COUMARIN DERIVATIVE TREATMENT: AN OBESERVATIONAL PROSPECTIVE STUDY TO ASSESS INCIDENCE OF ELEVATED INR, ITS ASSOCIATED RISK FACTORS AND THE PATIENT ADHERENCE

[1]Dr.Rajnandini Singha, [2]Dr.Riya Mariam, [1]Dr.ReemaRenjith,[3]K. Menaka

[1]Department of Pharm D, Department of Pharmacy, Nandha College of Pharmacy, Erode-638052, Tamil Nadu, India.

[2]Department of Pharmacology, University of Bedfordshire, University Square, Luton-LU13JU United Kingdom.

[3]Associate Professor, Department of Pharmacy Practice, Nandha College of Pharmacy, Erode 638052, Tamil Nādu, India.

DOI: 10.47750/pnr.2022.13.S10.111

Abstract

The Coumarin derivatives anticoagulant are narrow therapeutic drugs, used globally for the prevention of thromboembolic events. Coumarin derivatives are associated with a risk of bleeding that may restrict their use. Bleeding is the serious complication for the use of oral anticoagulation (Coumarin derivative) in the prevention and treatment of thromoboembolic complications. The purpose of this study is to determine the Incidence of elevated International Normalised Ratio (INR), its associated Risk factors and the Patient Adherence in Coumarin derivative treatment. The risk of bleeding is closely correlated with anticoagulation severity, among others. The key explanation for the risk of bleeding is the elevated INR. The International Normalised Ratio (INR) is a laboratory calculation of how long it takes to clot blood. It is used to assess the effects on the clotting function of oral anticoagulants (coumarin derivatives). The risk of severe haemorrhage (bleeding) is increased by INR values over 5 and INR less than 2 increases the risk of thromboembolism. Different risk factors, including drug interactions such as antibiotics, NSAIDS, food interactions, and other patient-specific risk factors, which change the stability of the level. To avoid bleeding and thrombotic events, the dosage of acenocoumarol and warfarin should be titrated according to INR stability.

Keywords: Coumarin derivative, Anticoagulants, Vitamin K Antagonists, Medication Adherence, Warfarin, Acitrom.

INTRODUCTION

Anticoagulants are the key agents for preventing and treating thromboembolic disorders, commonly referred to as blood thinners that prevent or decrease blood coagulation, prolonging coagulation time1,2. Coumarin derivatives (4-hydroxycoumarin compounds) are oral anticoagulants (OA) that prevent vitamin K from acting as a cofactor in the hepatic synthesis of the vitamin K-dependent coagulation factors II, VII, IX, and X (as well as the anticoagulants, proteins C and S)3,4. They are also called vitamin K antagonists. Available coumarin derivatives are acenocoumarol and warfarin. They have been used since decades as a standard therapy for prevention and treatment of diseases such as atrial fibrillation, heart valve replacement, ischemic stroke, post myocardial infarction or other thrombotic event5. However, the clinical benefit of VKA treatment is counterbalanced by a thrombotic risk (related to insufficiently effective prevention) and a haemorrhagic risk (related to excessively high doses of anticoagulant). The clinical management of VKA treatment is very complex (notably due to a narrow therapeutic safety window and great inter and intra individual variability in the response to anticoagulants) but is facilitated by monitoring the International Normalized Ratio (INR) 6. An INR range of 2.0-3.0 is generally an effective therapeutic range for people taking oral coumarin derivatives for disorders such as atrial fibrillation or blood clot. If the INR is too low blood clots will not be prevented, but if the INR is too high there is an increased risk of bleeding. Hence the patient should maintain the INR range according to the disease7. There are some risk factors that increase the risk of bleeding, for instance, vegetables such as broccoli, Brussels, kale, spinach, etc. containing high amounts of vitamin K, can interfere with warfarin therapy and minimize its effectiveness. In depth, Vitamin K is used by the liver to produce clotting factors, which are cells that help regulate bleeding and facilitate the formation of blood clots8. Warfarin interferes with this clotting mechanism by inhibiting an enzyme in the liver that uses vitamin K to form clotting factors. Warfarin can minimize the risk of a hazardous blood clot. Therefore, frequent INR monitoring and warfarin dose changes are often needed during anticoagulant therapy. Other factors include the use of concomitant drugs that is, Since warfarin is strongly bound to plasma proteins, other drugs such as (ibuprofen, cordarone, quinidine, sulfinpyrazone,

antibiotics, amlodipine, losartan) that compete for binding sites displace warfarin, thus enhancing the anticoagulant activity of VKAs, alter the pharmacodynamics and pharmacokinetics of coumarin derivatives9,10. This effect leads to increasing PT-INR. Most drug interactions influencing the metabolism of warfarin occur due to inhibition of the expression and/or activity of CYP450 enzymes involved in the metabolism of warfarin. This causes CYP2C9, leading to increased warfarin clearance and thus decreased anticoagulation effect. In addition to this, there are other factors too , such as liver disease, acute illness, ageing, alcohol intake, Furthermore, other significant factors have not been extensively evaluated (drug compliance, patient awareness of his/her treatment, and use of an anticoagulation booklet)11.

When patients receive more drugs to treat their chronic medical problems, non-adherence to medications is continuing. In the elderly population, this is also evident because of a deterioration in their mental and physical health12,13. The result of inadequate medication adherence may be life-threatening for some medications.

Such as warfarin, which has a very small therapeutic index. The medication is used to avoid thromboembolic complications from various disorders, including stroke, atrial fibrillation, venous thromboembolism, and valvular heart disease as a long-term oral anticoagulation14,15. When the therapeutic range is maintained, warfarin is successful, but when levels are below or beyond the intended range, it is associated with an increased risk of thrombosis and bleeding16.

The purpose of the research was to evaluate the level of patient awareness, their adherence to medication and their related risk factors for adverse effects in the study population and thus ensure safer and more efficient use of oral anticoagulants through the impact of interventions implemented by clinical pharmacists. In terms of bleeding and drug interaction, we have made a comparison between acitrom and warfarin, then concluded that acitrom is better than warfarin because it has less likelihood of bleeding and drug interactions and also has a better pharmacokinetic profile such as (shorter half-life, irreversible behaviour, better prothrombin time stability, less dependency on CYP2C90.

