

## DRUG UTILIZATION STUDY IN PATIENTS OF ACUTE CORONARY SYNDROME ON FOLLOW-UP VISITS AT A TERTIARY CARE CENTRE IN KOLKATA

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### **Abstract**

**Objective:** The main objective of drug utilization research is to assess the rationality of drug use. Incidence of Acute Coronary Syndrome (ACS) is rapidly increasing in India and causes high mortality. Long term survival in post-ACS patients depends largely on how well post-ACS period is managed. Our aim is to record drug utilization patterns in post-ACS patients during follow up visits and how much it conforms to standard treatment guideline.

**Method:** It is a prospective unicentric study, done at cardiology OPD of R.G.Kar Medical College, Kolkata. Prescriptions issued to study subjects (20-70 years of age, having ACS recently) are intercepted immediately after consultations and data recorded as per WHO guidelines on how to investigate drug use. **Assessment parameters-** 1. Pattern of different drug use [antiplatelets, beta blockers, angiotensin converting enzyme inhibitors (ACEI)/ angiotensin receptor blockers (ARB), Statins]. 2. To what extent the prescriptions conform to standard treatment guideline (AHA/ACC 2007 guideline). **Result:** 525 patients were included in this study. Drug utilization rates in all study subjects till date stands at Aspirin 100%, Atorvastatin 100%, clopidogrel/ prasugrel 98.29%, beta blockers 86.86% (mostly metoprolol), ACEI/ARB 87.43% (mostly ramipril). Non-cardiological drugs uses are also recorded. **Conclusion:** We found that DU 90% is achieved in this centre's drug use as per AHA/ACC 2007 guidelines but the average doses of some drugs are different from DDD.

**Keywords:** drug utilization, ACS, unicentric study

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### **Introduction**

The development of drug utilization research was sparked by initiatives taken in Northern Europe and the United Kingdom in the mid-1960s. The pioneering work of Arthur Engel in Sweden and Pieter Siderius in Holland alerted many investigators to the importance of comparing drug use between different countries and regions. Their demonstration of the remarkable differences in the sales of antibiotics in six European countries between 1966 and 1967 inspired WHO to organize its first meeting on Drug consumption in Oslo in 1969. This led to the constitution of the WHO European Drug Utilization Research Group (DURG).[1] The main aim of drug utilization research is to assess whether the drug treatment is rational or not. To reach this goal, methods for auditing drug therapy towards rationality are necessary. The early work did not permit detailed comparisons of the drug utilization data obtained from different countries. Researchers in United Kingdom, Norway and Sweden developed a new unit of measurement, initially called the agreed daily dose and later the defined daily dose (DDD). This unit was defined as

the average maintenance dose of the drug when used on its major indication in adults. The first study used antidiabetic drugs as an example. Drug utilization study attempts to answer following questions: [1]

1. why drugs are prescribed;
2. who the prescribers are;
3. For whom the prescribers prescribe;
4. whether patients take their medicines correctly;
5. what the benefits and risks of the drugs are.

Ischemic heart disease is already the leading cause of mortality in India. It is projected that ischemic heart disease will result in two and one-half million Indian deaths by 2020.[2] The term acute coronary syndrome refers to a range of acute myocardial ischaemic states. It encompasses unstable angina, non-ST segment elevation myocardial infarction (ST segment elevation generally absent), and ST segment elevation infarction (persistent ST segment elevation usually present).[3] An acute coronary syndrome may occasionally occur in the absence of electrocardiographic changes or elevations in biochemical markers, when the diagnosis is supported by the presence of prior documented coronary artery disease or subsequent confirmatory investigations.[4] In addition to primary prevention efforts, joint guidelines by the

American College of Cardiology (ACC) and the American Heart Association (AHA) in 2010 suggest secondary drug prevention measures to be used in patients with ACS.[5,6] In conjunction with diet and lifestyle modifications, these guidelines suggest the use of statin, beta-blocker, and renin-angiotensin aldosterone system inhibitor drug therapies in ACS patients.[5-6] Six-month mortality rates in the Global Registry of Acute Coronary Events (GRACE) were 13% for patients with NSTEMI ACS and 8% for those with unstable angina.[7] Long term survival rate in post acute coronary syndrome (A.C.S.) patients depends to a large extent on how well post A.C.S. period is managed. Primary objective of this study is to study drug utilization pattern in post acute coronary syndrome patients in their follow up visits and the secondary objective is to study how drug utilization pattern impacts health outcomes.

