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Absolute Need to Monitor Prothrombin Time while Administering Heparin: A Prospective Observational Study

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Abstract:-

- ***Purpose:***

Anticoagulants are administered for various vascular conditions; there is always a risk of bleeding with this class of drug. It is essential to monitor the prothrombin time and International Normalisation Ratio (INR) values to prevent side effects.

- ***Objective:***

Drug utilization evaluation of anticoagulants and to monitor outcomes of drug therapy.

- ***Methodology:***

A prospective cohort study carried out on 140 patients with cardiac complications who were on anticoagulant therapy. We collected all necessary data from the patient's case sheets, lab reports, and treatment charts. Patients were continuously monitored for the effectiveness of treatment, and any adverse effects on anticoagulant usage were monitored.

- ***Results:***

68% of the study population were males with cardiac problems who were treated with anticoagulants. As the age increases, the occurrence of cardiovascular events also increases. Enoxaparin (Clexane) (72%), at doses of 4000 IU or 6000 IU, was the majorly prescribed drug. The majority of the patients were in the safe zone with no risk of clotting or bleeding. A significant number had a risk of developing clots, and very few had the risk of bleeding. Minor ADRs like bruising and swelling were identified.

- ***Conclusion:***

Harmful drug-related reactions such as bruising, abdominal pain, swelling, and haematuria were observed after the anticoagulant therapy was initiated. Continuous monitoring has definitely reduced the incidence of adverse effects in connection with the administration of anticoagulant therapy.

Keywords:- *Heparin, Anticoagulants, Blood Clots, Cardiovascular Disease, Drug Utilization Pattern, Adverse Drug Reaction (ADR), Pharmacovigilance.*

I. INTRODUCTION

Pharmacovigilance of anticoagulants is an essential aspect of modern health systems, focused on identification, assessing the severity and preventing the adverse effects of drugs or issues associated with pharmaceutical products. Anticoagulants, a class of medications designed to prevent or reduce blood clotting, are among the most widely used drugs in clinical practice [1]. They play a crucial role in preventing thromboembolic events, such as strokes and deep vein thrombosis, thereby improving patient outcomes. The sole purpose of this research was to improve patient safety by monitoring the use of anticoagulant medication. Recent years have seen an upsurge in anticoagulant use; however, a patient pattern of drug use was not being followed. When the file fails to be updated, the therapy could go wrong and have adverse effects.

This experimental design seeks to completely examine the effectiveness of anticoagulants at an optimum level. Patients receive anticoagulants in accordance with their treatment priority for medicine use [2,3]. All patients treated with anticoagulants should have the coagulation parameters tested before starting the therapy. Variations from the normal level indicate a risk of development of a clot if the values are low and a risk of bleeding if the values are high. If a clot was identified or there is evidence that the development of a clot was established, anticoagulant therapy is initiated Intra Venous (IV), Sub cutaneous (SC), or orally according to the patient's condition [4]. Monitoring the INR value is essential when the patient is on oral anticoagulant, especially on warfarin therapy. The target range of INR values varies according to the medical condition of the patient [5].

Coagulation parameters must be monitored during and after the completion of the prescribed dose to assess the safe use of the anticoagulant and if required, a dose adjustment can be made [6]. If a side effect occurs, it must be treated with the

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appropriate dosage reduction or withdrawal of the drug if necessary. Ultimately, this pharmacovigilance report aims to contribute to the ongoing efforts to enhance the benefit-risk balance of anticoagulant medications, ensuring that patients receive the most effective and safe treatment for their medical conditions.

