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Drug Utilization Studies on Clopidogrel, Prasugrel and Ticagrelor in A Tertiary Care Hospital

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ABSTRACT

The objectives of this study were to evaluate the drug utilization pattern of Clopidogrel, Prasugrel and Ticagrelor, to compare the actual drug use with the standard prescribing guidelines, to ensure proper monitoring and to assess its appropriateness. It was a concurrent observational study conducted in the Cardiology and General Medicine Departments, PSG Hospitals, Coimbatore, Tamil Nadu, for a period of 6 months. A total of 205 patients were enrolled. Comparison of the drugs with respect to medication errors, drug interactions and appropriateness of usage was performed. Analysis of data was performed to find mean, standard deviation, frequency and percentage. The study population included 80% males and 20% females and most of them belonged to 50-69years. Clopidogrel was prescribed the most (79.5%) followed by Ticagrelor (18.5%) in both genders and all age groups. Prasugrel prescriptions were found rarely (2%). ACS and CAD were the predominant indications for which anti-platelets were prescribed. Based on the predetermined list of monitoring parameters, 84.8% (n=174) of subjects were monitored appropriately. 93.2% patients received WHO prescribed DDD of the antiplatelets. Nearly half of the subjects were switched to a newer anti-platelet after PCI/CABG. Our study concluded that Clopidogrel remains to be the most prescribed antiplatelet irrespective of gender and age. Newer anti-platelets are usually avoided in females and elderly population. This DUE provides significant information on the current usage pattern of the three drugs and encourages further research on extensive utilization of the newer anti-platelets in eligible candidates and also to promote cost-effective treatment.

INTRODUCTION

As per the World Health Report of 2016, 17.9 million people die each year from Cardiovascular Diseases (CVDs), an estimated 31% of all deaths worldwide. 85% of all CVD deaths are due to heart attacks and strokes.[1] Compared with other populations around the world, Coronary Artery Disease (CAD) occurs in Indians 5-10 years earlier and most common in patients aged 35-65years.[2]

Anti-platelet therapy is a first-line medical treatment for patients with Acute Coronary Syndrome (ACS). As there is an increase in number of complications for percutaneous interventions, there is a need for antiplatelet therapy in patients with arterial thrombosis. Clopidogrel response variability led to the development of other P2Y12 receptor inhibitors, such as Prasugrel and Ticagrelor. Hence, the current utilization trends of these drugs vary significantly on the basis of indications, gender, age, history, contraindications, etc.

Clopidogrel is highly effective in atherothrombotic complications. However, a significant number of patients continue to experience recurrent complications despite being treated, due to pharmacokinetics and interactions of drugs. Thus, the third generation antiplatelet agents play an important role in ACS preventions and to reduce its further complications. The drug utilization pattern varies widely among these drugs and thus its current use in practice needs to be evaluated.[3]

Clinical trials demonstrated that Prasugrel and Ticagrelor are more effective than Clopidogrel in the reduction of the composite of Myocardial Infarction (MI), stroke, and cardiovascular death over the 12- to 15-month period after the onset of ACS. Novel agents promoted cost containment benefits on comparison with Clopidogrel and thus ensured low cost health care security. However, novel agents presented with major bleeding risk in comparison with Clopidogrel. These agents were added as an alternative therapy to Clopidogrel but, there were no recommendations on choosing one specific drug over the other.

The American College of Cardiology/American Heart Association (ACC/AHA) 2016 guidelines address the recommendations on dual antiplatelet therapy (DAPT)-Aspirin plus a P2Y12 inhibitor, in patients with coronary artery disease. The three major P2Y12 inhibitors used in DAPT are:

CLOPIDOGREL:

Clopidogrel bisulphate is a prodrug that is metabolized to the active form (thiol derivative), that inhibits platelet aggregation by selectively and irreversibly binding to adenosine diphosphate (ADP) P2Y12 receptor, present on platelets. It was approved for use by the Food and Drug Administration (FDA) in 1997.

PRASUGREL:

Prasugrel hydrochloride is a thienopyridine which inhibits platelet activation and aggregation by irreversibly inhibiting ADP-P2Y12 platelet receptor. It is a prodrug and is rapidly metabolized to a pharmacologically active compound. This compound was introduced into the market in 2009.

TICAGRELOR:

Ticagrelor was approved by the FDA in 2011. It is a cyclopentyl tri-azolopyrimidine that reversibly interacts with platelet P2Y12-ADP receptor thereby preventing signal transduction, platelet activation and aggregation.