## **Materials and methods**

It is a longitudinal prospective unicentric study, done at the out-patient department of cardiology and at the department of pharmacology, R.G.Kar Medical college, Kolkata. All prescriptions issued to study subjects attending the cardiology clinic during this whole study period are intercepted after consultation and following data are recorded in data collection forms adapted from WHO guidelines on how to investigate drug use in health facilities. Patient (age group 20 yrs to 70 yrs) who have suffered acute coronary syndrome (unstable angina, ST elevation and non- ST elevation acute myocardial infarction, diagnosed by ECG and/or biochemical tests)" [8] in recent past and are attending cardiology outdoor of R.G.Kar Medical College, Kolkata are included in this study. Prescriptions obtained will be sorted and classified in accordance with WHO ATC/DDD (Anatomical Therapeutic Chemical/ Defined Daily Dose) classification system.[9] Following data are recorded from each prescription as adapted from WHO guidelines on how to investigate drug use in health facilities.[10]

1. Names, dose, dosage regimen, duration of all drugs prescribed-
2. average number of drugs per prescription (encounter)
3. percentage of drugs prescribed by generic name
4. percentage of encounters resulting in prescription of an antibiotic
5. percentage of encounters resulting in prescription of an injection
6. percentage of drugs prescribed from essential drugs list or formulary
7. average drug cost per encounter
8. PDD (prescribed daily dose) of each drug.

### ASSESSMENT PARAMETERS

1. Pattern of different drug use (*aspirin-clopidogrel, beta blockers, statins, ACE inhibitors/ angiotensin receptor blockers*)- dose, regimen, compliance, follow up.
2. How much the prescription conforms to standard treatment guideline. (American Heart Association/ American College of Cardiology 2007 guideline).

The parameter for comparison of drug dose is DDD (Defined daily dose). Defined daily dose (DDD) was defined as the average maintenance dose of the drug when used for its major indication in adults.

### Results

Total 525 patients were included in this study. Among them, 453 patients are male and 72 are female. Male: female ratio is 6.29:1. Regarding age distribution, 3 patients (0.57%) were below 30 years, 33 patients (6.29%) were between 31 to 40 years, 99 patients (18.86%) were between 41 to 50 years, 192 patients (36.57%) were between 51 to 60 years and 198 patients (37.91%) were between 61 to 70 years, indicating that incidence of acute coronary syndrome increases as the age of the patient increases.(figure 1)

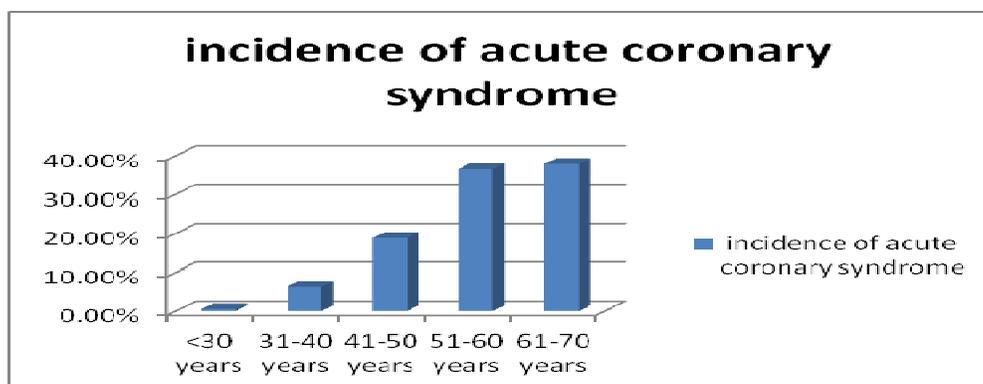
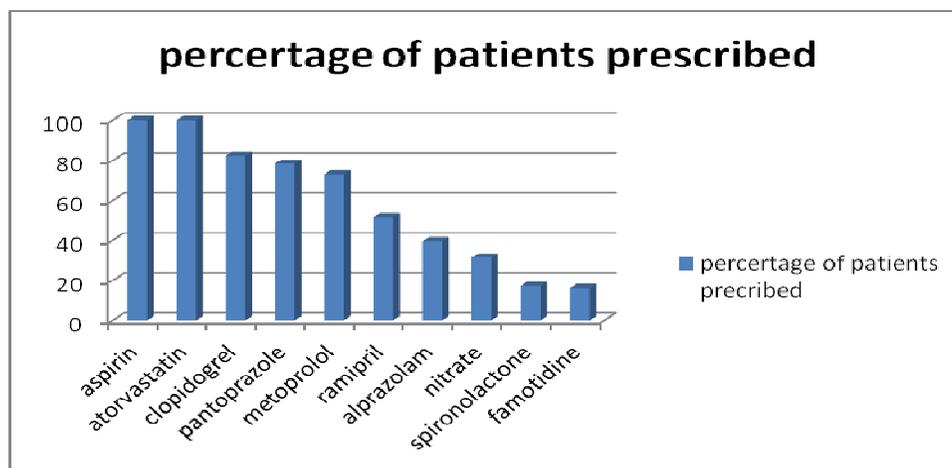


