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A PROSPECTIVE STUDY ON MONITORING AND EVALUATION OF WARFARIN/ACENOCOUMAROL IN A TERITIARY CARE HOSPITAL

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ABSTRACT

The study aimed is to monitor and evaluate warfarin/Acenocoumarol and determinants of increase in INR among inpatients associated with the therapy. A prospective study carried out on 143 patients at Care hospitals Nampally from October 2016-May 2017, patients were followed from date of admission until discharge. Each medication was checked for DDI's with comparison of Increase/Decrease INR by using Micromedex® online drug reference. Data were analyzed using statistical software, SPSS for windows version 10. The bleeding complications and independent variables was assessed using binary logistic regression analysis. Of the total 143 patients enrolled in the study, Male: females were 75(54.7%): 68 (47.5%). The mean age was 54.08 ± 14.4. According to the Micromedex® online drug reference, a total of 448 DDIs were identified. There were 3.2 ± 2.0 mean number of significant DDIs per patient. The most common type of interaction was Major type 230 (51.3%) while Moderate were 218 (48.6%). Each patient has three major DDI interactions. The frequent interacting drugs were Antibiotics 172 (38.3%). Of all 131(91.6%) of patients treated with Acenocoumarol shown 11(8.3%) of ADR's and 12 (8.3%) patients treated with warfarin shown 2(16.6%) of ADR's. Acenocoumarol is safe in all age groups. A total 13 ADRs were identified associated with antibiotics. Increase in INR value was found to be strongly associated with risk of bleeding (p=0.0341). Acenocoumarol is effective and safe in broad number of patient's which has shown lesser incidence of ADR's

when compared to warfarin. Bleeding complications occur due to improper management of warfarin/Acenocoumarol.

KEYWORDS: DDI's-drug-drug interactions, ADR-adverse drug interaction, INR-international normalized ratio, SPSS-statistical package for social sciences.

INTRODUCTION

The process by which the blood clots to form solid masses in the blood vessels are referred as "*Coagulation*" and the drugs used for the treatment of such clots are referred as "*Anticoagulants"*. Anticoagulants are also called as '*Blood thinners*' and they help in preventing heart attack or stroke occurring due to formation of clots. Warfarin/Acenocoumarol is known for its variable dose–response relationship, narrow therapeutic index, potential bleeding risk and the potential for numerous drug and dietary interactions. Monitoring the international normalized ratio (INR), a measure of warfarin's effect on clotting factors and the blood's propensity to clot, is therefore essential for maintaining the drug within its narrow therapeutic window of 2.0–3.0.[18] Maintaining the target INR is essential for patient safety. Below-target INR is associated with under anticoagulation, whereas above-target INR leads to hemorrhagic complications. Warfarin is a vitamin-k antagonist, as it interrupts the activation of vitamin-k in the body (which contributes for the formation of clots) and limiting the activation of vitamin K dependent clotting factors: II, VII, IX and X. It also inhibits the synthesis of anticoagulant proteins C, S and Z. Acenocoumarol is an anticoagulant that functions as a vitamin K antagonist (like warfarin). It is a derivative of coumarin. Adverse effects like Persistent nausea, stomach upset, Head ache, dizziness or weakness, Nose bleeds, Dark red or brown urine, Blood in the bowel movement or dale-colored stool, abdominal Pain, swelling or black purple skin (bruising), a serious fall or head injury. The treatment for warfarin reversal should be based on the indication for use, location of bleed, severity of bleed and the extent of INR elevation. Vitamin K Vitamin K is a specific antidote for warfarin. Fresh Frozen Plasma (FFP) The use of FFP for emergent reversal of elevated INRs in the presence of bleeding or high risk of bleeding. The combination of vitamin K and a prothrombin complex concentrate (e.g. Octaplex) is the treatment of choice for rapid reversal of warfarin.

AIMS AND OBJECTIVES

The main Aim of the study to determine the factors affecting the therapeutic efficacy of warfarin/Acenocoumarol, to control the INR within therapeutic range and assessment of

ADR's and DDI's and to improve the clinical outcome and quality life of patients on warfarin/Acenocoumarol.

- To determine the effect of INR with respect to warfarin/Acenocoumarol on age group and Gender.
- To determine the management of warfarin/Acenocoumarol dosing with respect to INR.
- To determine the risk of bleeding complication in association with INR within, below and above the specific range.
- To assess the Major and Moderate interactions.
- To determine the Adverse drug reactions related to warfarin/Acenocoumarol and their categorization based on Age, Gender, Class of drug, Severity of ADR's and Causality assessment ADR's.
- Comparison and % Age of Patients on warfarin and Acenocoumarol in terms of Efficacy safety and good clinical outcome.

MATERIAL AND METHODS

A prospective study was carried out on 143 patients at Care hospitals Nampally from October 2016 to May 2017 and patients were followed from date of admission until discharge. Each concurrent medication was collected and checked for DDI's with comparison of Increase/Decrease INR by using Micromedex® online drug reference. It also provides information about the mechanism and potential adverse outcomes of an interaction. Except some modifications (additions) by the authors, definitions below are adopted from Micromedex®. Drug-drug interaction is the alteration of a drug's pharmacologic or clinical response by co-administered drug. Drug interaction can be of minor, moderate and major type. Clinically significant DDI's. Drug-drug interactions resulted in clinically observable response (example: bleeding and/or change in INR for warfarin). Information about patient demographics (age, gender) warfarin indication, past medication history, medication regimen, co-morbidities, warfarin/Acenocoumarol dosing and duration of treatment, concomitant drugs, signs and symptoms of bleeding, and INR data along with other laboratory data on day to day basis. The determination of ADR's related to warfarin/Acenocoumarol were assessed based on Age, Gender, and Class of drug and the Severity of ADR's was measured by using Modified Hart wig, Siegel scale and Causality assessment by Naranjo's scale. The percentage of ADR's affected with warfarin/Acenocoumarol were also assessed. Data were analyzed using statistical software, SPSS for windows version 10. The relationship between bleeding

complications and independent variables (age, sex, type and number of co-medications, dose and duration of warfarin/Acenocoumarol treatment, INR value) was assessed using binary logistic regression analysis.