II. METHODOLOGY

A prospective observational cohort experimental design was developed and executed at a private multispecialty hospital located in Chennai, Tamil Nadu. The study was approved by the healthcare administrators and the duration of data collection was between January to June 2023. The sample size for the study was calculated using RAOSOFT online software. 140 was the targeted patient population, and we were able to achieve a sample size of 141 patients. Adults of both genders with cardiac complaints admitted to the wards and Intensive care unit (ICU) who were receiving anticoagulant therapy IV were only considered for the study. Patients who had severe active bleeding and patients who had undergone recent surgery were excluded from the study. Criteria were fixed according to the appropriate information needed for our study and incorporated into a patient data collection form [7]. Relevant data was collected from the case sheets, lab reports, and drug charts. Demographic information like age, gender, family history, social history, and previous medical and medication history were obtained from the patient's case sheet. Underlying disease condition, indications for anticoagulant therapy, coagulation profile, and kidney function were monitored. Medication charts were thoroughly reviewed for completeness of information before filling out the data collection form.

The patient's anticoagulant therapy type, dosage, frequency, route of administration, and duration of therapy were obtained from the treatment chart and followed throughout the course of treatment till discharged from the hospital. We checked and verified if the patients' received anticoagulants in accordance with their coagulation lab parameters and verified if it was within the acceptable range. A dose correction was made if necessary, according to the lab parameters reported. All relevant lab reports, such as serum creatinine, prothrombin time test, aPTT test, INR ratio, and hematological test results, were interpreted clinically and monitored for the treatment outcome. The patients were monitored to see if they developed any drug-related adverse effects that might likely develop during the course of treatment [8]. Every patient receiving anticoagulant therapy was monitored on a regular basis to observe any signs of incidents of adverse effects resulting from anticoagulant drug therapy given, which could be anything from slight bleeding to easy bleeding to severe bleeding disorders like hematuria, abdominal pain, swelling, and itchy skin.

On the first day of admission, a blood sample was taken from the patient. Before giving the patient their next dose of anticoagulant, the coagulation profile was checked. The parameters like Activated Partial Thromboplastin Clotting Time (APTT), Partial Thromboplastin time (PTT), INR and serum creatinine were noted. Any increase in these parameters may cause bleeding, and a reduction in these parameters causes blood clots. The parameters were maintained within the typical range not above or below. Finding the adverse effects that occurred in a patient after receiving an anticoagulant was made easier with the medication chart review and clinical reviews on the lab reports. The cases were followed up on a daily basis until discharge.

- *Statistical Analysis:*

All data were presented as numbers and percentages. Microsoft Excel was used to analyse the data.

III. RESULTS AND DISCUSSION

Prevention of the adverse effects with the usage of anticoagulants was done by monitoring the patients continuously after the administration of the drug based on their coagulation profile. The anticoagulants were used based on their clinical findings. The drug utilization pattern of anticoagulants in the ICU and in wards was analysed. All patients with cardiovascular complications—those who were admitted to the wards and ICU—were selected for the study. The interventions were done according to the outcome and the clinical status of the patients, focusing on the early identification of ADR. Data was collected over six months (from February 2023 to August 2023), and the patients were followed up daily on their clinical reports.