MATERIALS AND METHOD:

A prospective observational study was conducted using the data collected. The study was carried in various department of tertiary care hospital at Coimbatore, India. A six-month study was planned and information was collected. The inclusion and exclusion criteria to participate in the analysis was fulfilled in a total of 100 patients. Both males and females including patients undergoing coumarin derivative treatment with a high INR level of 5 were included. Critically ill patients (Cancer, End Stage Renal Diseases), pregnant and lactating women and those who are not willing to participate in this study were excluded.

A specially designed data collection form was prepared and patient data including demographic details, medical and medication history, social history, current medications, INR values during visits and the dose of their anti-coagulant etc., were obtained from the patient or care givers. The study was conducted accordingly by three phases. In which first phase includes preliminary literature survey, pilot scale study and ethical committee approval. Second phase contains data collection, data analysis, follow up of the selected candidates and Clinical Pharmacist intervention. Third phase comprises data compilation with recording and results. The severity of the drug-drug interaction was analysed using Lexicomp Drug interaction checker. The initial knowledge of the coumarin derivative was conducted by the standardized Morisky scale assessment by evaluating the patient is adhered or not. All patients included in the study received a standard care of treatment from the physician and various departments. Accordingly, Clinical Pharmacist counselling with interventions including awareness of coumarin derivatives, suspected adverse drug reactions, management, importance of proper follow up, time of administration and influence of dietary changes were considered during the study. On follow up, previous knowledge will be reassessed by the questionnaire and calculate the patient is adhered or not.

STATISTICAL TEST:

The statistical data was analysed using SPSS software and Chi- square using the information collected regarding all the cases. Percentages were calculated. Chi square test and P value of <0.05 was considered to be significant.

RESULTS:

The study included 100 patients who statisticalized the criteria for inclusion and exclusion. Out of 100 patients, warfarin and acitrom were used in 56 and 44 patients respectively. The analysis was focused on prospective observational data collections and all follow-ups were completed. In the study, there were no drop outs. Results were categorized in terms of age, gender, indications, elevated INR, bleeding risk, risk factors, drug - drug interaction, disease condition and patient adherence.

A. DISTIBUTION BASED ON AGE

The patients were categorized into three groups based on the age such as 1st group (20-50 years), the second group (51-75 years), and the third group (76-100 years). Second, categorization were based on elevated INR i.e., INR>5, INR>7, INR>10, respectively. The elevation of INR seen in first age group (20-50 years) is concluded that the patients in this group showed 40%, the second age group (51-75 years) showed 57%, and the third age group showed 3%. Therefore, the second category, i.e., middle age, showed a greater risk of increased elevated INR. The results are given in table 1and 2, and figure 1.

Table 1. The elevation of INR based on age were classified as INR>5, INR>7, INR>

Age category	**INR>5**	**INR>7**	**INR>10**	**Total (%)**
26-50	23	10	7	40%
51-75	37	16	4	57%
76-100	2	1	0	3%
Total	62	27	11	100%

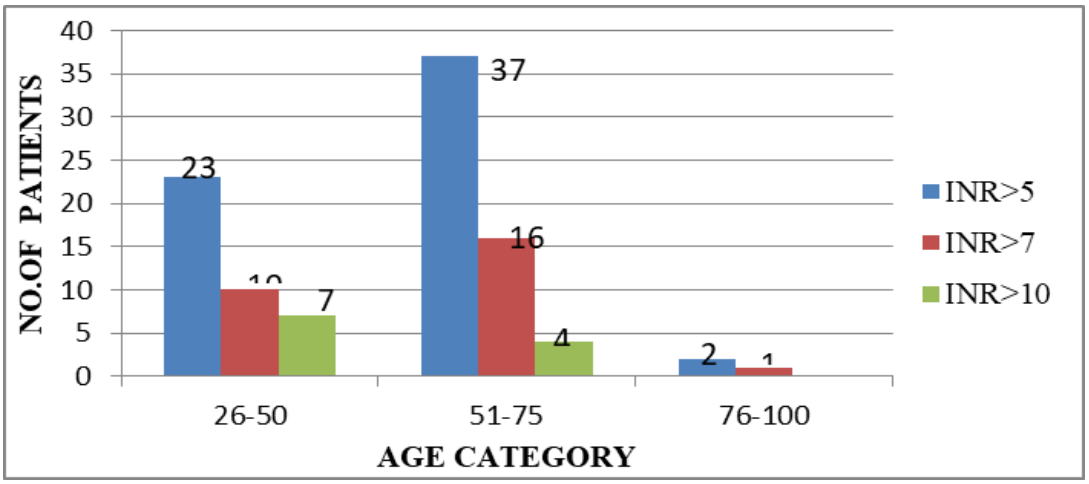
Chi-Square Test:

From these Chi-square results, it is observed that p value is less than 0.05 given in table 2. Hence there is association between patient age and elevated INR.

Table 2:

Pearson Chi-Square value	Degrees of freedom	P value
4.035	4	0.004

FIGURE 1: DISTRIBUTION OF AGE CATEGORY BASED ON ELEVATED INR



B. DISTRIBUTION BASED ON GENDER

Our study found that warfarin and acitrom were consumed in different genders, i.e. male and female. Compared to males (47%), females (53%) were highly administered with warfarin and acitrom. The results are depicted in in Table 3 and 4, and figure 2 based on the INR values.

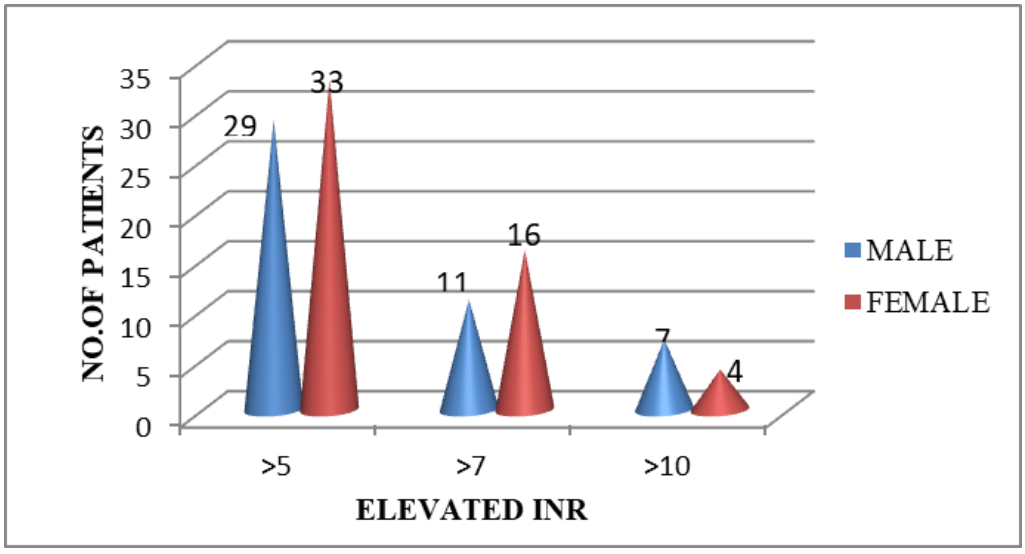
TABLE 3: DISTRIBUTION of INR VALUE BASED ON GENDER