Moderate drug interaction: A type of drug interaction that may cause deterioration of a patient's clinical status, requiring additional treatment, hospitalization or extension of hospital stay. This needs close monitoring of the patient. It may necessitate discontinuation of treatment.[17]

Major drug interaction: A type of potentially life threatening interaction, capable of causing permanent damage, and necessitating additional treatment, hospitalization or extension of hospital stay. Such interaction necessitates discontinuation of the treatment.[17]

Clinically significant DDIs: Drug-drug interactions resulted in clinically observable response
(example: bleeding and/or change in INR for warfarin).[17]

1. **To determine the effect of INR with respect to warfarin/Acenocoumarol on age group and gender.[1]**

Table-1.

DEMOGRAPHIC CHARACTERISTICS		
GENDER		**NUMBER (%)**
	MALE	75 (52.4%)
	FEMALE	68 (47.5%)
	TOTAL (%)	143 (100%)
AGE GROUP	9-39 (YOUNG)	8 (5.5%)
	40-64 (MIDDLE AGE)	47(32.8%)
	>65 (GERIATRICS)	88 (61.5%)
	TOTAL	143 (100%)
	MEAN±SD	54.08±14.4

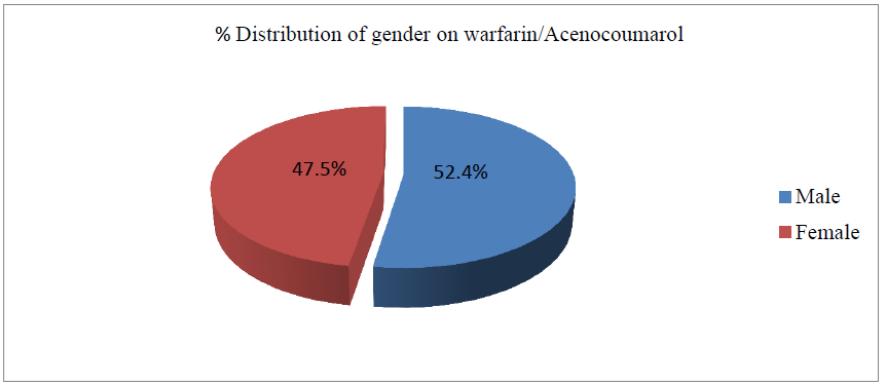

Figure-1.

Out of the total 143 patients enrolled in the study, 75 (52.4%) were males and 68 (47.5%) were females.

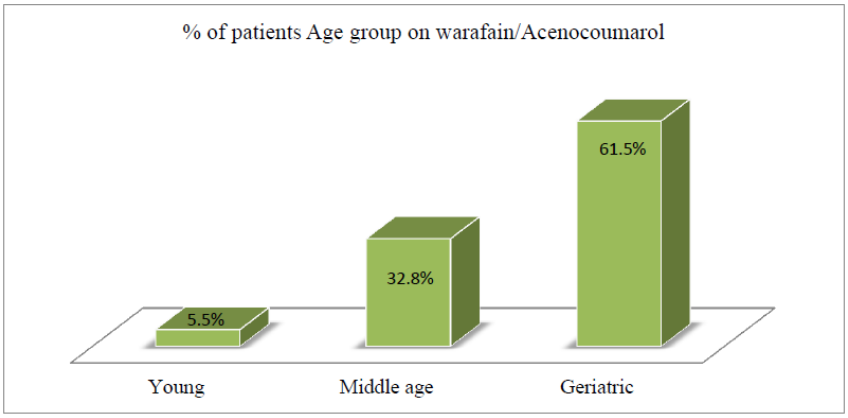

Figure-2.

Amongst different age group the mean age was 54.08±14.4 and majority of the participants 88(61.5%) were >65 age group.

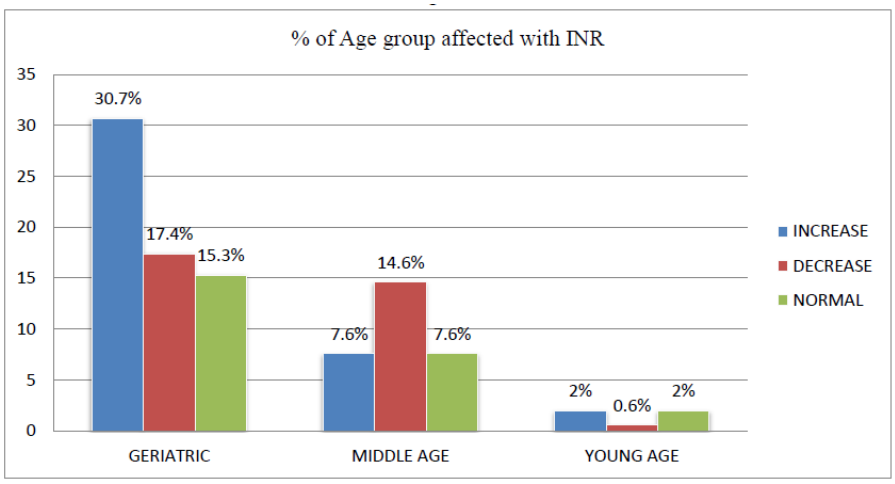

Figure-3.

Table-2.

Sr. No	AGE GROUP	INCREASE (%)	DECREASE (%)	NORMAL (%)
1	Geriatrics	44 (30.7%)	25(17.4%)	19(15.3%)
2	Middle age	11(7.6%)	21(14.6%)	17(7.6%)
3	Young	3(2.0%)	1(0.6%)	4(2.0%)
Total		143(100%)		

Above of all 143 patients INR was high in Geriatrics 44(30.7%) followed by middle age 11(7.6%) and lastly young age 3(2.0%). The major patients affected with INR in geriatrics is due to delay in drug metabolism, excretion rate, age related factors and co-morbid disease condition. Out of total sample studied 91.6% (131) received Acenocoumarol and only 8.3% (12) received warfarin.