Figure 1- age wise incidence of acute coronary syndrome

Among 525 patients, incidence of unstable angina, non ST elevation acute myocardial infarction and ST elevation acute myocardial infarction are 144 (27.43%), 48 (9.14%) and 333 (63.43%) respectively. Diabetes mellitus has a strong association with acute coronary syndrome is supported from the result of this study because 135 patients out of 525 (25.71%) acute coronary syndrome patients had concomitant diabetes mellitus.

The top ten drug used are Aspirin (in 100% cases), Atorvastatin (100%), Clopidogrel (82.29%), Pantoprazole (78.29%), Metoprolol (72.93%), Ramipril (51.43%), Alprazolam (39.43%), Isosorbide mononitrate (31.43%), Spironolactone (17.14%) and Famotidine (16%).(figure 2)



**Figure 2- top ten drugs prescribed with their percentage of use**

Regarding the prescription data, following answers were obtained.

Average number of drugs per prescription were 7.71.

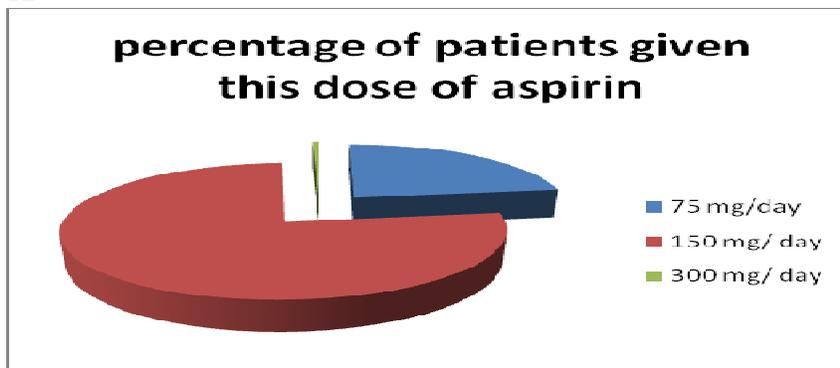
Percentage of drugs prescribed in generic name was 4.37%. Enalapril, atenolol and famotidine was prescribed mainly in generic names.

