

FIG. 3: AGE GROUP CATEGORIZATION WITH INTERACTIONS IN THE STUDY PATIENTS

Diseases/Co-morbidities in the Study Patients: From our study patients, patients with myocardial infarction (17.94%) were observed more followed by hypertension (13.23%), Acute Coronary Syndrome (11.21), Diabetes Mellitus (11.23), Arrhythmias (8.23%) and other co-morbidities like cerebral vascular accident, acute coronary syndrome, rectal cancer, congestive cardiac failure, and sepsis. **Table 3** and **Fig. 4** showed the details of Diseases/Co-morbidities in the study population.

TABLE 3: DISEASE/CO-MORBIDITIES IN THE STUDY PATIENT

Disease/Co-morbidities	Patients (%)
Cerbro Vascular Accident (CVA)	5.66
Acute Coronary Syndrome (ACS)	11.21
Pulmonary Edema (PULEDEMA)	3.52
Acute Gastroenteritis (AGE)	2.35
Acute pancreatitis	3.52
Myocardial Infarction (MI)	17.94
Rectal cancer	5.67
Arrhythmia	8.23
Hypertension (HTN)	13.23
Congestive Heart Failure (CHF)	3.52
Diabetes Mellitus (DM)	11.23
Sepsis	7.05
Seizure	3.52
Urinary Tract Infection (UTI)	3.35

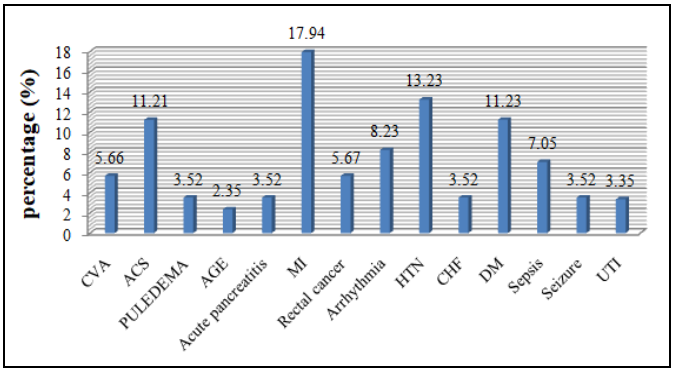

FIG. 4: DISEASE/CO-MORBIDITIES IN THE STUDY PATIENT

Category of Anticoagulants used in Study Population: Among 224 studies population, 25 patients administered Heparin, 51 patients of Enoxaparin, 43 patients of Fondaparinux, 24 patients of Acenocoumarol, 19 patients of Warfarin and 36 patients of Dabigatran. Among all the study, patients were commonly associated with Enoxaparin (22.76%) were observed to be high and followed by Fondaparinux (19.19%) and Dabigatran (16.07%). **Table 4** and **Fig. 5** showed the details of patients' category of anticoagulants.

TABLE 4: CATEGORY OF ANTICOAGULANTS USED IN STUDY POPULATION

Anticoagulant agent	Percentage (%)
Heparin & Derivatives	
Heparin	11.16
LMWH	
Enoxaparin	22.76
Fondaparinux	19.19
Coumarin Derivatives	
Acenocoumarol	10.71
Warfarin	8.48
Direct thrombin inhibitors	
Dabigatran	16.07

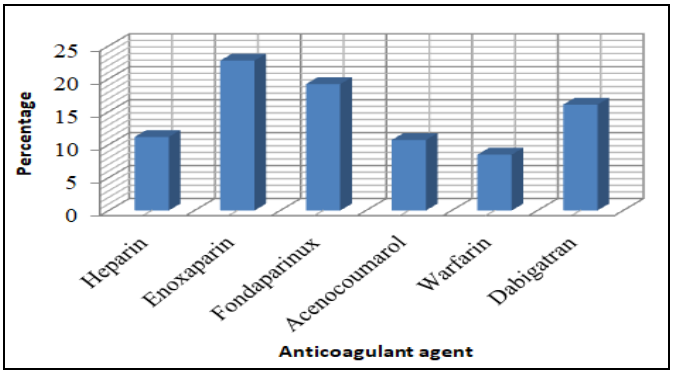

FIG. 5: CATEGORY OF ANTICOAGULANT USED IN STUDY POPULATION

Category of Anti-platelets used in Study Population: In the study, Among 224 study population of Clopidogrel was found to be prescribed to the largest number (18.75%) Antiplatelet agent used in patients, followed by Tirofiban (11.16%) and Aspirin (7.14%) **Table 5** and **Fig. 6** showed the details of patients' category of Antiplatelets.