2. To determine the management of warfarin/Acenocoumarol dosing with respect to INR[2]

Patients with increased or decreased INR were placed on anti-coagulation therapy as mentioned below in the table

Table-3.

Day Therapy	INR Value	Standard Dose Adjustment	Actual dose (given)
Day 1		5 mg daily (2.5 mg daily if high sensitivity to warfarin/Acenocoumarol identified)	2mg
In 2-3 days after initiation	< 1.5	3-4 mg daily	4mg
	1.5-1.9	2-3 mg daily	4mg
	2.0-2.5 > 2.5	2.5 mg daily 1mg and recheck INR next day	2mg
In additional 2-3 days After last INR check	< 1.5	4-5 mg daily	4mg
	1.5-1.9	3-4 mg daily	3mg
	2.0-3.0	2.5 – 4 mg daily	2mg
	> 3.0	Hold warfarin, recheck in 1-2 days	Hold

Warfarin/Acenocoumarol dosing should be adjusted based on current INR measurements no change in the dose is needed in patients with previously stable INR or with therapeutic range of < 0.5. According to UW health clinical Guidelines from the 9th edition ACCP, clinical practice guidelines. The day 1 therapy is 5mg daily and the actual observed dose is 2mg. In 2-3 days, the recommended dosing whose INR is <1.5 is 3-4mg and actual observed dose is

4mg, for INR 1.5-1.9 recommended dose (2-3mg) actual observed dose is 4mg. INR 2.0-2.5 and > 2.5 recommended dose (2.5mg daily) actual observed dose is 2mg, INR 2.0-3.0 recommended dose (2.5-4mg), actual observed dose 2mg and INR > 3.0 recommended dose (old), actual dose hold for 1 day and recheck.

3. To determine the risk of bleeding complication in association with INR within the specific range.[4]

Of all the samples, whose INR value <2.0 are 48(33.56%), 2.0-3.0 are 40(28%), 3.1- 4.9 are 38(26.57%), > 5.0 are (17 (12%))

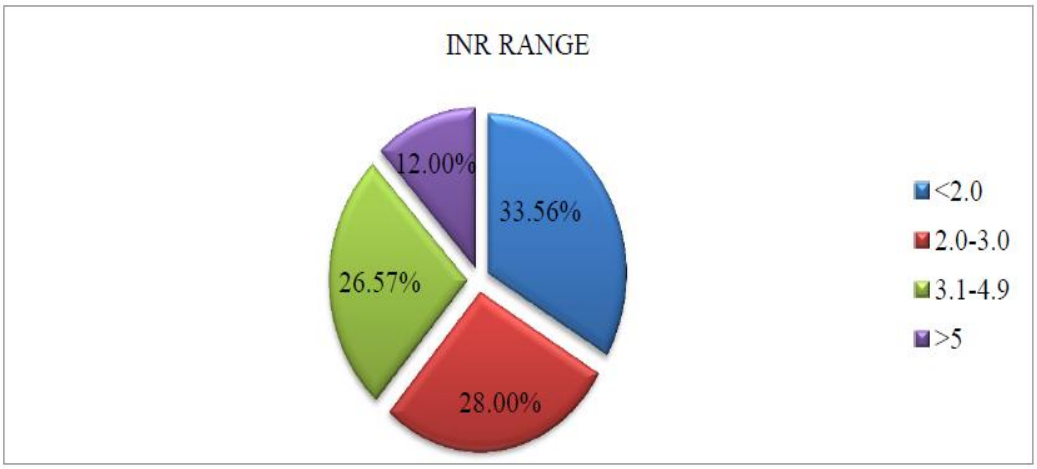

Figure-4.

Of all patients studied, 40(28%) were on the target INR (2.0-3.0) at the time of evaluation for drug interaction and bleeding; while 48(33.56%) had INR value below <2.0, while INR between 3.1- 4.9 were 38(26.57%). Followed with 17(12%) patients had INR >5.0.

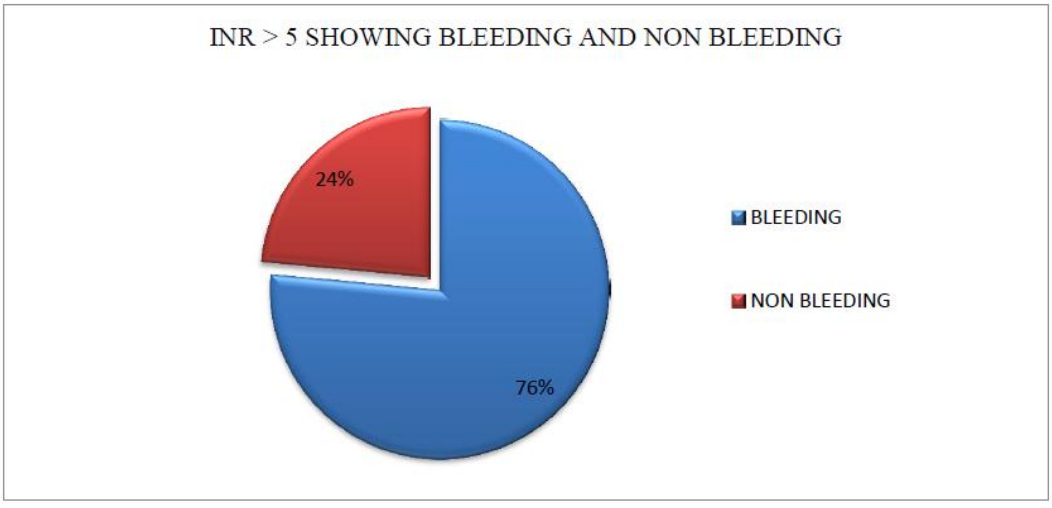

Figure-5.