GENDER	INR>5	INR>7	INR>10	TOTAL IN %
MALE	29	11	7	47 %
FEMALE	33	16	4	53 %
TOTAL	62	27	11	100 %

Table 4 Chi-square test

Pearson Chi-Square value	Degrees of freedom	P value
6.122	2	0.047

FIGURE 2: DISTRIBUTION OF GENDER BASED ON ELEVATED INR



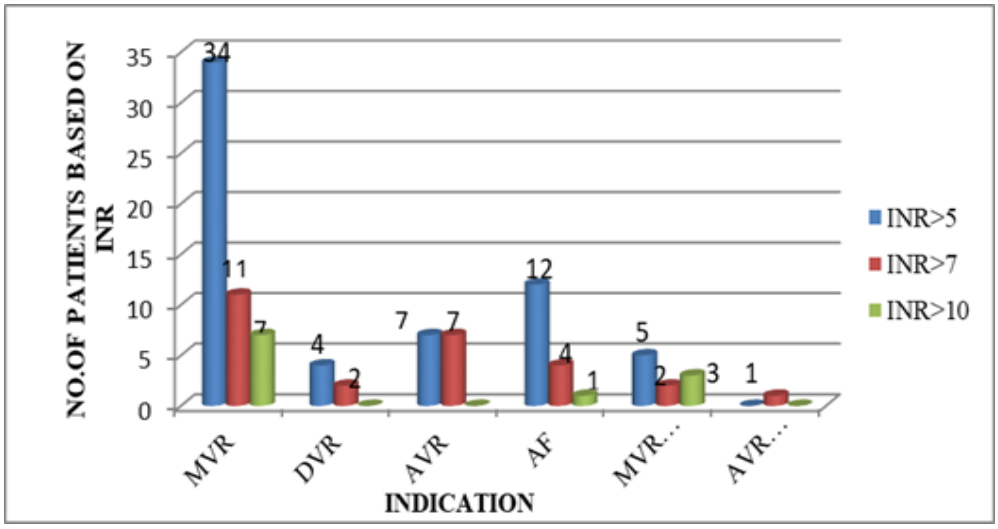
C. DISRTIBUTION BASED ON INDICATION

Warfarin and acitrom were prescribed to 100 patients with different indications. Some of indications may play a major role in elevated INR and bleeding risk. Therefore, categorization of indication with their elevated INR were done, and it was concluded that MVR (Mitral valve replacement) (52%) showed the highest compared to other indication i.e., AVR (Atrial valve replacement) (14%), DVR (Double valve replacement) (6%), AF (Atrial fibrillation) (17%), MVR-AF (10%) and AVR-AF (1%). The table 5 and figure 3 explain about the results

TABLE 5: DISRTIBUTION BASED ON INDICATION AND INR VALUE

INDICATION	INR>5	INR>7	INR>10	TOTAL (IN PERCENTAGE)
MVR	34	11	7	52%
DVR	4	2	0	6%
AVR	7	7	0	14%
AF	12	4	1	17%
MVR-AF	5	2	3	10%
AVR-AF	0	1	0	1%

FIGURE 3: DISTRIBUTION OF INDICATION BASED ON INR VALUE



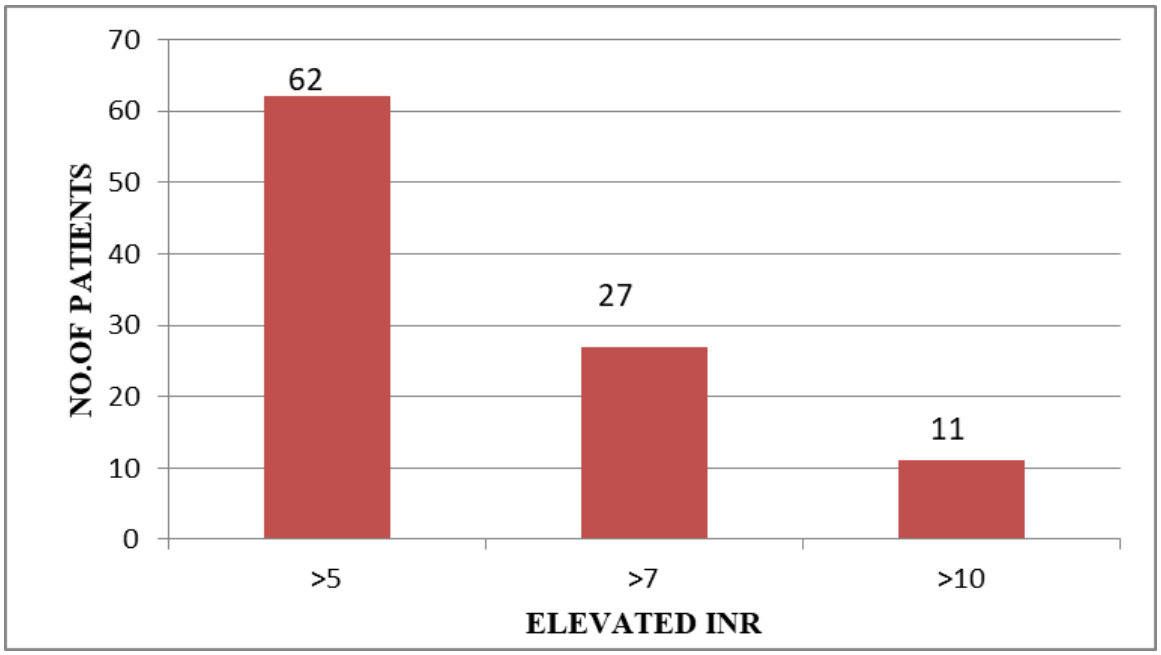
D. DATA DISTRIBUTION BASED ON ELEVATED INR

Patients taking warfarin and acitrom were classified into 3 elevated INR classes i.e. INR>5, INR>7, and INR>10, and bleeding risk. The highest number of patients falls in group of INR>5 (62%) compared to INR>7 (27%) and INR>10 (11%). The results are explained in table 6 and figure 4.