TABLE 5: CATEGORY OF ANTI-PLATELETS USED IN STUDY POPULATION

Antiplatelet agent	Percentage (%)
Aspirin	7.14
Clopidogrel	18.75
Tirofiban	11.16

Category of Thrombolytic Agents used in Study Population: In the study, among 224 studies population of 42 patients were found to be having 18.75% of Streptokinase agent used.

Number of Drug Interaction in Study Population: In our study, among 224 studies population of 17 (7.58%) patients were found to be having one interaction, 15 (6.69%) patient were observed to have two interactions, 10 (4.46%) were observed to have three interactions and followed by 9 (4.01%), 5 (2.23%), 7 (3.12) and 2 (0.89%) patients were observed four, five, six and seven interactions respectively. **Table 6** and **Fig. 7** showed the details of patients' drug interactions.

TABLE 6: DETAILS OF PATIENTS' DRUG INTERACTIONS IN STUDY POPULATION

No. of drug interactions	No. of patients	Percentage (%)
1	17	7.58
2	15	6.69
3	10	4.46
4	9	4.01
5	5	2.23
6	7	3.12
7	2	0.89

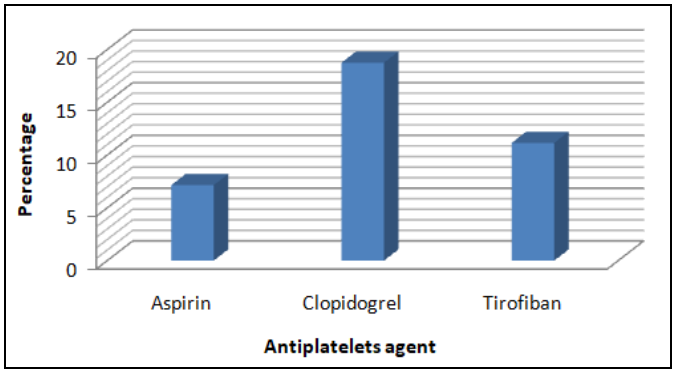

FIG. 6: CATEGORY OF ANTI-PLATELETS USED IN STUDY POPULATION

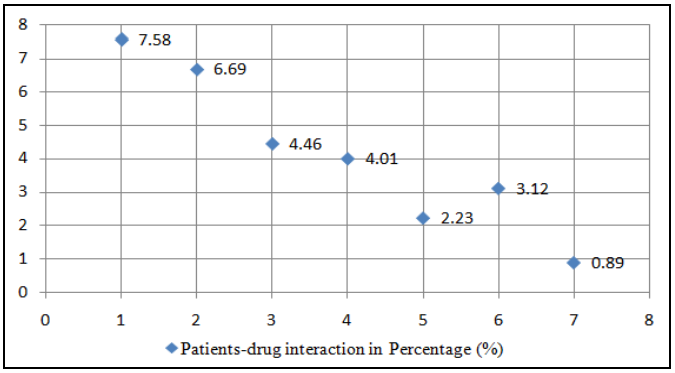

FIG. 7: DETAILS OF PATIENTS' DRUG INTERACTIONS IN STUDY POPULATION

The severity of the Drug Interaction among Study Population: Among the all 224 studies population, the interaction observed in the study patient were found to be major 51 (22.76%), moderate 9 (4.01%) and minor 5 (2.23%) category severity.