Increase in INR value was found to be strongly associated with risk of bleeding (P value = 0.0341). Of all the patients, the INR >5 was seen in 17 patients; where 13(76%) have shown bleeding and the remaining 4(24%) patients have shown nonbleeding complications. Bleeding complications mostly occurred in the age group of 55 to 65. With this we conclude that the patients whose INR is >5 are at a higher risk of bleeding, and it is more probable to occur in geriatrics.

4. To determine the types of surgical procedures among patients on warfarin/Acenocoumarol therapy.[5]

There were 6.0 ± 3.3 mean number of medications prescribed per patient at the time of screening for drug interaction. The most common indication for warfarin/Acenocoumarol therapy in this population was for prevention and treatment of Cardiology 69.9%, neurology 5%, nephrology 4.1% and internal medicine 21%. Among cardiology, the types of surgical procedures underwent in 100 patients were {MVR (37) followed by RHD (35), CABG+MVR (21) and CABG+IABP (7)}.

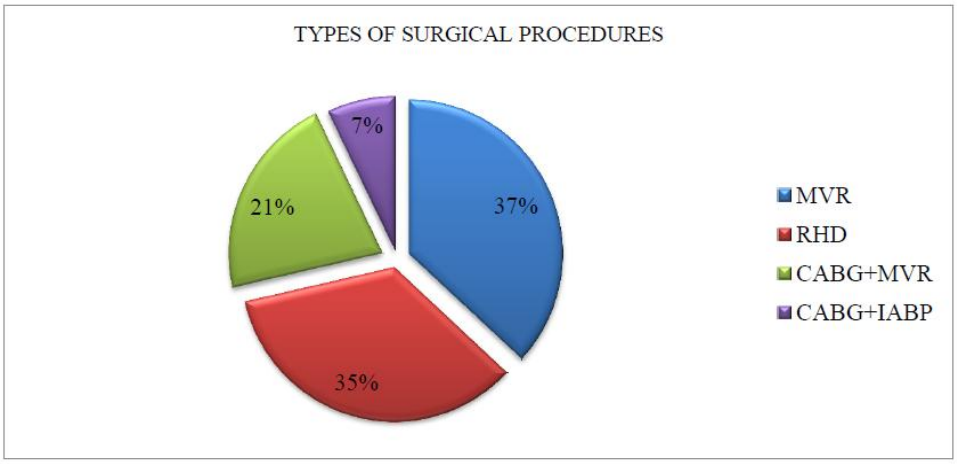

Figure-6.

5. To Assess the Major and Moderate interactions[6]

Table-4.

DRUG CLASS	DRUGS	NO.OF PATIENTS	LEVEL OF INTERACTION	
			MAJOR	MODERATE
ANTI-BIOTICS	PIPERACILLIN	7	6	-
	LEVOFLOXACIN	72	52	-
	AMOXICILLIN	48	48	-
	AZITHROMYCIN	9	4	-
	CIPROFLOXACIN	6	5	-
	OFLOXACIN	2	2	-
	CEFIXIME	1	1	-
	CEFTRIZINE	1	1	-
	CEPHAZOLIN	5	5	-
	CLARITHROMYCIN	2	2	-
	METRONIDAZOLE	2	2	-
	CEFEPERAZOLE	1	-	1
	CEFTRIAXONE	57	-	45
ANTI-DEPRESSANTS	ALPRAZOLAM	25	10	-
	AMITRIPTYLINE	5	1	-
	SERTRALINE	1	1	-
CARDIOVSCULAR	AMIODARONE	81	23	-
	CLOPIDOGREL	47	12	-
	SPIRONOLACTONE	83	-	46
	TELMISARTAN	1	1	-
NSAID'S	ACETAMINOPHEN	72	-	35
	ACECLOFENAC	16	1	-
	ASPIRIN	85	41	-
ACID SUPRESSING	PANTOPRAZOLE	88	-	70
	RABEPRAZOLE	3	-	2
ANTI-COAGULANTS	HEPARIN	64	-	19
	ENOXAPARIN	22	12	-
	TENECTEPLASE	1	1	-

According to the Micromedex® online drug reference, a total of 448 significant DDIs with warfarin/Acenocoumarol were identified. There were 3.2 ± 2.0 mean number of significant DDIs per patient. The most common type of interaction was Major type 230 (51.3%) while Moderate were 218 (48.6%). Each patient has at least three major DDI interactions. Total 448 significant drug interactions were noticed. The most frequent interacting drugs were Antibiotics 172 (38.3%), followed by cardiovascular 88(19.6%), NSAIDS 76 (16.9%), acid suppressing 72 (16.0%) and anti-depressant 12 (5.19%). 0f all patients studied, 40(28%) were on the target INR (2.0-3.0) 48 (33.56%) had INR value below <2.0 INR between. 3.1- 4.9

were 38(26.57%) Followed with 17(12%) patients had INR >5.0. 17 patients had INR value of >5. Bleeding complications occurred in 13 (76.4%) patients out of 17 patients.

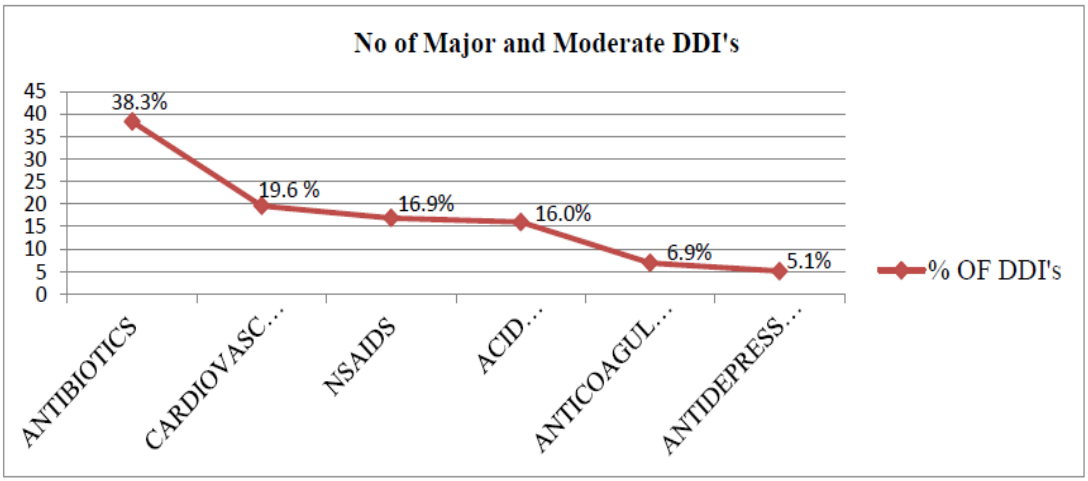

Figure-7.