DEFINED DAILY DOSE (DDD):

In the Anatomical Therapeutic Chemical (ATC) classification system, the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. ATC/DDD Index 2019 is a searchable version of the complete ATC index with DDDs which enables to find ATC codes and DDDs for substance name and/or ATC levels.

The defined daily dose (DDD) is a statistical measure of drug consumption, defined by the World Health Organization (WHO). It is used to standardize the comparison of drug usage between different drugs or between different health care environments. WHO defines DDD as "the assumed average maintenance dose per day for a drug used for its main indication in adults." Only one DDD is assigned per ATC code and route of administration (e.g. oral formulation).

Formula used to calculate DDD:

$$\textbf{Drug usage in DDD} = \frac{Items\ issued\ x\ amount\ of\ drugs\ per\ item}{DDD}$$

Individual therapeutic doses may differ from DDD as they are based on individual characteristics such as age, weight, type and severity of disease and pharmacokinetic considerations. DDDs provide a fixed unit of measurement independent of price, currencies, package size and strength which aid the researcher to assess trends in drug utilization and to compare between population groups.

RATIONAL DRUG USE:

The magnitude and nature of inappropriate drug utilization in several clinical settings have worsened over the past decades. Therefore it is of prime importance to shed light on adverse impacts of this inappropriateness. The rational use of drugs require that patients receive medication appropriate to their clinical needs, in doses and frequencies, that meet their own individual requirements for an adequate period of time and at the lowest cost to them and their community. Monitoring medicine use and using the collected information to develop, implement and evaluate strategies to correct inappropriate drug use can be employed to promote rational drug therapies.

The aim of this study was to compare the prescribing pattern and evaluate the factors affecting the choice of drug and hence assess the current practice of drug usage. Utilization patterns of Clopidogrel, Prasugrel and Ticagrelor does not fully parallel with package labels and guideline recommendations which promote further research on comparing recommended use and actual clinical practice. This study evaluated the aptness of drug usage and compared the drug utilization of these drugs with DDD and the established guidelines in a tertiary care hospital.

This study brings into the spotlight the existing prescribing pattern and utilization trends of the three major P2Y12 inhibitors – Clopidogrel, Prasugrel and Ticagrelor and thus contributes to the healthcare system by providing important information to the prescribers. This will allow for providing indispensable care to the patients and also to avoid causing incongruity in therapy.

MATERIALS AND METHODS

This study was a concurrent DUE performed in the Cardiology and General Medicine departments in PSG Hospitals, Coimbatore, Tamil Nadu, for a duration of 6 months. The study included 205 patients, both genders, above 18 years, admitted in the respective departments, prescribed with Clopidogrel, Prasugrel and Ticagrelor alone or in combination. The study was approved by the Institutional Review Board. Informed consent was obtained from the patients or their legally accepted representatives. The required data was collected by interviewing the individual patients and from their in-patient records. The appropriateness of drug use was assessed on the basis of their dose, indication, monitoring parameters and contra-indications/precautions. Data, mainly prescribing indicators, was analysed statistically using SPSS version 22 and the mean, standard deviation, frequency and percentage were calculated.

RESULTS

1. PATIENT DEMOGRAPHICS:

The demographic details include gender, age, smoking, alcohol use, family history of cardiac conditions and co-morbidities. These results provide an insight into the risk factors that have contributed to their clinical condition. Out of 205 patients, 80% of them were males (n=164) and 20% were females (n=41) and all patients belonged to either of the two departments- Cardiology and General Medicine. Male subjects represented a higher percentage than the female subjects. All the patients were classified into 5 age-groups. Majority of the study subjects belonged to age-group of 50-69 years (n=105, 51.2%), followed by 30-49 years (n=66, 32.2%) and 70-89 years (n=29, 14.1%). Most of the male and female subjects fall into the age category of 50-69 years. Mean age for male patients was **54.4 ± 11.77years** and for female, **60.85 ± 11.12years**. This reveals that the age of female patients requiring treatment with antiplatelet agents is higher than the male patients.