percentage of encounters resulting in prescription of an antibiotic- nil

percentage of encounters resulting in prescription of an injection- nil

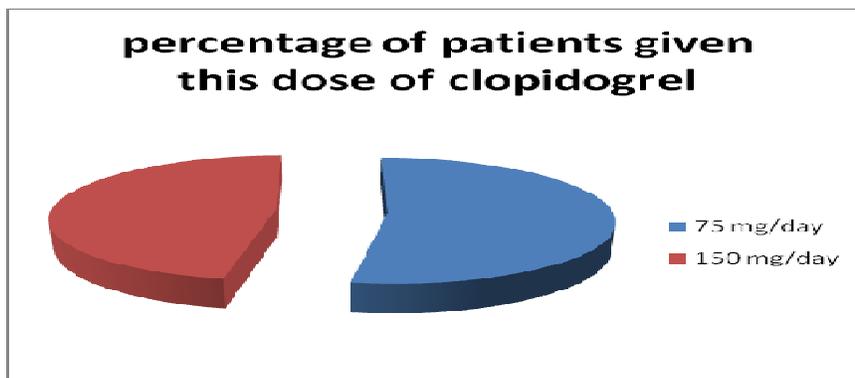
percentage of drugs prescribed from essential drugs list or formulary- 40.88%. out of the all prescribed drugs, aspirin, enalapril, losartan, atenolol, metoprolol, amlodipin, spironolactone, furosemide, hydrochlorothiazide, isosorbide mononitrate, alprazolam, metformin and ranitidine are included in the essential drug list of India.

Regarding the drugs for main indication, aspirin was prescribed to all patients (100%), among them 120 patients (22.86%) were given 75 mg aspirin per day, 402 patients (76.57%) were given 150 mg aspirin per day, 3 patients were given 300 mg aspirin per day.(figure 3)



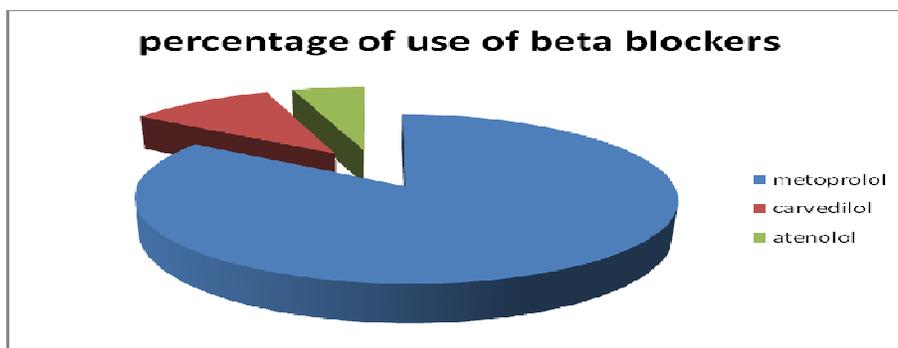
**Figure 3- use of aspirin in different doses**

Clopidogrel were prescribed in 432 patients (82.29%), among them 228 (52.78%) were given 75 mg/day and 204 (47.22%) were given 150 mg/day. Prasugrel were given to 84 patients (16%) in 10 mg/day dose.(figure 4)



**Figure 4- use of clopidogrel in different doses**

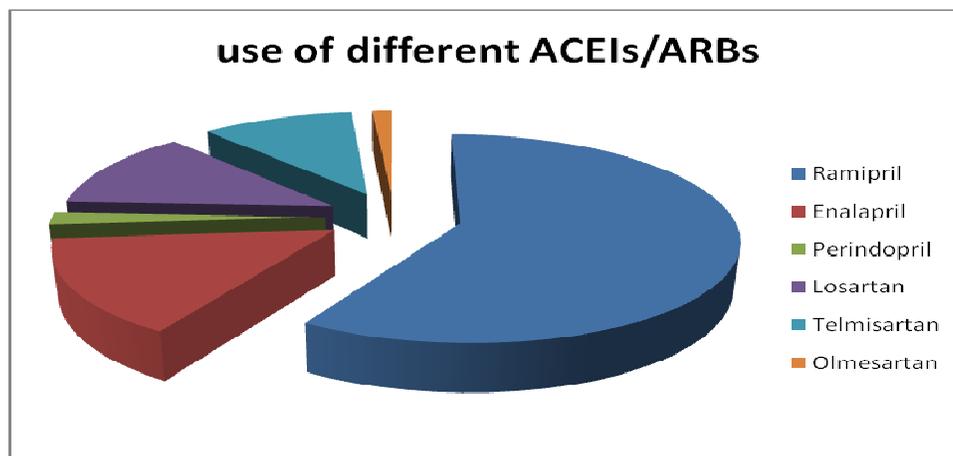
9 patients out of 350 (1.71%) were not given clopidogrel/ prasugrel. Beta blockers were prescribed in 456 patients (86.86%), among them, metoprolol were given in 384 patients (84.21%), carvedilol in 48 (10.53%) and atenolol in 24 patients.(5.26%). (figure 5)



**Figure 5- use of different beta blockers**

Metoprolol was used in different dose from 12.5 mg/day to 100 mg/day. 49.22% of metoprolol users were having 50 mg/day dose.