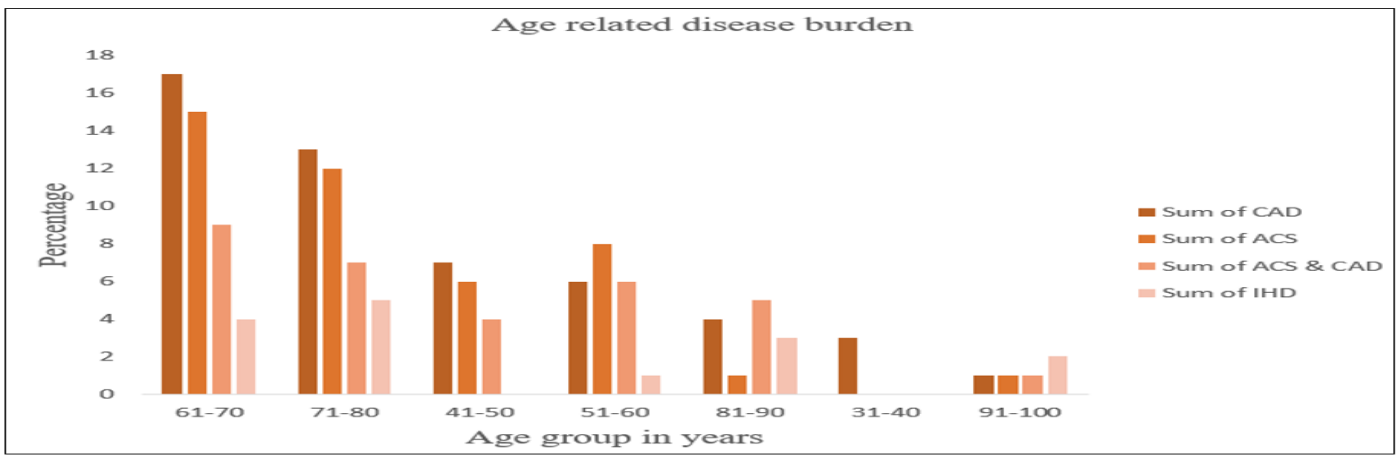

Fig 1 Age Related Disease Burden

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Prevalence of cardiovascular risk was found to be higher among male patients (68%) than female patients (32%). The results were similar to the study conducted by Khan MA et al., [9] which showed men were more commonly affected than women, and incidence typically increased with age. The majority of the population was found between the age groups of 60 and 80 years as indicated in the figure 1. Cardiovascular disease, like coronary artery disease (CAD), Acute coronary syndrome (ACS), Ischaemic heart disease (IHD), CAD along with ACS, were collectively higher between 61 and 80 years. This clearly indicated ageing can cause cellular degeneration and organ dysfunction. With the progression of age, the altered pharmacokinetics can cause a decline in renal and hepatic function. This can be the cause of the higher prevalence among this study population. A similar report was seen in the study conducted by Alzubaidi N et al [10]. These patients had coronary artery angiography **(**CAG), and percutaneous transluminal coronary angioplasty (PTCA). Janardan J et al. had a similar conclusion on the surgical procedure and antiplatelet usage [13].