6. To determine the effect of Adverse drug reactions related to warfarin/Acenocoumarol and their categorization based on Age, Gender, and Class of drug, Severity assessment of ADR's and Causality assessment of ADR's. [7]

A. ADRs categorized according to gender

Table-5.

Sr. no	Gender	No. of ADR's	Percentage (%)
1	MALE	6	46.1%
2	FEMALE	7	53.8%
TOTAL		13	100%

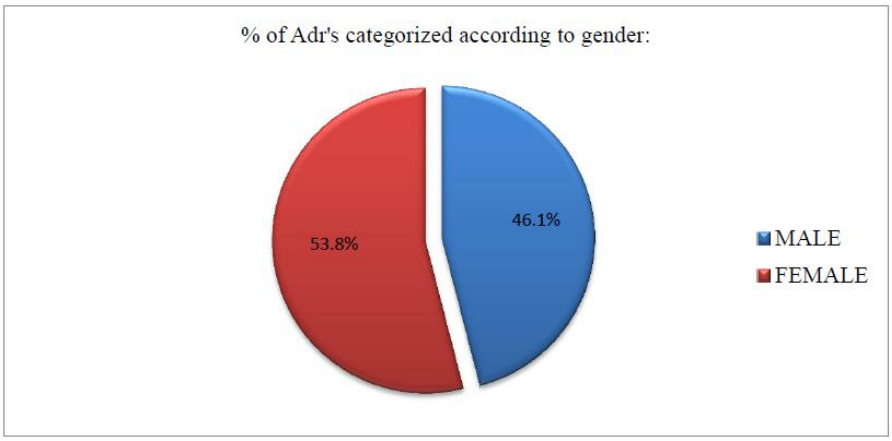

Figure-8.

A total of 13 ADRs were identified out of which 6(46.1%) were male patients and 7 (53.8%) were female patients. Female patients showed the higher affected gender with ADRs

B. ADRs categorized according to Age group[19]

Table-6.

Sr. no.	Age Distribution	No. of Patients	Percentage (%)
1	Adults (9-39)	1	7.6%
2	Middle age (40-64)	3	23.0%
3	Geriatric (> 65)	9	69.2%
TOTAL		13	100%

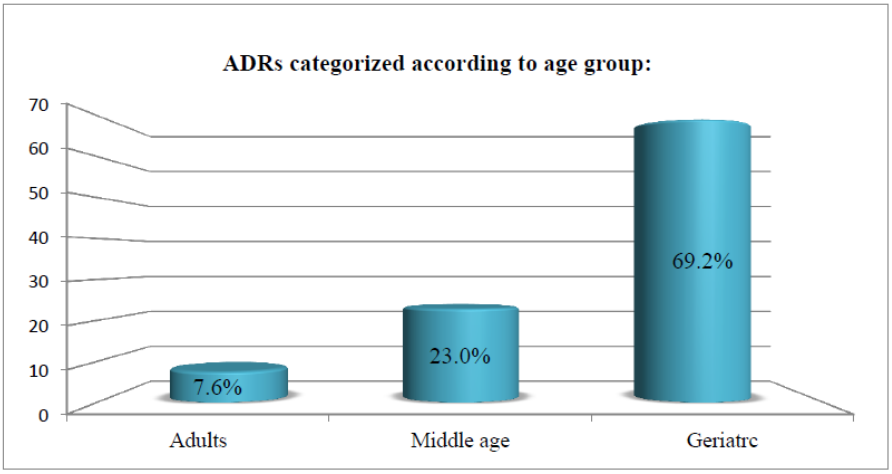

Figure-9.

Age was found to be an important criteria in the fact that the patients in the age group >65 geriatrics experienced maximum ADRs 9 (69.2%), followed by 3 (23.0%) in the middle age and in the adults 1(7.6%). Out of 13 ADRs Reported , Geriatrics patients reflecting the major age group were affected with ADRs because of age related retardation of drug metabolism.

C. ADRs categorized according to gender and age group of patients[19] Table-7

Sr. no	Age distribution	Male	% age	Female	%age
1	Adult	1	7.6%	0	0%
2	Middle age	2	15.3%	1	7.6%
3	Geriatrics	3	23.0%	6	46.1%
Total		6	45.9%	7	53.7%