Common Drug-Drug Interactions Observed Among the Studies Population:

TABLE 7: SHOWED DETAILS OF DRUG-DRUG INTERACTIONS IN THE ANTICOAGULANT AGENTS

Drug	Interacting Drug	Frequency	Effect	Severity	Management
Heparin	Aspirin	3	Aspirin may enhance the anticoagulant effect of Heparin	Major	The risk of bleeding appears to be increased and should be monitored accordingly
	Losartan Olmesartan Telmisartan	3	Heparin may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers	Moderate	Monitoring serum potassium concentrations closely in patients receiving angiotensin II antagonists in combination with heparin
Enoxaparin	Aspirin Clopidogrel	5	May enhance the anticoagulant effect of Anticoagulants	Moderate	Increase monitoring diligence for signs and symptoms of bleeding if these agents are used concomitantly
Dabigatran	Aspirin	2	The risk for bleeding may be increased	Major	Consider therapy modification
	Clopidogrel; Prasugrel	3	the risk of bleeding may be increased	Major	Consider therapy modification
Acenocoumarol	Phenytoin	3	Vitamin K Antagonists may increase the serum concentration of Phenytoin	Major	Consider therapy modification
	Cefixime Cefotaxime Cefpodoxime Ceftriaxone	2	Cephalosporins may enhance the anticoagulant effect of Vitamin K Antagonists	Moderate	Monitor for elevated INR and bleeding
Fondaparinux	Aspirin	2	Salicylates may enhance the anticoagulant effect of Anticoagulants	Moderate	Increase monitoring for signs and symptoms of bleeding if these agents are used concomitantly

TABLE 8: SHOWED DETAILS OF DRUG-DRUG INTERACTIONS IN THE ANTIPLATELET AGENTS

Drug	Interacting Drug	Frequency	Effect	Severity	Management
Aspirin	Clopidogrel	5	Increased risk of bleeding may result	Moderate	Monitor for increased evidence of reduced platelet function (*e.g*., bleeding, bruising, *etc*.)
	Ciprofloxacin (Systemic); Levofloxacin (Systemic)	2	Aspirin may decrease the serum concentration of Quinolone Antibiotics	Moderate	Consider administering quinolone antibiotics at least 2 h before, or 6 h after, buffered aspirin ingestion
Clopidogrel	Acenocoumarol Dabigatran Enoxaparin; Fondaparinux; Heparin;	3	Agents with Antiplatelet Properties may enhance the anticoagulant effect of Anticoagulants.	Moderate	Increase monitoring for signs and symptoms of bleeding if these agents are used concomitantly.

TABLE 10: SHOWED DETAILS INTERACTIONS IN THE STUDY PATIENTS

Interacting drugs	Interaction effect	N	Observed effect	Documentation	N
Aspirin + Tirofiban	Bleeding	2	Gum Bleeding	Fair	1
Enoxaparin + Tirofiban	Bleeding	1	Gum Bleeding	Fair	1
Clopidogrel + Tirofiban	Bleeding	3	Gum Bleeding	Fair	1
Aspirin + Clopidogrel	Bleeding	2	Gum Bleeding	Fair	1
Aspirin + Enoxaparin	Bleeding	3	Gum Bleeding	Fair	2
Aspirin + Ramipril	Decreased Ramipril Efficacy	4	Creatinine Increased	Good	1
Aspirin + Furosemide	Decreased Diuretic Effect	2	Creatinine Increased	Good	2
Acenocoumarol + Enoxaparin	Bleeding	3	Increased PT/APTT	Good	1
Acenocoumarol + Levofloxacin	Bleeding	4	Increased PT/APTT	Good	1
Acenocoumarol + Amitriptyline	Increase or Decrease Effect of Acenocoumarol	2	Increased PT/APTT	Good	1
Acenocoumarol + Tramadol	Bleeding	3	Increased PT/APTT	Good	1
Acenocoumarol + Rabeprazole	Potentiating of Anticoagulant Effect	2	Increased PT/APTT	Good	2
Aspirin + Ramipril	Decreased Ramipril Efficacy	2	Creatinine Increased	Good	1
Heparin + Clopidogrel	Bleeding	2	Gum Bleeding	Good	1
Aspirin + Acenocoumarol	Bleeding	2	Increased PT/ INR	Good	2
Acenocoumarol + Pantoprazole	Increased PT and INR	2	Increased PT/ INR	Good	2
Acenocoumarol + Prednisolone	Increased Risk of Bleeding	3	Increased PT/ INR	Good	2