TABLE 6: DATA DISTRIBUTION BASED ON ELEVATED INR

INR	NO.OF PATIENTS (n=100)	PERCENTAGE (%)
>5	62	62.0 %
>7	27	27.0 %
>10	11	11.0 %
TOTAL	100	100 %

FIGURE 4: DATA DISTRIBUTION BASED ON ELEVATED INR



E. DISTRIBUTION OF ELEVATED INR BASED ON BLEEDING RISK

The patients who were taking anticoagulants suffered from bleeding as one of the side effects. The results given in table 7 and 8, and figure 5 explained the outcome of bleeding risk in patients with anticoagulants.

TABLE 7: DISTRIBUTION OF ELEVATED INR BASED ON BLEEDING RISK

ELEVATED INR	BLEEDING RISK	NO BLEEDING RISK	TOTAL (IN PERCENTAGE %)
>5	30	32	62%
>7	18	9	27%
>10	10	1	11%
TOTAL (%)	58%	42%	100%

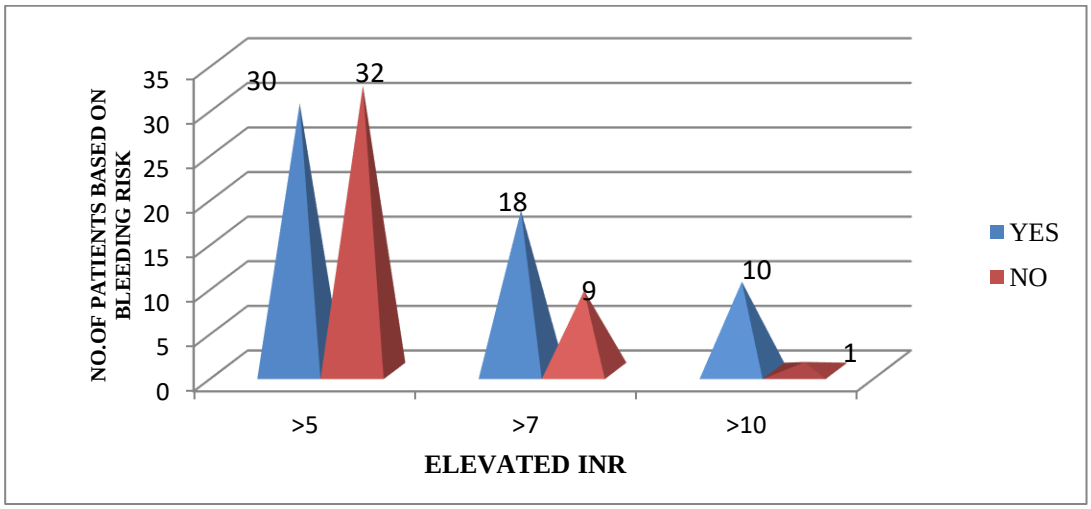
Chi-Square Test

From this Chi-Square test, it is observed that the p value is less than 0.05. Hence there is association between INR and bleeding risk.

Table 8:

Pearson Chi square value	Degree of Freedom	P value
8.075	2	0.014

FIGURE 5: DISTRIBUTION OF ELEVATED INR BASED ON BLEEDING RISK



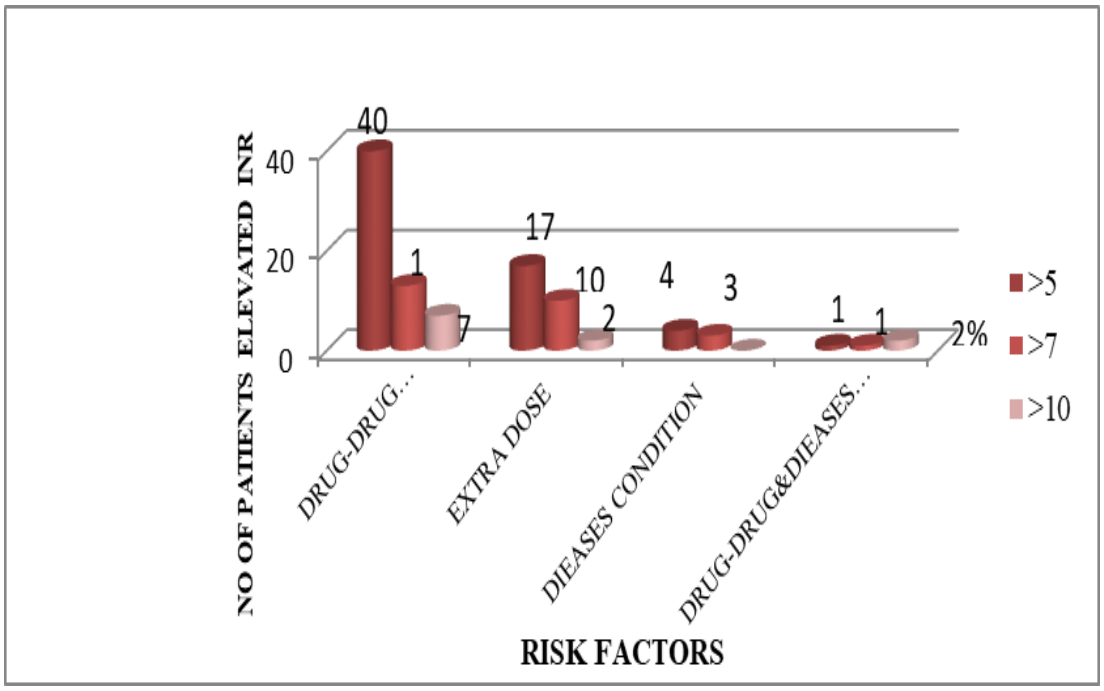
F. DISTRIBUTION BASED ON RISK FACTORS

Our study Classified Various Risk factor that were the cause of Elevated INR and bleeding risk. The notable risk factors were Drug-drug interactions, Extra dose, Disease condition and drug - drug and disease condition. The major risk factor was Drug-drug interactions (60%) compared to extra dose (29%), disease conditions (7%) and drug-drug interaction & disease condition (4%). The results are given in table 9 and figure 6.