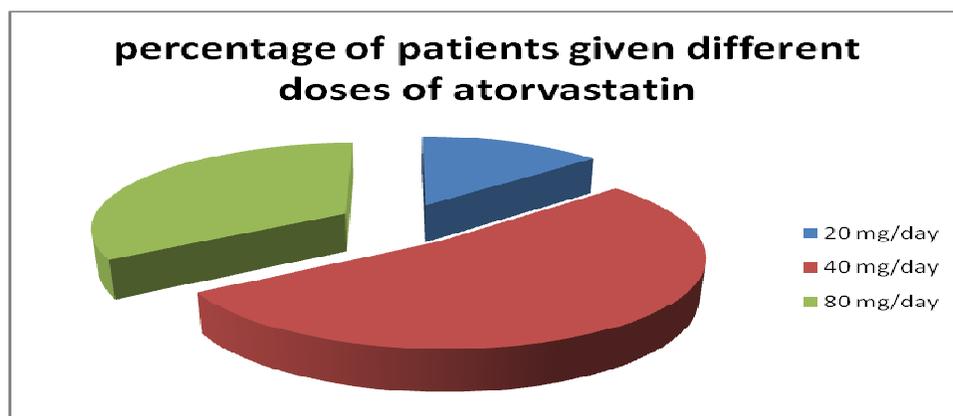
Angiotensin converting enzyme inhibitors/ angiotensin receptor blockers were given in 459 patients (87.43%), among them ramipril was given in 270 patients (58.62%), enalapril in 69 patients (15.03%), perindopril in 9 patients (1.96%), losartan in 57 patients (12.42%), telmisartan in 48 patients (10.46%), olmesartan in 6 patients (1.31%). (figure 6)



**Figure 6- use of different ACE inhibitors/ ARBs.**

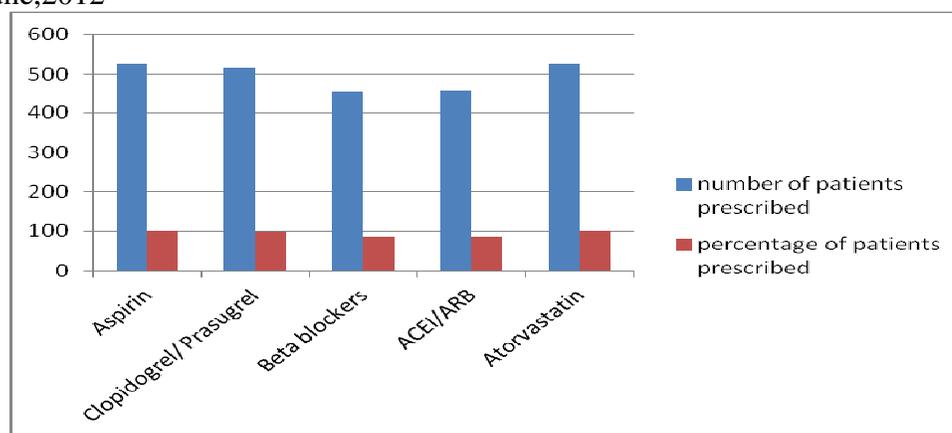
Among ramipril users, 120 patients (44.44%) were given 2.5 mg/day and 123 (45.56%) were given 5 mg/day dose. 6 patients received 1.25 mg/day and 21 patients received 10 mg/day dose.