Acenocoumarol + Ceftriaxone	Increased Risk of Bleeding	2	Increased PT/ INR	Good	2
Acenocoumarol + Pantoprazole	Increased PT and INR	4	Increased PT/INR	Good	1
Aspirin + Atenolol	Decreased Antihypertensive Effect	2	BP Fluctuation	Good	1
Aspirin + Clopidogrel	Bleeding	3	Gum Bleeding	Fair	1
Aspirin + Heparin	Bleeding	2	Gum Bleeding	Fair	2
Aspirin + Tirofiban	Bleeding	3	Gum Bleeding	Fair	1
Heparin + Clopidogrel	Bleeding	1	Gum Bleeding	Fair	1
Heparin + Tirofiban	Bleeding	2	Gum Bleeding	Fair	2

TABLE 9: SEVERITY OF THE INTERACTION IN STUDY POPULATION

Severity of interaction	No. of patients	Percentage %
Major	51	22.76
Moderate	9	4.01
Minor	5	2.23

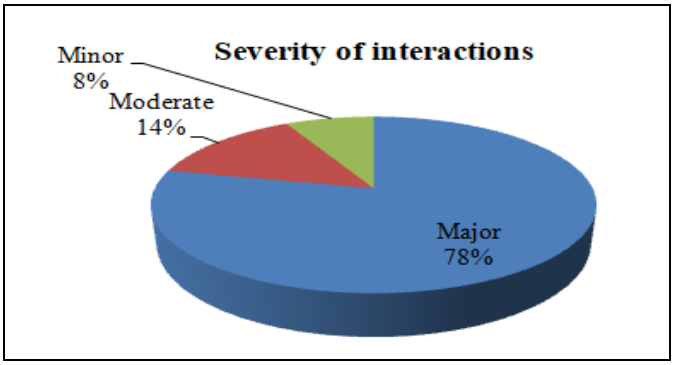

FIG. 8: SEVERITY OF THE INTERACTION IN STUDY POPULATION

Observed Clinical Effects of Drug-Drug Interactions in studies population: We had observed the effect of drug in the study, among the all 224 studies population and is omitted 14 patients (6.25%) were found to be increased gum bleeding, 9 patients (4.01%) observed increased PT/INR and followed by 6 patients (2.68), 4 patients (1.79%) and 1 patient (0.45%) were found to be Increased PT/APTT, Increased Creatinine and BP fluctuation respectively.

TABLE 11: OBSERVED EFFECT OF DRUG-DRUG INTERACTION

Clinical effect	Management	No. of patients	%
Gum Bleeding	Monitored for signs and symptoms of bleeding if these agents are used concomitantly	14	6.25
Increased PT/INR	Monitored for elevated INR and bleeding	9	4.01
Decreased Antihypertensive Effect	Monitored for BP fluctuation	1	0.45
Creatinine Increased	Considered therapy modification	4	1.79
Increased PT/APTT	Monitored for increased evidence of reduced platelet function (*e.g.*, bleeding, bruising, *etc.*)	6	2.68

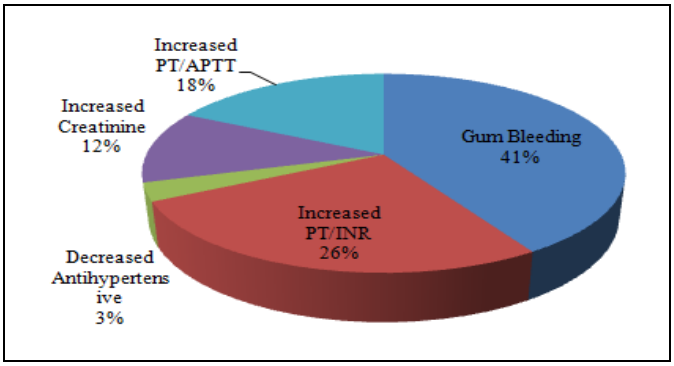

FIG. 9: OBSERVED EFFECT OF DRUG-DRUG INTERACTION

Validation of Questionnaire from Nursing HOD's: In our study, we administered a questionnaire regarding blood thinning agents to the entire nursing department HOD's and assessed the validation of the questionnaire and categorized the questions into very relevant, relevant, some relevant and not relevant. And observed educational and regulatory interventions were needed. Effective work practices improved the knowledge and professional behavior that minimize the risk and improve the quality of life.