Table 1: Gender wise age distribution

Age Group (years)	Male		Female		Total
	n	%	n	%	
19-29	4	2.43	0	0	4
30-49	56	34.14	10	24.4	66
50-69	86	52.43	19	46.34	105
70-89	17	10.4	12	29.3	29
90-99	1	0.6	0	0	1
Total	**164**	**100**	**41**	**100**	**205**

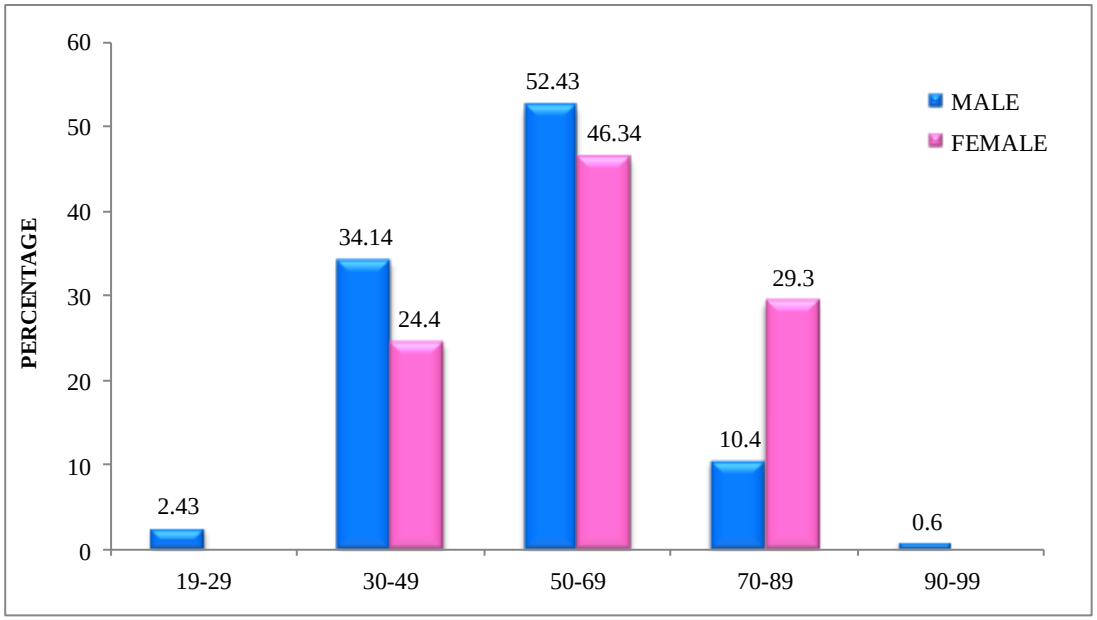

Figure 1: Gender wise age distribution percentage

In this study, excluding the ex-smokers and active smokers, a greater percentage of patients (n=98, 47.8%) were identified to be non-smokers. Similarly, a higher percentage of patients (n=108, 52.7%) were identified to be non-alcoholics. Family history can predispose people to cardiac diseases such as MI. This association is also evident with diabetes, hypertension, etc., which contributes to cardiac-related disorders. A notable sector of the patient population (n=42, 20.5%) had a family history of diabetes, followed by a lesser portion subjects with a family history of hypertension (n=36, 17.6%) and MI (n= 26, 12.7%). Patients who had a significant family history was about 55.2% (n=113). The presence of co-morbidities might affect the disease prognosis, selection of anti-platelet agent and the development of Adverse Drug Reactions (ADRs). The most common co-morbidity observed was diabetes mellitus

(n=124, 60.5%), followed by hypertension (n=96, 46.8%). Other co-morbidities were dyslipidemia (29.3%) and organ-related disorders of the heart (30.2%), kidneys, lungs, liver or blood, malignancy and others.

2. INDICATIONS

The indications, for which the anti-platelets were prescribed, were categorized under ACS (including ST-Elevated MI [STEMI] and Non ST-Elevated MI [NSTEMI]), CAD (including Single, Double and Triple Vessel Diseases [SVD, DVD, TVD]), Heart Failure (HF), Stroke and others (Left Ventricular [LV] clots, tachycardia, etc.). All patients exhibited either one or more than one of the above indications. The most common cardiac indication was found to be ACS (n=185, 90.2%).

3. ANTI-PLATELET DRUGS

a. Distribution of anti-platelets:

Out of 205 patients, maximum received Clopidogrel (n=163, 79.5%). This share was followed by Ticagrelor (n=38, 18.5%). Four patients received Prasugrel, which constituted only about 2% of the study population. This significant result shows the disinclination in prescribing Prasugrel.