TABLE 9: DISTRIBUTION OF RISK FACTORS BASED ON ELEVATED INR

RISK FACTORS	INR>5	INR>7	INR>10	TOTAL (%)
DRUG-DRUG INTERACTIONS	40	13	7	60%
EXTRA DOSE	17	10	2	29%
DISEASES CONDITION	4	3	0	7%
DRUG-DRUG&DISEASE CONDITIONS	1	1	2	4%
TOTAL	62	27	11	100%

FIGURE 6: DISTRIBUTION OF RISK FACTOR BASED ON ELEVATED INR



G. DISTRIBUTION ON DRUG-DRUG INTERACTIONS

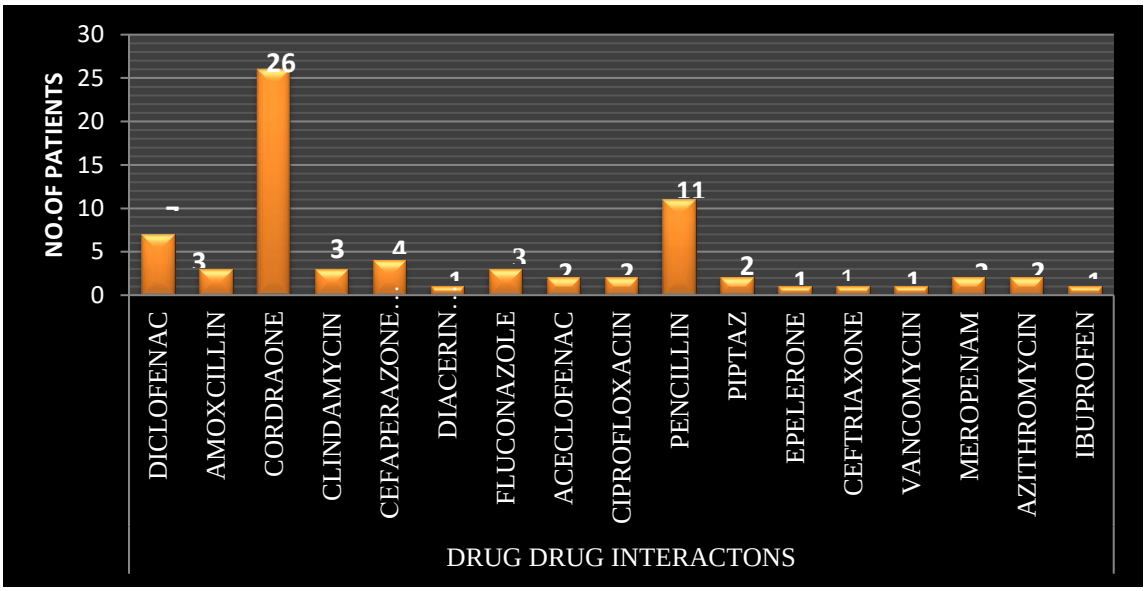
Drug-drug interaction with warfarin and Acitrom are the major cause of increase elevated INR. Among all the drugs, Cordarone (37%) showed more interactions with the coumarin derivative and also showed interactions with other drugs such as Penicillin (16%), Diclofenac (10%), Cefaperozone sulbactam (5%), Amoxicillin (4%), Clindamycin (4%), Fluconazole (4%), Aceclofenac (3%), Ciprofloxacin (3%), Piperacillin tazobactam (3%) Meropenam (3%). The results are given in table 10 and figure 7.

TABLE 10: DISTRIBUTION ON DRUG-DRUG INTERACTIONS

DRUG INTERACTION	**NO.OF PATIENTS**	**TOTAL (%)**
CORDARONE	26	37%
PENCILLIN	11	16%
DICLOFENAC	7	10%
CEFAPERAZONE SULBACTAM	4	5%
AMOXICILLIN	3	4%
CLINDAMYCIN	3	4%
FLUCONAZOLE	3	4%
ACECLOFENAC	2	3%
CIPROFLOXACIN	2	3%
PIPERACILIN TAZOBACTAM	2	3%
MEROPENAM	2	3%
AZITHROMYCIN	2	3%
DIACERIN GLUCOSAMINE	1	1%

EPELERONE	1	1%
CEFTRIAXONE	1	1%
VANCOMYCIN	1	1%
IBUPROFEN	1	1%
TOTAL	72	100%

FIGURE 7: DISTRIBUTION ON DRUG-DRUG INTERACTION



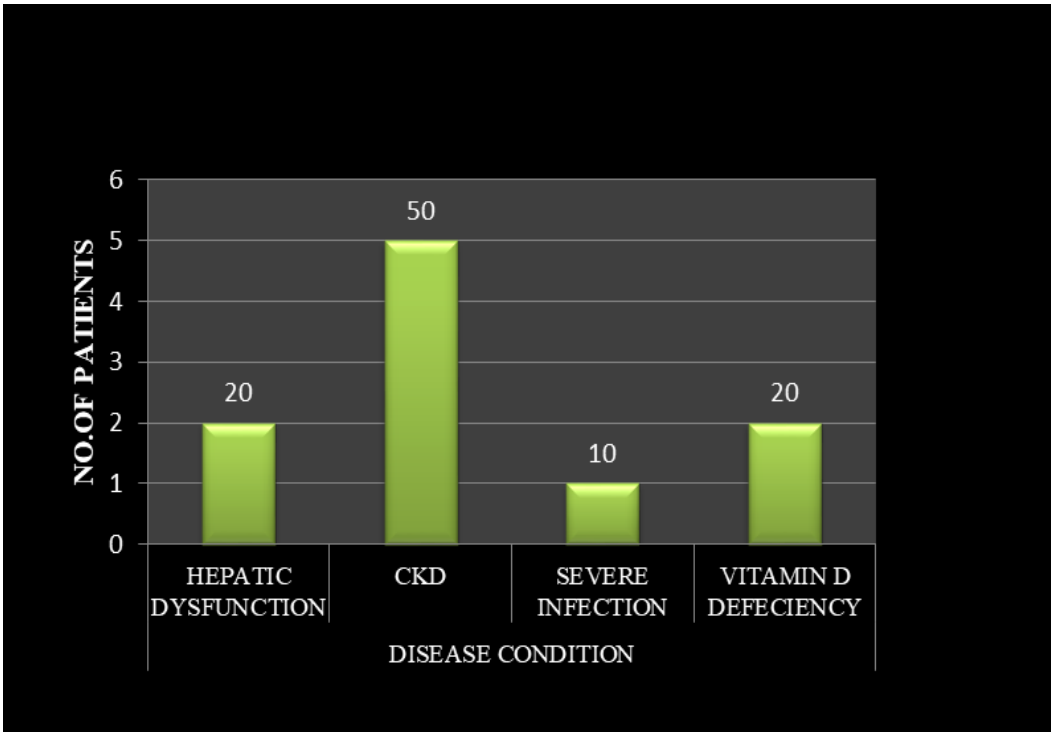
H. DISTRIBUTION BASED ON DISEASE CONDITION

The disease conditions are analyzed based on elevated INR and bleeding risk in conditions such as Hepatic dysfunction (20%), chronic renal disease (50%), severe infection (10%), and vitamin D deficiency (20%) were given in table 11 and figure 8.