DISCUSSION: Anticoagulants are the centerpiece therapy for the acute as well as long term prevention and treatment of thromboembolic disorders. As per the literature, current US prevalence estimate of AF is approx 2.6 million persons, and it is predicted to reach 12 million persons by the year 2050. Crowther MA *et al*., 1999; 198 patients were administered anticoagulants and patients were categorized into age groups which showed, 48 (21.42%) were belonging to age group of 60 to 69 years which covered majority of patients in the study, followed

by 42 (18.75%) patients in age group of 70 to 79 years. Age group of 61 to 70 years was the most common in both genders.[4] And compared with this data observed that Koaron C 2003; in 48 patient's cases where PT, INR & tests were performed in 12 patients PT, INR & aPTT levels were increasing despite anticoagulant therapy, however in such patients the dose of anticoagulant drug administered was not further altered. Also in the therapy, enoxaparin showed lesser efficacy than with acenocoumarol as the PT, INR and aPTT values with enoxaparin therapy showed an increase compared to normal values [5]. Taken together, Hylek EM *et al*., 1996; the results presented here indicate that more attention needs to be paid to ensure safe use of anticoagulants and diuretics, often used in elderly patients who experience far more ADRs compared with children or younger adults. Targeting education and prevention actions on these two drug classes could help to reduce the incidence rate of ADR related hospitalizations [6].

Ultrasound data were not available for this study Hering D *et al*., 2005; which limited our evaluation of the hemodynamic status of dissections. Stroke severity (*i.e*., NIHSS score) at presentation was not prospectively recorded, but we found no association between antithrombotic choice and the ischemic symptoms at presentation or the presence of infarction on brain imaging. Traumatic CAD patients were also included in our study; their hospital courses may have only allowed for AP treatment due to the risk of bleeding in the acute period [7]. Hurlen M *et al*., 2002; Study was underpowered to detect the differences in the risk of recurrent ischemic events. Previous estimates suggest that thousands of patients are needed to compare the efficacy of anticoagulation to antiplatelet therapy in preventing recurrent stroke in patients with CAD. Clinicians should identify patients at risk for late bleeding after PCI and implement strategies to reduce the overall risk of bleeding, thereby improving patient outcomes.[8] Makris M *et al*., 2010; Aspirin inhibits platelet activation through TXA2 pathway but does not affect activation through ADP pathway. Clopidogrel inhibits platelet activation through ADP pathway. As it blocks platelet activation by a mechanism different from aspirin, the combination therapy with aspirin may offer benefits over either drug used alone.

According to the CURE trials, clopidogrel and aspirin decrease the rate of the combined end point of cardiovascular deaths, non-fatal MI or stroke by 20% in patients with acute coronary syndromes when compared to aspirin. High-risk patients presenting with acute coronary syndromes should receive clopidogrel on admission at conservative centers and if appropriate after coronary angiography in aggressive centers. In the hospital where our study was done, this combination has been in use for more than 5 years, and it was found to reduce the mortality rate of patients within a year of acute coronary syndromes significantly. The only major side effect seen was GI bleeding and bleeding at arterial puncture sites [9]. However, it is essential that a simple, inexpensive and widely approved test, like aPTT and INR, be available for clinical use, occasionally, in patients with severe hemorrhagic complications, recurrent thrombotic episodes or before percutaneous interventions and surgery.

Aspirin was prescribed in low dose for treatment and prevention of IHD. Its use is justifiable with the total number of patients with cardiovascular disease. However, it should be prescribed with caution in patients aged 80 years or more due to lack of evidence for benefit versus risk, O'Donnell M *et al*., 2008 [10]. Prescribing drugs with a generic name, avoiding irrational use of drugs, and poly-pharmacy can help in reducing the cost of treatment and economic burden. Presence of multiple co-morbidities and use of more parenteral and antimicrobial drugs are responsible for greater economic burden in expired than survived patients.

CONCLUSION: This study was concluded in brief that major complications are seen with oral anticoagulants which emphasise the need for a constant monitor and patient education. The therapy with these drugs needs to be cost-effective and reduce the complications associated with their use. Improving patient knowledge on correct dosage will boost up the present healthcare in the hospital setting. However, it seems prudent to choose the anticoagulant drug therapy on a patient-specific basis. Effective work practices that minimize the risk and improve the quality of life; educational and regulatory interventions were needed which includes improving the knowledge, and professional behavior of pharmacists,

pharmacy assistants, and drug sellers will determine the final impact on the health system.

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CONFLICT OF INTEREST: Certify that we have no conflict of interest.

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