Table No. 2: Distribution of anti-platelets

Anti-Platelets	No. of Patients (n)	Percentage (%)
Clopidogrel	163	79.5
Prasugrel	4	2
Ticagrelor	38	18.5
Total	205	100

b. Age-wise distribution of anti-platelets:

The choice of anti-platelet may differ based on the age-group. The age of patients was categorized into 5 groups and the distribution of anti-platelets in each age-group was determined.

This result affirms that, for Clopidogrel, an increasing usage trend towards increasing age can be seen.

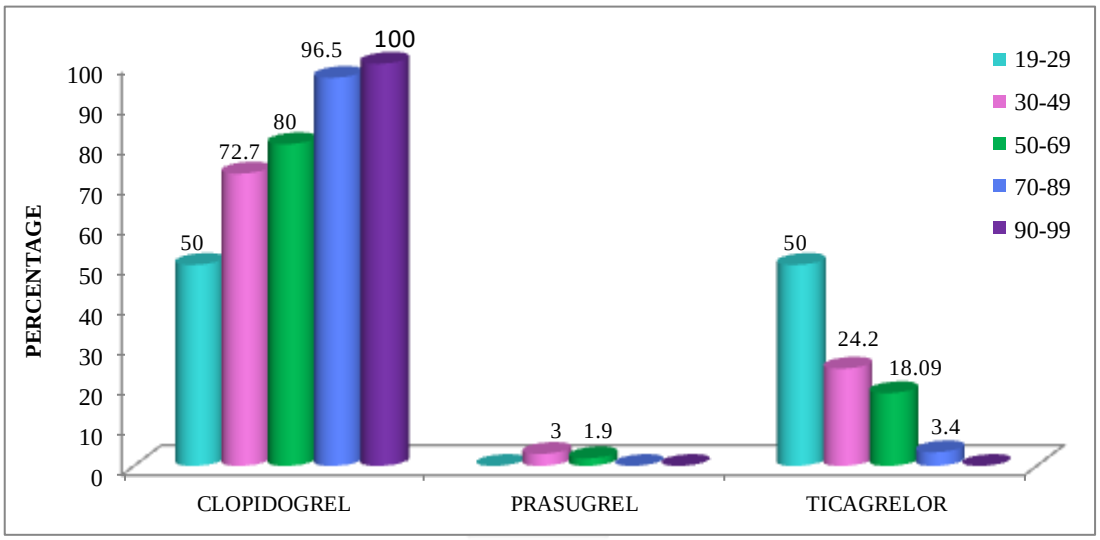

Figure No. 2 Age-wise percentage distribution of anti-platelets

c. Gender-wise distribution of Anti-platelets:

A sector of male gender receives newer anti-platelets- Prasugrel (2.4%) and Ticagrelor (21.3%), whereas, its use in the female gender is reasonably less. 92.7% (n=38) of females receive Clopidogrel and only 7.3% (n=3) receive Ticagrelor.

4. MONITORING PARAMETERS:

Monitoring parameters are essential in predicting disease prognosis or adverse drug reactions. There are common and serious/fatal adverse drug reactions that are reported for each drug. In order to prevent these, vigilant monitoring of certain monitoring parameters for each drug is essential. These predetermined set of monitoring parameters include:

Clopidogrel: Platelet count, Prothrombin Time- International Normalized Ratio (PT INR), Hepatic enzymes, Serum Creatinine (S.Cr), Hemoglobin (Hb), Packed Cell Volume (PCV)/ Hematocrit.

Prasugrel: Complete Blood Count (CBC)-with platelet count, PT INR, Blood Pressure (BP), Lipid profile, Electrocardiogram (ECG).

Ticagrelor: Serum creatinine, CBC-with platelet count, ECG, Peripheral Capillary Oxygen Saturation ($SpO_{2)}$.

a. Appropriateness of monitoring:

Based on the above list of parameters, appropriateness was determined for each drug. If more than two of the required parameters are not monitored, it was considered as inappropriate monitoring.84.8% (n=174) of subjects were monitored appropriately.

b. Anti-platelet wise appropriateness of monitoring parameters:

Table No. 3: Anti-platelet-wise appropriateness of monitoring parameters

Monitoring Parameters	Clopidogrel		Prasugrel		Ticagrelor		Total (n)
	n	%	n	%	n	%	
Appropriate	140	85.8	3	75	31	81.5	174
Inappropriate	23	14.1	1	25	7	18.4	31
Total	163	100	4	100	38	100	205

Clopidogrel had the highest percentage of appropriate monitoring (85.8%, n=140). 25% (n=1) and 18.4% (n=7) of subjects treated with Prasugrel and Ticagrelor respectively were not monitored appropriately as per the criteria used in this study.