TABLE 11: DISTRIBUTION BASED ON DIEASES CONDITION

DIEASES CONDITION	**NO.OF PATIENTS**	**TOTAL.IN PERCENTAGE (%)**
HEPATIC DYSFUNCTION	2	20%
CHRONIC KIDNEY DIEASES	5	50%
SEVERE INFECTION	1	10%
VITAMIN.D DEFICIENCY	2	20%
TOTAL	10	100%

FIGURE 8: DISTRIBUTION BASED ON DIEASES CONDITION



I. DISTRIBUTION OF DRUGS BASED ON BLEEDING RISK AND CATEGORISATION OF BLEEDING RISK

In contrast, Warfarin (64%) and Acitrom (36%) showed a higher risk of bleeding than Acitrom. The bleeding risks are classified as Gum Bleeding (48%), Nose Bleeding (24%), Hematuria (12%), and Hemoptysis (16%). The results are given in table 12 and 13, and figure 9 and 10.

TABLE 12: DISTRIBUTION OF DRUGS BASED ON BLEEDING RISK

DRUGS BASED ON BLEEDING RISK	**NO.OF PATIENTS**	**TOTAL.IN PERCENTAGE (%)**
WARFARIN	37	64%
ACITROM	21	36%
TOTAL	58	100%

FIGURE 9: DISTRIBUTION OF DRUGS BASED ON BLEEDING RISK

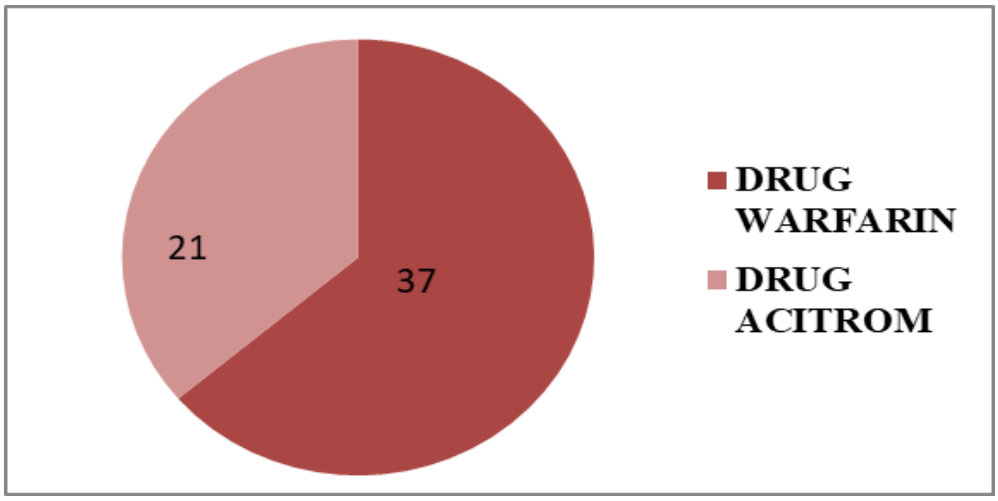
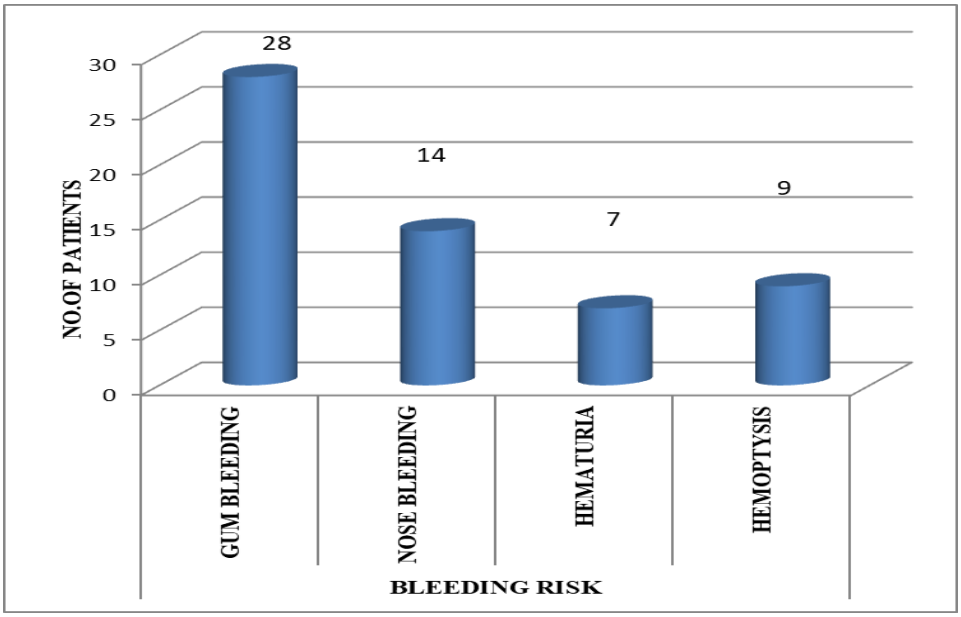


TABLE 13: CATEGORIZATION OF BLEEDING RISK

BLEEDING RISK	PATIENTS (58)	TOTAL (%)
GUM BLEEDING	**28**	**48%**
NOSE BLEEDING	**14**	24%
HEMATURIA	**7**	12%
HEMOPTYSIS	**9**	16%