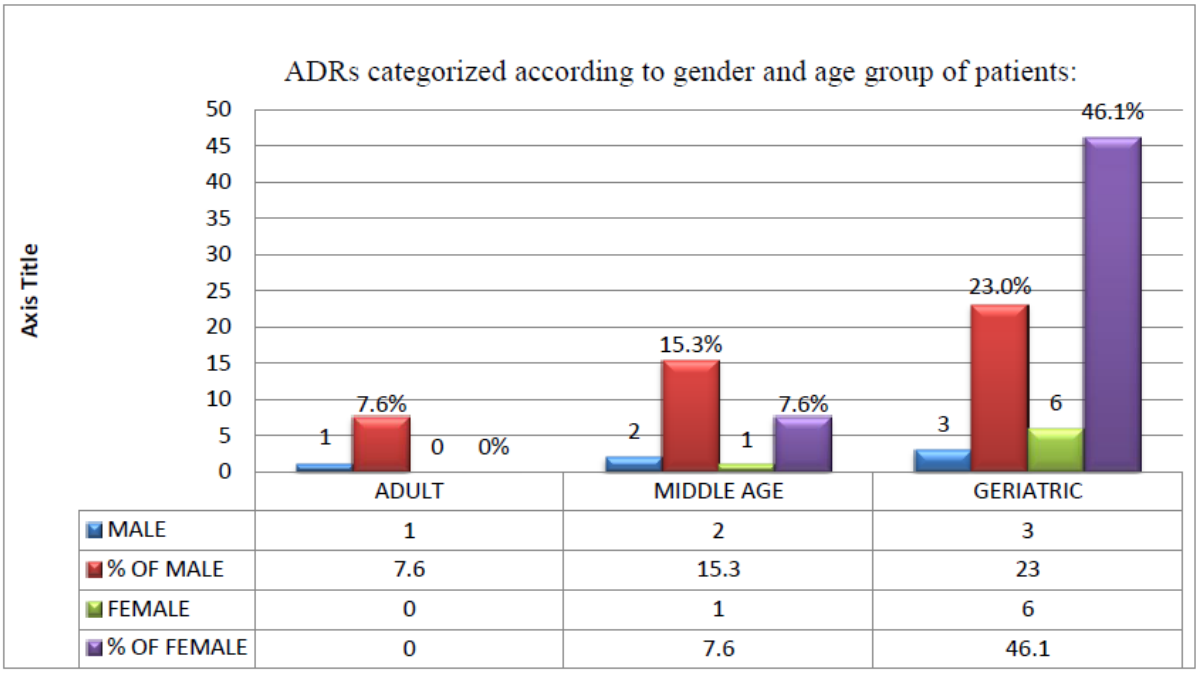

Figure-10.

Amongst the various age groups of Patients, Female geriatrics 6(46.1%) are more prone with ADR's followed by male geriatric 3(23.0%), middle age male 2(15.3%), female 1(7.6%), adult male 1(7.6%) and there were no ADR's were seen in female adults.

D. Severity of ADRs by Modified Hart wig and Siegel scale[19]

The severity assessment of ADRs with modified Hart wig and Siegel scale showed that 13 subjects had ADRS, of which 1(7.69%) ADRs were mild, 4 (30.7%) ADRs were moderate and 8 (61.5%) ADRs were severe. No lethal effects were observed or produced.

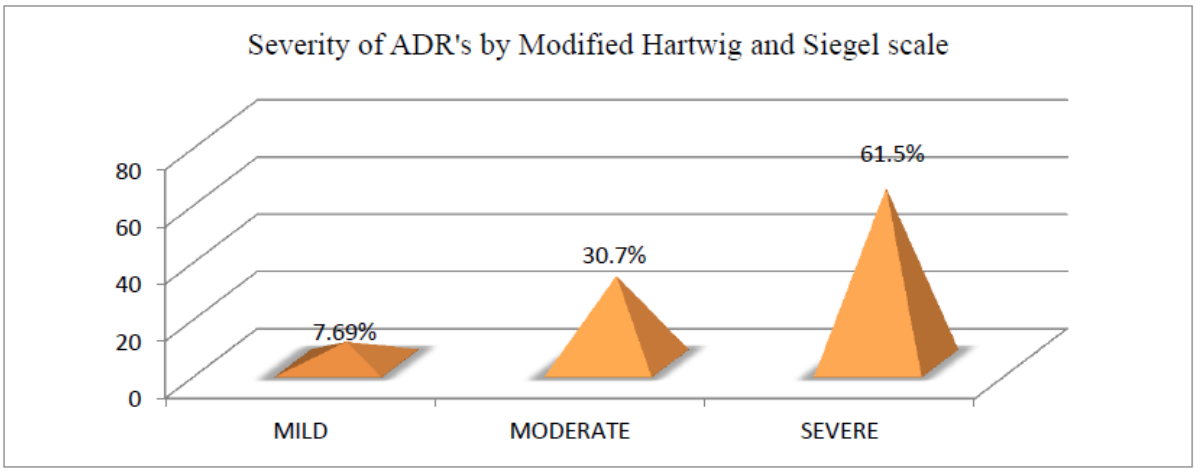

Figure-11

Percentage (%) of ADR's associated with warfarin and Acenocoumarol[19]

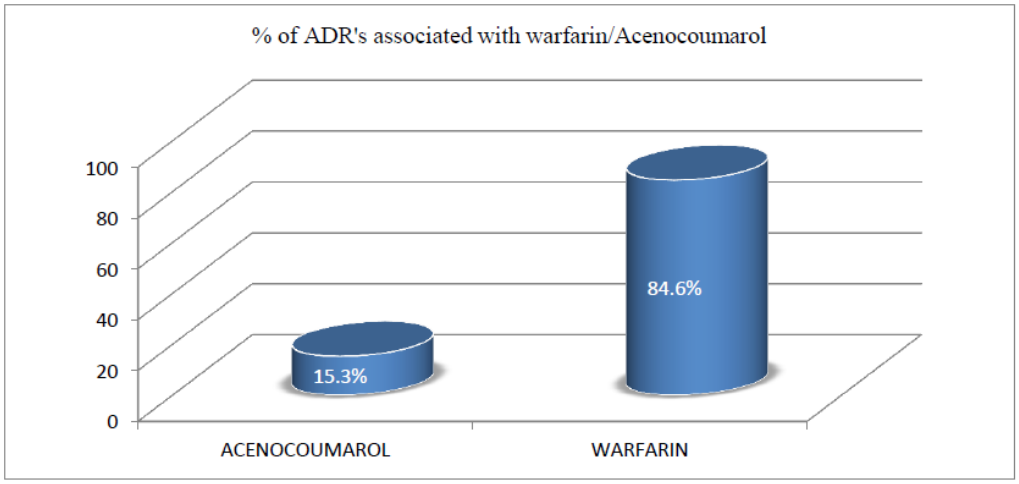

Figure-12.