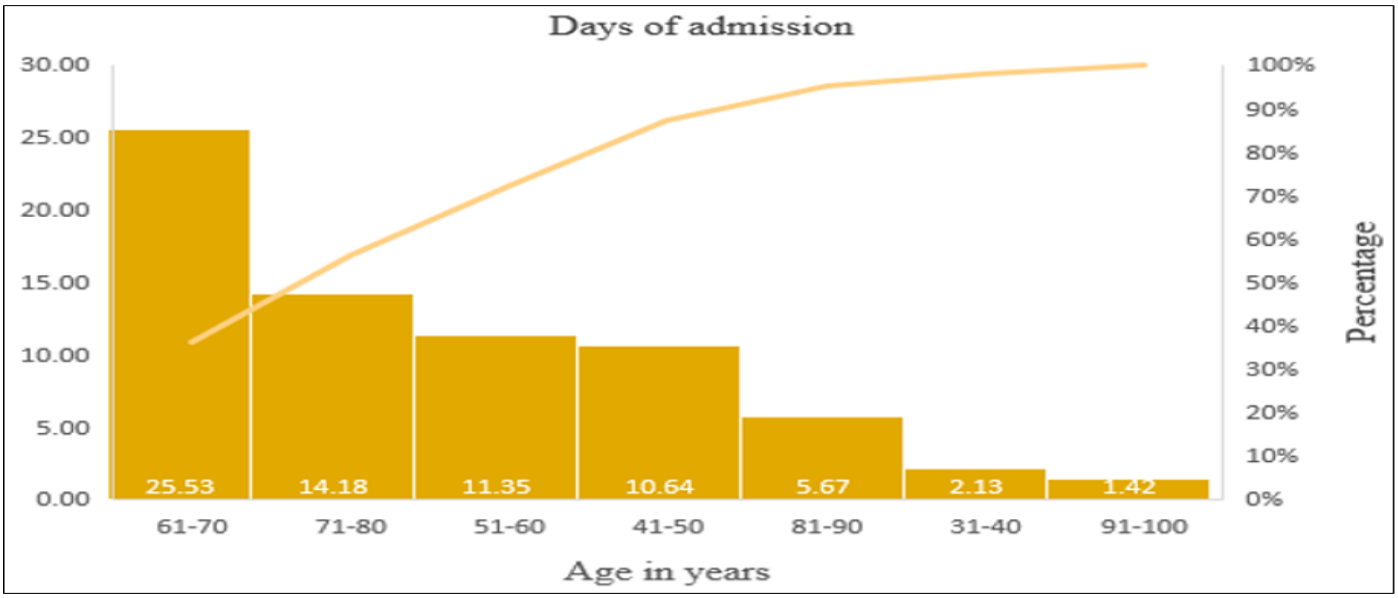

Fig 2 Number of Days of Hospital Stay

The number of patients admitted to the ICU were slightly higher than the number admitted to the wards for any cardiac complaints which was similar to the study reports of Alzubaidi N et al [10]. 90% of the population between the age oups of 61 and 70 was admitted for an average of 25 days as indicated in the figure 2. 71 - 80 years of age had an average length of hospital stay as 14 days. The least number of days of admission was found amongst 91 to 100 years; this could be due to the possibility of a very small population size in this age group.

Table 1 Coagulation Profile and Serum Creatinine Values

Coagulation profile	Reference values	Percentage (%)
APTT	< 27 seconds	41
	27 – 35 seconds	53
	> 35 seconds	6
PTT	< 12.05 seconds	53
	12.05–15.3 seconds	41
	>15.3 seconds	6
INR	< 0.8	6
	0.8 – 1.5	91
	>1.5	3
Serum creatinine	<0.7 mg/dl	18
	0.7- 1.5 mg/dl	63
	>1.5 mg/dl	19

The APTT (Activated Partial Thromboplastin Clotting Time) is more commonly used to monitor therapy when blood thinners like heparin or low molecular weight heparin (LMWH) are administered. 53% of the study population had APTT values within the normal range. 41% had it below the guidelines' recommended value; these patients are at high risk of developing blood clots. 6% had a very high level of APTT value, indicating a risk for bleeding after the therapy was initiated which is evident in the table 1.

PTT is a blood test that measures the time taken for blood to clot. Maintaining the right levels of PTT is crucial for the effective treatment outcomes; if the levels are too high, it increases the risk of bleeding, and too low values equally

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has a potential risk for clotting. While analysing the data, 41% of the study population had the PTT levels within the recommended range of 12.05 to 15.3. The majority of the population (53%) had very low PTT levels of <12.05 and still had a high risk of blood clot formation. These patients were monitored and recommended for dose adjustment. A small percentage (6%) had a high PTT value > 15.3, who were at risk of bleeding. Close monitoring of these cases was essential as indicated in the table 1.

91% of the study population had a safer INR limit between 0.8 and 1.5; this indicated that the treatment is tailored to the needs of the patients. Only a very small percentage had a deviation from the normal INR range.

Serum creatinine levels revealed that 63% of the patient population had normal serum creatinine levels. 18% had less than 0.7 mg/dl, and 19% had high creatinine levels above 1.5 mg/dl, which indicates that 19% of the population needs a closer watch for dose adjustment.

Table 2 Drug Utilization Pattern of Heparin Injection

Enoxaparin %	**Enoxaparin 1250 IU**	**0.71**
	Enoxaparin 4000 IU	35.46
	Enoxaparin 6000 IU	36.88
Dalteparin %	Dalteparin 10000 IU	7.09
	Dalteparin 15000 IU	5.67
	Dalteparin 18000 IU	0.71
Heparin %	Heparin 1250 IU	2.13
	Heparin 2500 IU	5.67
	Heparin 4000 IU	0.71
	Heparin 5000 IU	4.96

The drug utilization pattern of heparin injection indicates enoxaparin remains the major injectable anticoagulant prescribed in this group with an average of 73% as seen in the table 2. Heparin and Dalteparin were prescribed more or less in equal proportion. A similar study conducted by Shivashankar V et al. showed a controversial report of using 55% of heparin and 34% of enoxaparin, which indicated that our study showed better patent care because of more careful selection of the type of heparin to be utilized to minimise the risk of side effects [11].