FIGURE 10: CATEGORIZATION OF BLEEDING RISK



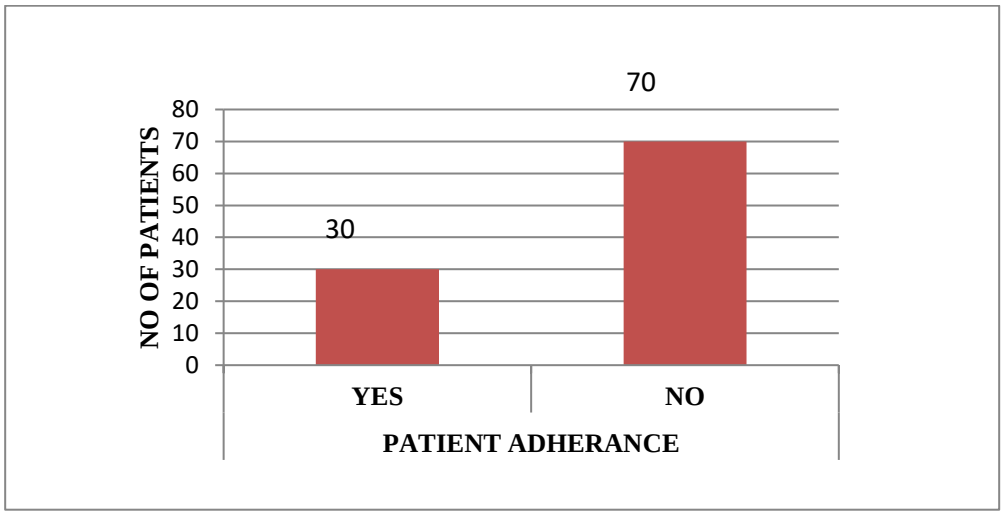
J. DISTRIBUTION BASED ON MEDICATION ADHERENCE

The Modified Morisky scale assessed patient adherence, indicating that 30% of patients were correctly adhered to and 70% were not adhered. The results are given in table 14 and figure 11.

TABLE 14: DISTRIBUTION BASED ON MEDICATION ADHERENCE

MEDICATION ADHERENCE	NO.OF PATIENTS	TOTAL.IN PERCENTAGE (%)
YES	30	30%
NO	70	70%
TOTAL	100	100%

FIGURE 11: DISTRIBUTION BASED ON MEDICATION ADHERENCE



DISCUSSION

Coumarin derivatives are associated with a risk of bleeding that may restrict their use. The risk of bleeding is closely correlated with anticoagulation severity, among others. The key explanation for the risk of bleeding is elevated INRs17,18. In our study, 100 patients were enrolled in the hospital prescribed with acitrom and warfarin associated with elevated INR >5 and bleeding risk

Hilde A. M. Kooistra et al19,20 observed that several studies have found that the risk of bleeding increased with age in people using a VKA. This higher risk could be explained in part by the VKA's inadequate control. Increased comorbidities, co-medications, fall risks, and vulnerability to gastrointestinal bleeding are all possible explanations as people get older. Because the risk of thrombosis is increased in the elderly, anticoagulants can prevent more thrombotic episodes21,22. As a result, a higher risk of bleeding may be acceptable in exchange for fewer thrombotic events23.

Additionally, This study showed that the higher number of elevated INR level was found between the age group of 51-75 years (57%), whereas in 26-50 years (40%) and 76-100 years (3%). This could be explained by the several factors such as comorbidities, polymedications, and dementia (Table 1).

Bina Ahmed et al24,25 have revealed that Women who undergo percutaneous coronary intervention (PCI) are older than men and have a higher rate of renal failure, anaemia, and diabetes mellitus than men. Women with Acute Coronary Syndrome (ACS) had a higher unadjusted death rate than men, and they use less of the guideline-recommended medications (early invasive treatment, thienopyridines, and glycoprotein inhibitors [GPIs]). The decision to withhold guideline-recommended antiplatelet medication due to increased bleeding risk in women should be based on an individualized risk-benefit analysis in the context of this increased cardiovascular risk. Although it's uncertain whether the sex-specific risk of higher cardiovascular events exists after comorbidities are taken into account, the link between bleeding and female sex does25,26,27.

Furthermore, from the result, it was observed that females (53%) were more prone to have elevated INR when compared to males (47%). A vast majority of mechanical heart valve patients were in males, whereas the most patients with thromboembolism were in females. This can be a contributory cause to the results favoring males. On the contrary, females (53%) were significantly younger at baseline, thus more prone to elevated INR and bleeding risk.

Itthidet et al28 investigated that because higher rates of thromboembolic complications have been reported when the mechanical valve is in the mitral position compared to when the mechanical valve is in the aortic position, current American and European clinical guidelines recommend a higher international normalized ratio (INR) for anticoagulant therapy after mechanical mitral valve replacement.

The patients who prescribed with warfarin and acitrom were indicated for Multi valve replacement (52%), double valve replacement (6%), atrial valve replacement (14%), atrial fibrillation (17%), MVR-AF (10%) and AVR-AF (1%).

The result also indicated that 58% had a risk of bleeding and 42% had no risk of bleeding. This indicates that patients with bleeding risk was shown more in INR level > 5 (52%) compared to >7 (27%) and >10 (11%), respectively.

Lu et al29 investigated 70 patients on concurrent warfarin and amiodarone treatment retrospectively. Individuals on combined medication had a higher probability of obtaining a supratherapeutic INR of >5 than those on warfarin alone, according to the study. Although the study found that the risk was greatest during the first 12 weeks of amiodarone medication, stratifying the risk throughout this time frame was impossible. This highlights the significance of closely monitoring INR after starting amiodarone in warfarin-treated individuals. The proportion of patients who had their INR measured within the first several weeks after starting amiodarone was researched with the goal of describing anticoagulation monitoring. The result showed that among the risk factors, the occurrence of drug interaction (60%) was higher compared to the other risk factors. The study reported that patients with INR level >5 showed more drug-drug interactions.

In this present study, the patients with bleeding risk were more in Drug-drug interactions (62%). Cordarone (37%) showed more interactions with the coumarin derivative and also showed interactions with other drugs such as penicillin (16%), diclofenac (10%), cefaperozone sulbactam (5%), amoxicillin (4%), clindamycin (4%), fluconazole (4%), aceclofenac (3%), ciprofloxacin (3%), piperacillin-tazobactam (3%) and meropenam (3%). The comparison showed acitrom (45%) has got less drug interactions than warfarin (55%).

Michael F. Harrison et al30 revealed that many of the procoagulant and anticoagulant proteins required for maintaining hemostasis are synthesized in the liver. Although it is commonly assumed that cirrhosis and liver disease are linked to an increased risk of bleeding, evidence suggests that other factors such as sepsis, hepatorenal syndrome, hypotension, and endothelial dysfunction, rather than isolated cirrhosis and liver disease, contribute to this bleeding tendency.30 In addition, this study (Table.13) states that elevated INR and bleeding risk were also associated with other disease conditions such as Hepatic dysfunction (20%), chronic renal disease (50%), severe infection (10%), and vitamin D deficiency (20%).

The result also indicated that warfarin (64%) showed higher bleeding risk when compared to acitrom (36%).