Of all 13 the patients with ADR's 2(15.3%) were associated with warfarin and 11(84.6%) with Acenocoumarol. Warfarin is the major drug which is associated with ADR's

Naranjo's causality assessment of ADRs[19]

Table-8.

Sr. No	Type of reaction	Number of ADR'S (%)
1	Definite	1(7.7%)
2	Probable	12(92.3%)
3	Possible	0(0%)
4	Doubtful	0(0%)
Total		13(100%)

The suspected ADRs were calculated by using Naranjo's causality assessment scale. It was observed that out of 13 ADR's 12 (92.3%) were probable type of reaction, definite reaction were 1(7.7%), 0 (0%) were possible and 0 (0%) doubtful**.**

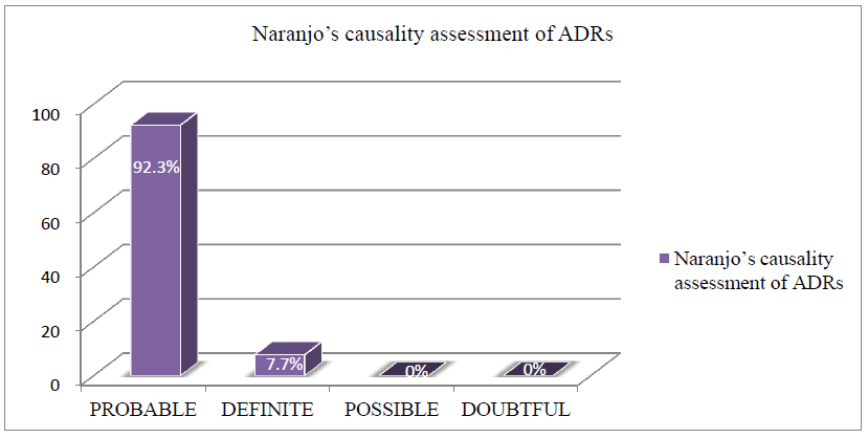

Figure-13.

The suspected ADRs were calculated by using Naranjo's causality assessment scale. It was observed that out of 13 ADR's 12 (92.3%) were probable type of reaction, definite reaction were 1(7.7%), 0 (0%) were possible and 0 (0%) doubtful**.**

G. ADR's categorized according to the Drug class[19]

Table-9.

Sr. No	Type of therapy	No of Patients affected with ADR's	Percentage (%)
1	Anti-Biotics	9	69.2%
2	Anti-Depressants	2	15.3%
3	Anti-coagulants	2	15.3%

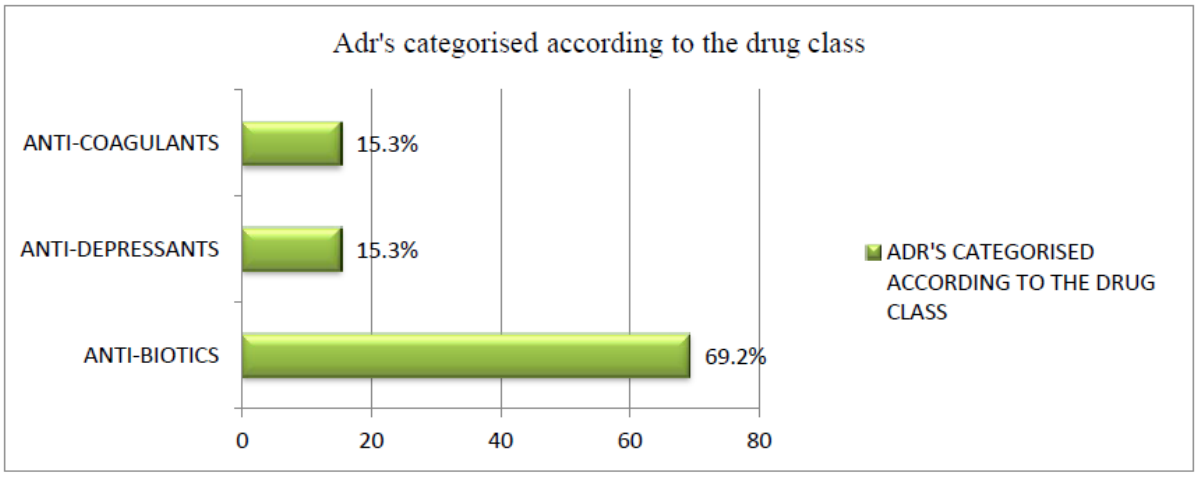

Figure-14.

In this study, ADR's are associated with certain drugs it was found that ADR's were most commonly associated with antibiotics (levofloxacin, ciprofloxacin, amoxicillin, clarithromycin, ceftriaxone, azithromycin) in 9 (69.2%) of patients, anti-depressants Drugs (alprazolam, zolpidem, sodium valproate) 2 (15.3%) of patients followed by anti-coagulants (warfarin, heparin, enoxaparin) in 2(15.3%) of patients. Antibiotics were the major drug class associated with ADRs followed anti-depressants and anti-coagulants.

7. Comparison and % Age of Patients on warfarin and Acenocoumarol in terms of Efficacy safety and good clinical outcome.

Table-10.

Sr. no.	Type of drug	Total no Of patients	Percentage (%)	No of Patients with ADR's
1	Acenocoumarol	131	91.6%	2
2	Warfarin	12	8.3%	11
MEAN±SD		-	7.20±3.08	13

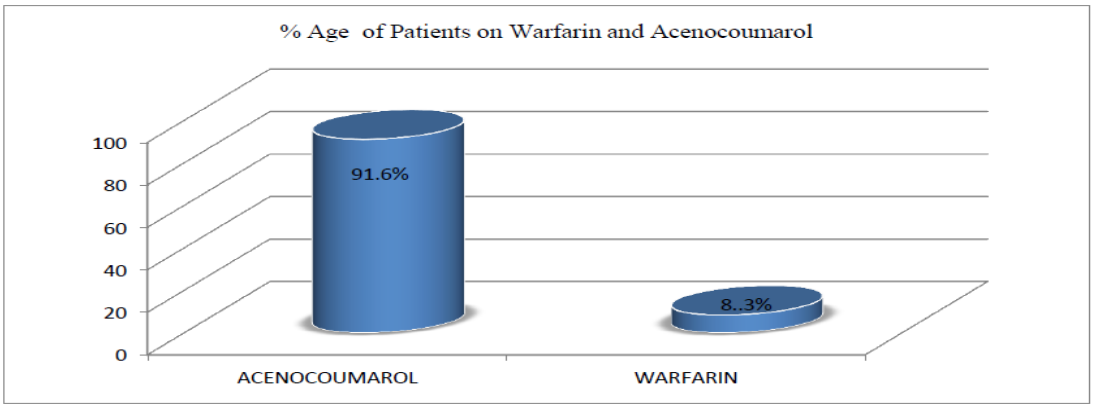

Figure-15.