Atorvastatin was given to 100% of patients and among them, 72 (13.71%) were given 20 mg/day dose, 276 (52.57%) were given 40 mg/day dose and 177 (33.71%) were given 80 mg/day dose. (figure 7)



**Figure 7- use of atorvastatin in different doses**

Drugs for main indication in post- acute coronary syndrome are utilized in following percentages- aspirin in 100% patients, clopidogrel-prasugrel in 98.29% patients, beta blockers in 86.86% patients, ACE inhibitors/angiotensin receptor blockers in 87.43% patients and atorvastatin in 100% patients. (figure 8)



**Figure 8- percentage of use of 5 drugs for main indication in post acute coronary syndrome patients**

Use of nicorandil (6.86% patients), cilostazole (9.71%), calcium channel blockers (17.71%, amlodipine and diltiazem), spironolactone (17.14%), diuretics (16%, thiazide and loop diuretics), proton pump inhibitors (78.29%), H2 receptor blockers (16%), anxiolytics (39.43%), nitrates (31.43%) were noted also.

While comparing the average daily dose of the drug with WHO/ATC defined daily dose, it was found that the average prescribed daily doses of clopidogrel, ramipril, enalapril, telmisartan and atorvastatin are higher than their DDD but average prescribed daily doses of metoprolol, atenolol, carvedilol are lower than their DDD.(table 1)

**Table 1- difference between DDD of different drugs and their average prescribed dose in his centre**

Drug (ATC/DDD code)	Average Dose	DDD
Clopidogrel	103.45 mg/day	75 mg/day
Metoprolol (C07AB02)	38.94 mg/day	150 mg/day
Ramipril (C09AA05)	4.65 mg/day	2.5 mg/day
Atorvastatin (C10AA05)	48.59 mg/day	20 mg/day
Atenolol (C07AB03)	50 mg/day	75 mg/day
Carvedilol (C07AG02)	11.37 mg/day	37.5 mg/day
Enalapril (C09AA02)	6.15 mg/day	10 mg/day
Telmisartan (C09CA07)	47.27 mg/day	40 mg/day
Olmesartan (C09CA08)	40 mg/day	20 mg/day
Losartan (C09CA01)	50 mg/day	50 mg/day

Adverse drug reactions were noted and it included Prasugrel induced excess bleeding in 12 patients out of 84 receivers (14.29% incidence), ACE inhibitors induced dry cough in 16 patients out of 348 receivers (4.60%) beta blockers induced bradycardia, vertigo in 11 patients out of 456 receivers (2.41%).

## Discussion

In a similar study done at Saudi Arabia, it included 562 patients with the diagnosis of ACS, 407 (72.4%) were men and 155 (27.6%) were women. The age ranged from 26 to 100 years with an average  $60.6 \pm 13.7$  years and a median of 60 years. The majority of cases were Saudis (502, 89.3%). The distribution of diagnosis was unstable angina (UA) (307, 54.6%), ST-elevation myocardial infarction (190, 33.8%), and non-ST-elevation myocardial infarction (65, 11.6%). More than half of the patients (287, 51.1%) were diabetic. Aspirin, clopidogrel, and statin therapies were given to the majority of patients (98.4, 82.6, and 89.3%, respectively). On the other hand,  $\beta$ -blockers and ACEI (or angiotensin 2 receptor blockers) were given to a less proportion of patients (69 and 59%, respectively).[11]

So there the uses of certain adjunctive pharmacotherapies, specifically  $\beta$ -blockers (69%) and ACEI (or angiotensin 2 receptor blocker) (59%) for patients admitted with ACS were not optimum and underutilized. This does not achieve a high level of care compared with what is recommended in international guidelines. These pharmacotherapies have an important role in improving survival on such patients, as documented by several studies. On the other hand, the uses of other adjunctive pharmacotherapies, specifically aspirin, clopidogrel, and lipid-lowering therapy (statin) (98.4, 82.6, and 89.3%, respectively) were optimal and in concordance with the international recommended guidelines.

The underutilization of  $\beta$ -blockers and ACEI can reflect on patient's survival. Such underutilization is a multi-factorial problem and may stem from misperceptions regarding drug safety profile or from concerns about adverse effects. Other reasons may be related to patient's compliance with treatment and physician's attitude in complying with the evidence-based practice. Such a gap in practice resulting from underutilization of adjunctive pharmacotherapies has been reported in different studies, where similar observation was noticed (in the Estonian experience underutilization of such an important adjunctive therapy was recognized) and found that only 40% of their patients were treated by combinations of  $\beta$ -blockers, ACEI/angiotensin 2 receptor blockers, and statin.