CONCLUSION

Our analysis reported the occurrence of elevated INR and bleeding risk associated with Coumadin derivatives in both inpatient and outpatient. This research concludes that Acitrom is better than Warfarin because it has less chance of bleeding and drug interactions and also has a better pharmacokinetic profile, such as (shorter half-life, irreversible actions, better stability of prothrombin time, less dependence on CYP2C9). Patient adherence to the treatment of coumarin derivatives seemed to have a key role in preserving the level of INR within the therapeutic range; in fact, non-adherence was investigated as a cause of instability of INR. Therefore, patient education seems to be an important method for patients to stick to the recommended medications.

ACKNOWLEGEMENT

I would like to express heart full thanks to my guide and the administration of Nandha College of pharmacy for their support.

CONFLICT OF INTEREST:

It is certify that we have no conflict of interest.

REFERENCES

1. Hirsh J, Dalen J, Anderson DR, Poller L, Bussey H, Ansell J, Deykin D, Brandt JT. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest. 1998; 114(5): 445S-469S.
2. Horton JD, Bushwick BM. Warfarin therapy: evolving strategies in anticoagulation. Am Fam Physician. 1999; 59:635–646.
3. Micromedex. Warfarin drug evaluations. Micromedex@Healthcare Series 2000; 106.
4. Dager WE, Branch JM, King JH, White RH, Quan RS, Musallam NA, Albertson TE. Optimization of inpatient warfarin therapy: Impact of daily consultation by a pharmacist-managed anticoagulation service. Ann Pharmacother. 2000; 34:567–572.
5. Aithal GP, Day CP, Kesteven PJ, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. Lancet. 1999; 353(9154):717–719.
6. Hirsh J, Dalen J, Anderson DR, Poller L, Bussey H, Ansell J, Deykin D. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest. 2001; 119(1):8S–21S.
7. Wells PS, Holbrook AM, Crowther NR, Hirsh J. Interactions of warfarin with drugs and food. Ann Intern Med. 1994; 121(9):676–683.
8. Tadros R, Shakib S. Warfarin - indications, risks and drug interactions. Aus Fam Physician. 2010; 39(7):476–479.
9. Loewen P, Dahri K. Risk of bleeding with oral anticoagulants: an updated systematic review and performance analysis of clinical prediction rules. Ann Hematol. 2011; 90(10):1191–1200.
10. Flaherty ML, Kissela B, Woo D, Kleindorfer D, Alwell K, Sekar P, Moomaw CJ. Et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. Neurology. 2007; 68(2):116–121.
11. Flaherty ML. Anticoagulant-associated intracerebral hemorrhage. Semin Neurol. 2010; 30(5):565–572.
12. Eroglu M, Cinar O, Cevik E, Yamanel L, Durusu M, Inal V, Comert B. The analysis of cases admitted to intensive care units from emergency department due to complications related to Warfarin treatment. Turk J Emerg Med. 2011; 11(1):9–12.
13. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US emergency department visits for outpatient adverse drug events, 2013-2014. JAMA. 2016; 316(20):2115–2125.
14. Eroglu SE, Altinok Denizbasi A, Ozpolat C, Akoglu H, Ecmel Onur O, Akoglu Unal E. The investigation of the relation between INR levels and risk of complication in patients with a history of Warfarin use. Marmara Medical Journal. 2012; 25(3):138–142.
15. Sayhan MB, Oguz S, Yuksel V, Huseyin S, Sayhan ES, Yagci G. The analysis of patients admitted to the emergency department due to complications related to Warfarin treatment. JAEM. 2014; 13(4):194–198.
16. Anthony CJ, Karim S, Ackroyd-Stolarz S, Fry A, Murphy NG, Christie R, Zed PJ. Intensity of anticoagulation with warfarin and risk of adverse events in patients presenting to the emergency department. Ann Pharmacother. 2011; 45(7-8):881–887.
17. McMahan DA, Smith DM, Carey MA, Zhou XH. Risk of major hemorrhage for outpatients treated with warfarin. J Gen Intern Med. 1998; 13(5):311–316.
18. Palareti G, Leali N, Coccheri S, Poggi M, Manotti C, D'Angelo A, Pengo V. et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. Lancet. 1996; 348(9025):423–428.
19. Lindh JD, Holm L, Dahl ML, Alfredsson L, Rane A. Incidence and predictors of severe bleeding during warfarin treatment. J Thromb Thrombolysis. 2008; 25(2):151–159.
20. Ebell MH. Predicting the risk of bleeding in patients taking warfarin. Am Fam Physician. 2010; 81(6):780.
21. Shireman TI, Mahnken JD, Howard PA, Kresowik TF, Hou Q, Ellerbeck EF. Development of a contemporary bleeding risk model for elderly warfarin recipients. Chest. 2006; 130(5):1390–1396. doi: 10.1378/chest.130.5.1390.
22. Shepherd AM, Hewick DS, Moreland TA, Stevenson IH. Age as a determinant of sensitivity to warfarin. Br J Clin Pharmacol. 1977; 4(3):315–320.
23. Hilde A. M. Kooistra, PhD; Agneta H. Calf, MD; Margriet Piersma-Wicher. Risk of Bleeding and Thrombosis in Patients 70 Years or Older Using Vitamin K Antagonists. AMA Int Med. 2016; 176(8):1176-1183.
24. Bina Ahmed, MD and Harold L. Dauerman, MD. Women, Bleeding, and Coronary Intervention Circulation. 2013; 127(5): 641-649.
25. Colleen S, Joseph MM, Ralph BD, Daniel L, Jarvis WL, Philip AW, Emelia JB. Warfarin and aspirin use and the predictors of major bleeding complications in atrial fibrillation (the Framingham Heart Study). Am J Cardiol. 2004; 94(7): 947-951.
26. Pengo V, Legnani C, Noventa F, Palareti G. Oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and risk of bleeding. A Multicenter Inception Cohort Study. Thromb Haemost. 2001; 85(3): 418-22.
27. Itthidet K and Rungroj K. Optimal INR level for warfarin therapy after mechanical mitral valve replacement. BMC Cardiovascular Disorders. 2019; 19(97): 1-8.
28. Lu Y, Won KA, Nelson BJ, Qi D, Rausch DJ, Asinger RW. Characteristics of the amiodarone warfarin interaction during long-term follow-up. Am J Health Syst Pharm. 2008; 65(10): 947-952.
29. Michael FH. The Misunderstood Coagulopathy of Liver Disease: A Review for the Acute Setting. West J Emerg Med. 2018; 19(5): 863–871.