Out of 131(91.1%) of patients treated with Acenocoumarol and 12(8.3%) with warfarin, from which 13 patients were associated with ADR's. 2(15.3%) were associated with Acenocoumarol and 12(84.6%) with warfarin. Warfarin is the major drug which is associated with ADR's Acenocoumarol is effective and safe in large number of patient's i.e., which has shown lesser incidence of ADR's when compared to warfarin. It offers an advantage over warfarin in terms of better stability of anti-coagulant effect in maintaining normal INR range.

And also due to its economic advantage Acenocoumarol may be suitable oral anticoagulant for long term use in countries like India.

To determine the observed INR in accordance to target INR of anti-coagulant treatment of warfarin/Acenocoumarol after surgical procedure[15]

The following targeted INR and duration of therapy were taken from the PATRICIA WIGLE at all, ACCP Updated Guidelines on Anticoagulation *April 15, 2013; Volume 87, Number 8.* **(**Warfarin/Acenocoumarol) the observed INR in rheumatic mitral valve disease was found to be high (3.42) when compared to recommend INR (2.0-3.0) and in myocardial infraction after stent replacement the observed INR was found to be 3.42 when compared to recommended dose (2.0-3.0).

Table-11.

Indications, Goals and Duration of Warfarin/Acenocoumarol Therapy			
Indication (ACCP recommendation grade)	**Target INR (range) (ACCP recommendation)**	**Duration of therapy (ACCP recommendation grade)**	**Observed INR range**
DVT of the leg or PE			
First episode	2.5 (2.0 to 3.0)	3 months	2.0
Second episode	2.5 (2.0 to 3.0)	3 months (2B)	2.4
Atrial fibrillation or flutter			
Intermediate to high risk of stroke	2.5 (2.0 to 3.0)	Indefinite	2.0
Mitral stenosis	2.5 (2.0 to 3.0)	Lifelong	2.22
After stent placement and high risk of stroke	2.5 (2.0 to 3.0)	Bare-metal stent (1 month) and drug-eluting stent (3 to 6 months)	2.22
Coronary heart disease			
High-risk patients with myocardial infarction without a stent	2.5 (2.0 to 3.0)	Bare-metal stent (1 month) and drug-eluting stent (3 to 6 months)	2.0
High-risk patients with myocardial infarction and after stent placement.	2.5 (2.0 to 3.0)	Bare-metal stent (1 month) and drug-eluting stent (3 to 6 months)	3.42
Valvular heart disease			
Rheumatic mitral valve disease.	2.5 (2.0 to 3.0)	Long-term	3.12
Mechanical prosthetic heart valves	2.5 (2.0 to 3.0)	Long-term	2.0

9. Management of anticoagulation therapy where the INR is below<1.3[16]

The following therapy whose INR is below <1.3 is compared with the standard guidelines Of PATRICIA WIGLE at all, ACCP Updated Guidelines on Anticoagulation, *April 15, 2013; Volume 87, Number 8.*

The observed dose for 1.0-1.3 INR is 4mg and suggested maintenance dose is 5-7.5mg, for 1.4-1.5 is 3mg (5mg), 1.6-1.8 is 2.3mg (5-2.5mg), >1.9 is 2mg(2.5mg) and >2.0 is 1mg (hold for 1 day then start 2.5mg). Through this we conclude that dose should be given based on patient related factor and its guidelines and close monitoring of patients is necessary.

Table-12.

If INR result is	Suggested maintenance dose is	Observed maintenance dose is
1.0-1.3	5-7.5mg	4mg
1.4-1.5	5mg	3mg
1.6-1.8	5/2.5mg alternating	2-3mg
>1.9	2.5mg	2mg
>2.0	Hold x 1 day, then 2.5mg	1mg

CONCLUSION

The appropriate management of drug interactions and other related factors can enhance the efficacy and safety of warfarin/Acenocoumarol therapy. Acenocoumarol is effective and safe in broad number of patient's which has shown lesser incidence of ADR's (drug induced coagulopathy) when compared to warfarin. Bleeding complications occur due to improper management of warfarin/Acenocoumarol which leads to increase in INR. Efficacy and safety of Acenocoumarol has been evaluated in atrial fibrillation, cardiac valve replacement, after myocardial infarction, treatment of deep vein thrombosis, after major surgeries and after critical illness requiring prolonged hospitalization. Frequent monitoring of INR value would play a vital role to predict the treatment outcomes on patients of warfarin/Acenocoumarol. DDI's were highly prevalent due to anti-biotics and other co prescribed drugs. In the study where the concomitant drugs were altering the therapeutic efficacy of warfarin/Acenocoumarol, on the other hand the inhibiting drugs were also more prevalent in causing an increased risk of coagulopathy. Thus the risk factors associated with warfarin/Acenocoumarol are old age, diabetes mellitus, hypertension, liver disease, renal impairment. Due to its economic advantage Acenocoumarol may be suitable as an oral anticoagulant for long term use. Thus, clinicians should be aware of potential drug-drug interactions and monitor patients based on patient related factors age, gender, disease, concomitant drugs and International normalized ratio closely to improve the clinical outcome and quality life of patients on warfarin/Acenocoumarol.

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