5. DRUG INTERACTIONS

All drugs that are reported to interact with the anti-platelets were identified and listed. These were classified into major and moderate drug interactions. These were further accounted as significant interactions when suitable dosage or required monitoring and other such conditions were not fulfilled.

a. Drug interactions with Clopidogrel:

All significant drug interactions with Clopidogrel are major except for Atorvastatin, which has a moderate interaction. The most repeated interaction occurs with Aspirin (n=16, 25.3%), followed by Enoxaparin (n=15, 23.8%) and Atorvastatin (n=12, 19%).

b. Drug interactions with Prasugrel:

Both significant drug interactions with Prasugrel are major. Two interactions with Aspirin and one with Heparin were observed.

c. Drug interactions with Ticagrelor:

The most frequent significant drug interactions of Ticagrelor were observed with Aspirin (85.7%, n=12) and it's a major interaction. One interaction each was seen with Heparin and Enoxaparin, which were moderate interactions.

6. DEFINED DAILY DOSE (DDD):

Defined daily dose is described in WHO/DDD index for each drug under the ATC category. DDD for Clopidogrel is defined as 75mg/day, for Prasugrel it is 10 mg/day and for Ticagrelor it is 180 mg/day. The drug usage was calculated for each patient using the aforementioned formula and its appropriateness was assessed based on this DDD.

a. Appropriateness based on DDD:

About 93.2% of all patients, were treated using the daily maintenance doses as prescribed by the WHO/DDD and were considered as appropriate, whereas 6.9% (n=14) were prescribed with another available dose of the drug and considered as inappropriate based on DDD alone.

b. Anti-platelet wise appropriateness based on DDD:

The appropriateness of DDD was also estimated for each anti-platelet. It was found that Prasugrel, prescribed for all 4 patients was at the defined DDD. Clopidogrel had 92.6% (n=151) and Ticagrelor had 94.7% (n=36) appropriateness in DDD.

7. CONTRAINDICATIONS (CI) AND/OR PRECAUTIONS:

A list of contraindications and precautions/warnings for the use of anti-platelets was sorted out. Patients having any contraindications to the use of anti-platelets or require special monitoring/precautions before treating with the anti-platelets were identified.

a. Contra-indications and/or precautions to the use of Clopidogrel:

Out of 163 patients prescribed with Clopidogrel, only 8 (4.91%) were identified to have such precautions or contra-indications. Among all of the identified contra-indications/precautions for all anti-platelets, only one patient had an actual contra-indication i.e., an active bleed.

b. Contra-indications and/or precautions to the use of Prasugrel:

All patients who were treated with Prasugrel had precautions to be taken care of, while on treatment. No actual contra-indications were found among Prasugrel users.

c. Contra-indications and/or precautions to the use of Ticagrelor:

The precautions to be taken, prior to treatment with Ticagrelor was required for about 16 (42.1%) patients prescribed with Ticagrelor. The most commonly required precaution was in patients who were planned for Coronary Artery By-pass Graft (CABG) or Coronary Angiography (CAG). The use of Ticagrelor must be done with caution and with appropriate monitoring in these patients.

Table No. 4: CI/Precautions to the use of Clopidogrel, Prasugrel and Ticagrelor

CI/Precautions to Clopidogrel use	**Count (n)**	**%**
Active bleed	1	12.5
Low platelet count	3	37.5
Atrial fibrillation	2	25
Use of Heparin/Warfarin	2	25
Total	8	100
CI/Precautions to Prasugrel use		
Weight <60kg	2	50
Planned for CABG/CAG	1	25
Stop 5 days prior to surgery	1	25
Total	4	100
CI/Precautions to Ticagrelor use		
Hypotension	4	25
AV Block	1	6.2
Dyspnea	2	12.5
Planned for CABG/CAG	9	56.2
Total	16	100

8. SWITCHING OVER BETWEEN ANTI-PLATELETS

During the hospital stay or after admission, the anti-platelet was switched over from one to another for 15.6% (n=32) of the patients. The switch was usually done from Clopidogrel to a newer anti-platelet. Out of all the patients who were switched from one to another anti-platelet, 46.3% (n=25) patients had undergone either a PCI or a CABG.