Another study from Spain showed underutilization of adjunctive pharmacotherapies after myocardial infarction in a primary care setting, where  $\beta$ -blockers were prescribed in only 50.2% of cases, ACEI in only 32.5% of cases, and lipid-lowering therapy in only 52% of cases.[12]

A study of drug utilization pattern in patients of unstable angina, done at tertiary care centre in southern India [13] showed more than 95% of the patients received antiplatelet agents and more than 90% received hypolipidemics within 24 hours of hospital admission as well as on discharge. The combination of clopidogrel plus aspirin has been shown to confer a 20% reduction in cardiovascular death, MI, or stroke as compared to aspirin alone, in both low and high-risk patients with UA/NSTEMI.[14] For secondary prevention, clopidogrel alone is at least as effective as or modestly more effective than aspirin.[15] In their study, 70.4% of the patients within 24 hours of admission and 66.3% of the patients at the time of discharge were prescribed a dual antiplatelet therapy of aspirin and clopidogrel. Atorvastatin was by far the most commonly used hypolipidaemic agent in our study, being prescribed in 88.7% and 91.7% of the patients within 24 hours of admission and at discharge respectively. These prescription rates are much

higher than those reported by the CRUSADE (59.65% for statins on discharge) or CREATE investigators (53.9% for hypolipidaemics during hospitalization).[16-17]

Among the beta blockers, metoprolol was most commonly prescribed. The Create investigators reported the use of beta blockers in 61.9% of the NSTEMI patients. Various studies have reported the use of beta blockers ranging from 44.7% to 81.6%.[16-18]

Another drug utilization in acute coronary syndromes associated with diabetes and hypertension was done in Princess Esra, a tertiary hospital in Hyderabad, India in 2010 involving 140 patients and it showed use of Antiplatelet drugs in 94.20% patients, beta blockers in 60% patients (mostly metoprolol), Calcium channel blockers & Misc. antianginal drugs in 52.86% patients, ACE Inhibitors in 45.71%, AT II antagonists in 24.29% patients.(19)

In our study, In Department of Cardiology, ICVS, R.G. Kar Medical College, Kolkata, the drugs for post acute coronary syndrome patients were utilized optimally with Drug utilization rates in all study subjects stands at Aspirin 100%, Atorvastatin 100%, clopidogrel/ prasugrel 98.29%, beta blockers 86.86% (mostly metoprolol), ACEI/ARB 87.43% (mostly ramipril) with DU 90% conforms to standard treatment guideline (AHA/ACC guideline 2007). Among some patients who were not prescribed beta blockers or ACE inhibitors/ARB or clopidogrel/prasugrel had some contraindication or adverse effects of those drugs.

Despite adequate utilization, it has been seen that the average prescribed daily dose of atorvastatin, clopidogrel and ACE inhibitors/ARBs are higher than their WHO/ATC defined daily dose and that of beta blockers are lower than their WHO/ATC defined daily dose. In a meta-analysis shows early, intensive statin therapy reduces death and CV events after four months of treatment.(20) Early and intensive statin therapy started within 14 days of hospitalization for acute coronary syndrome significantly reduces death and cardiovascular events, according to the results of another pooled analysis of trials examining high-dose therapy. The benefit, say investigators, begins at four months but is sustained for two years, resulting in a 19% reduction in the risk of death and cardiovascular events. Though in many previous study has shown that clopidogrel in 150 mg/day dose does not provide more benefit than 75 mg/day dose after acute coronary syndrome, in another recent study, for patients undergoing percutaneous coronary intervention, the 150-mg/day clopidogrel maintenance dose is associated with stronger platelet inhibition, improvement of endothelial function, and reduction of inflammation, compared with the currently recommended 75-mg/day regimen; those effects might have a role in the clinical benefit observed with clopidogrel and may provide the rationale for using the higher maintenance regimen in selected patients.(21)

## Conclusion

DU 90% is achieved in this centre's drug use as per AHA/ACC 2007 guidelines but the average doses of some drugs are different from DDD. Use of Aspirin, clopidogrel, beta blockers, statins, ACE inhibitors/ ARBs are satisfactory. The small percentages of patients who were not given all the drugs had some contraindications or adverse effects due to that drugs.

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