Enoxaparin being the most commonly used LMWH dose of 6000 IU and 4000 IU was contributing equally to an average of 35% each. This is followed by an equal percentage of use of injections: Dalteparin 10000 IU, Heparin 2500 IU, Dalteparin 15000 IU, and Heparin 5000 IU. A very small percentage of Heparin 1250 IU, Heparin 4000 IU, Dalteparin 18000 IU, and Enoxaparin 1250 IU were used for the clot prevention. Tang N et al., in his study concluded that LMWH was desirable and not necessary monitoring was essential and was used conventionally after percutaneous coronary intervention, which helped in reducing the incidence of ischemic events [12].

Subcutaneous route of administration of LMWH was quite common, and an average of 45% had once daily (OD) dose; this was subsequently followed by twice daily administration of LMWH subcutaneously. A small proportion had an IV Twice a day (BID) and Four times a day (QID).

Table 3 Antiplatelet Therapy

Monotherapy	**Percentage**
T.Clopidogrel 75 mg	28.37
T.Ecosprin 75 mg	24.82
T. Ecosprin 150 mg	3.55
T. Ticagrelor 90 mg	2.84
Dual therapy	
T.Ecosprin 75 mg + T. Ticagrelor 90 mg	22.70
T.Ecosprin 75 mg + T.Clopidogrel 75 mg	7.80
T. Ecosprin 150 mg + T.Clopidogrel 75 mg	7.80
T. Ecosprin 150 mg + T. Ticagrelor 90 mg	0.71

Antiplatelet therapy was prescribed to all the patients at the time of discharge as prophylaxis. 28% were prescribed with tablet clopidogrel 75 mg, and 25% were prescribed with tablet ecosprin 75 mg. A smaller percentage were receiving tablet ecosprin 150 mg and tablet ticagrelor 90 mg, respectively as seen in the table 3. The results were similar to the study conducted by Barnes GD et al., which showed clopidogrel may be used for a longer period of time in case of ACS [14]. Depending on the risk for coagulation, few patients needed a combination of antiplatelet therapy. The most widely used combination was tablet ecosprin 75 mg with tablet ticagrelor 90 mg; this combination contributed to 23%, which was followed by the combination of tablet ecosprin 75 mg with tablet clopidogrel 75 mg and tablet ecosprin 150 mg with tablet clopidogrel 75 mg, more or less equally. Barnes GD et al. also concluded that aspirin is often combined with clopidogrel/ prasugrel/ ticagrelor for dual antiplatelet therapy [14].