DISCUSSION

This drug utilization study shows that maximum patients received Clopidogrel (n=163, 79.5%). and only 2% received Prasugrel. This significant result shows the reluctance in prescribing Prasugrel. This is parallel to the study of Sheikh Rezaei et al., 2017, Sirker A et al., 2018 and Carraba N et al., 2017, but has a slight divergence from the study of Kibum Kim et al., 2017 where the number of Ticagrelor and Prasugrel prescriptions were almost equal.

The choice of anti-platelet may differ based on the age-group. This study finding affirms that, for Clopidogrel, an increasing usage trend towards increasing age can be seen, which means that as age advances, the preferred choice of anti-platelet remains to be Clopidogrel. The reverse is true with Ticagrelor, wherein, as age increases, we could detect a decline in the use of Ticagrelor. This result is analogous with the study of Kibum Kim et al., 2017.Yet, a study by Tarantini et al., 2018 says that the newer anti-platelets need not be withheld solely because of elder age and that its benefits and risks are similar to the non-elderly population.

This study reveals that a sector of male gender receives newer antiplatelets, Prasugrel (2.4%) and Ticagrelor (21.3%), whereas, its use in the female gender is reasonably less. About 92.7% (n=38) of females receive Clopidogrel and only 7.3% (n=3) receive Ticagrelor. This result was identical to the study by Cirillo P et al., 2019. The BleeMACS study by Grodecki K et al., 2018 has also explained this gender-related differences in antiplatelet therapy. According to a review by Ahamed B et al., 2013, as compared with men, women undergoing PCI are older and have a higher prevalence of renal insufficiency, anemia, and diabetes mellitus. Although it is unclear whether the sex-specific risk of increased cardiovascular events persists after adjustment for comorbidities, the association between bleeding and female sex persists after adjustment for confounding clinical factors. This could be the reason for lesser number of Prasugrel prescriptions, especially in the female population.

Patients having any contraindications to the use of anti-platelets or require special monitoring/precautions before treating with the anti-platelets were identified. Out of 163 patients prescribed with Clopidogrel, only 8 (4.91%) were identified to have such precautions or contra-indications. Only one patient had an actual contra-indication i.e., an active bleed. All four patients treated with Prasugrel had precautions to be taken care of, while on treatment. The precautions to be taken, prior to treatment with Ticagrelor was required for about 16 (42.1%) patients. This observation is comparably related to the study by Alexopoulos D et al., 2013.

About 93.2% of all patients were treated using the daily maintenance doses as prescribed by the WHO/DDD and were considered as appropriate, whereas 6.9% (n=14) were prescribed with another available dose of the drug and considered as inappropriate, based on DDD alone. Yet, this may be appropriate with the clinical condition of the patient.

During the hospital stay or at discharge, the antiplatelet was switched over from one to another for 15.6% (n=32) of the patients. The switch was usually done from Clopidogrel to a newer anti-platelet. Out of all the patients who were switched, 46.3% (n=25) patients had undergone either a PCI or CABG.

The recommendations on how and why to switch between antiplatelets was elaborated in a study by Capranzano P et al., 2019 and its practical considerations were recorded in the study by De Luca L et al., 2016. Similar to these studies, the switching of anti-platelets has been performed in this study population, in order to improve clinical outcomes in ACS patients.

CONCLUSION

Our study has identified that Clopidogrel remains to be the most prescribed anti-platelet irrespective of gender and age. Newer anti-platelets are usually avoided in females and elderly population. Prasugrel prescriptions were found rarely. The mean age of female patients prescribed with anti-platelets is higher than that of males. The indication, dose (DDD), monitoring and contra-indications were analyzed for appropriateness. ACS and CAD were the predominant indications for which anti-platelets were prescribed. More than 90% of subjects received a dose of anti-platelet equal to that of WHO prescribed DDD. Nearly half of the subjects who have undergone a PCI/CABG were switched over from Clopidogrel to a newer anti-platelet for better clinical outcomes in patients.

This DUE provides significant information on the current usage pattern of the three drugs and encourages further research on extensive utilization of the newer anti-platelets in eligible candidates and also to promote cost-effective treatment. This study emphasizes improving medical care and cost-containment and ensuring safe, effective and appropriate drug usage.

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