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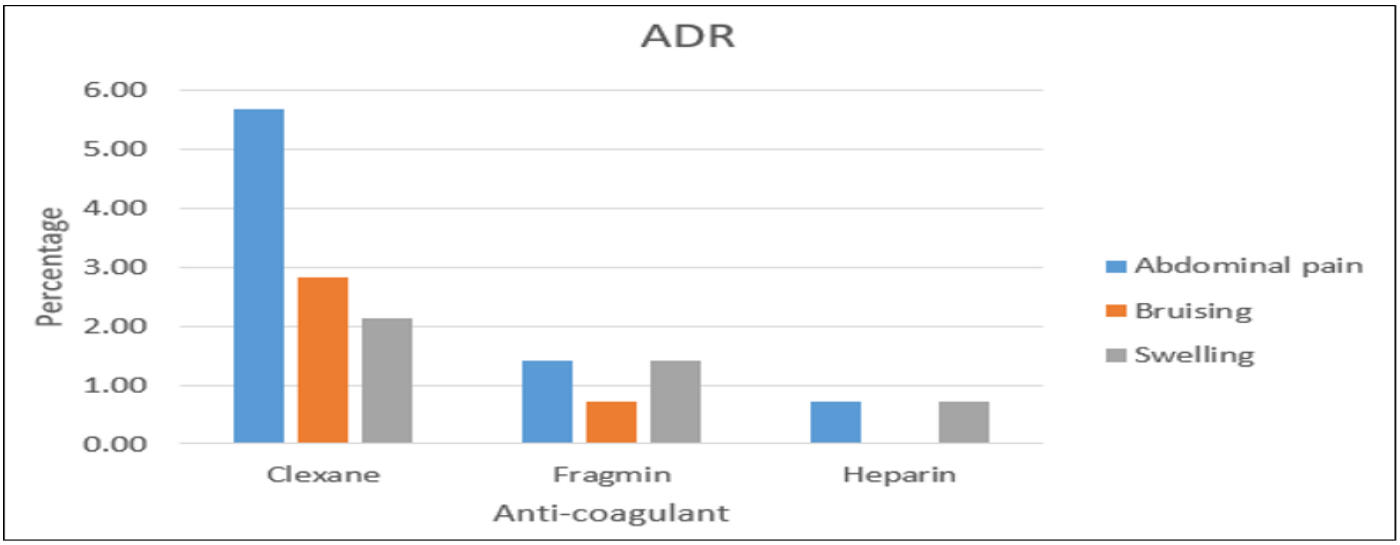

Fig 3 Adverse Effect

Only a small population developed any ADR as seen in the figure 3, which indicated that the drug therapy employed was appropriate and the right dose of anticoagulant was administered. Close monitoring and careful dose calculation were the reasons behind this safety profile. Despite being able to identify mild abdominal discomfort and a few bruising and swelling. The study conducted by Kassere S et al. on adverse drug reactions monitoring of anticoagulants showed that the hematuria (68.29%) was most frequently reported due to low molecular weight heparin (85.37%) [15]. Our study also had a similar outcome, as enoxaparin (clexane) did cause the majority of ADR in our study as compared to heparin. Also, the drug utilization of enoxaparin (73%) is significantly and should be taken into consideration.

IV. CONCLUSION

Adult males between the ages of 60 and 80 had a higher prevalence of cardiovascular risk. Acute coronary syndrome and coronary artery disease were commonly identified cardiac conditions in our study. Coronary artery angiography (CAG) and percutaneous transluminal coronary angioplasty (PTCA) were the surgical procedures frequently performed. These conditions were medically managed by administering enoxaparin, dalteparin, and heparin while admitted to the hospital. At the time of discharge, oral antiplatelet therapy, either as a single antiplatelet therapy or as a dual therapy, was recommended according to the severity and risk of clot formation as a prophylaxis for cardiovascular conditions. Enoxaparin was used predominantly during admission and ecosprin at the time of discharge.

Clinical reports on the coagulation profile indicated the majority of the clotting factors, like APTT, PTT, and INR, were found to be within the recommended range, and the therapy was safe in this population.

Very few incidences of ADR were observed during the hospital stay, which included mild abdominal pain, bruising, and swelling. When an adverse effect appeared, the dose reduction was made according to the presenting clinical condition.

Anticoagulants were administered as part of their treatment regimen; the majority of the adverse effects were preventable but could not be avoided. Profound monitoring, administering the right dose at the right time, and routinely evaluating coagulation markers before delivering the next dose helped in minimizing the side effects.

➢ *Abbreviations*:

- INR: International Normalisation Ratio
- IU: International Unit
- IV: Intra Venous
- SC: Sub Cutaneous
- ICU: Intensive care unit
- ADR: Adverse Drug Reaction
- APTT: Activated Partial Thromboplastin Clotting Time
- PTT: Partial Thromboplastin time
- CAD: Coronary artery disease
- ACS: Acute coronary syndrome
- IHD: Ischaemic heart disease
- LMWH: Low molecular weight heparin
- OD: once daily
- BID: Twice a day
- QID: Four times a day
- CAG: Coronary artery angiography
- PTCA: Percutaneous transluminal coronary angioplasty

➢ *Funding:*

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