Cross-sectional, Case Cohort, Observational Study to Assess Drug Utilization of Rosuvastatin, Clopidogrel, and Aspirin Fixed-dose Combination in Indian Patients with Stable Acute Coronary Syndrome – R-GOLD Study

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Abstract

Background: Atherosclerotic cardiovascular disease is one of the most common causes of mortality and morbidity globally. As cardiovascular diseases are usually having multiple mechanisms in their pathogenesis and frequent presence of co-existing risk factors, the choice and role of fixed dose combinations (FDCs), whenever suitable, are advised with rationality.

Objective: The objective of this study was to assess the prescription pattern of fixed-dose drug combinations (FDCs) of rosuvastatin, clopidogrel, and aspirin in Indian patients with the acute coronary syndrome (ACS) and in post-coronary intervention. This study was also aimed to evaluate the prevalence of comorbid conditions and co-prescribed drugs with FDC of rosuvastatin, clopidogrel, and aspirin.

Subjects and Methods: RGOLD was a cross-sectional and observational study in which total of 13,410 patients with ACS and post-coronary intervention were enrolled across India from Jul-2018 to Jul-2019 and data were collected retrospectively. Patient information, including demography, medical history, and treatment details, was collected retrospectively by 457 clinicians using a structured data collection form. Our primary aim was to assess cardiac medication use at discharge, defined as dual antiplatelet therapy (aspirin and P2Y12 inhibitor) and statin therapy as FDC.

Results: Baseline demographics, mean age 57.7±11 years, gender 76.7% males and 23.3% females, mean height 163.9±9.9 cm, and mean weight 73.1±11.7. Most patients were having a family history of ACS (66.6%) and risk factor of high blood cholesterol (55.9%). Most patients (41.9%) were prescribed FDC of rosuvastatin, clopidogrel, and aspirin for the treatment of unstable angina/ACS. Rosuvastatin 10 mg+ clopidogrel 75 mg+ aspirin 75 mg dose (77.6%), 1–3 years (41.8%) of treatment duration, and evening time of dosing (51.2%) of FDC of rosuvastatin, clopidogrel, and aspirin were observed to be common among study patients. Hypertension (72.6%), diabetes (51.8%), and obesity (33.6%) were common comorbid conditions, while anti-hypertensive drugs (75.5%), anti-diabetic drugs (46.9%), and lipid-lowering drugs (41.4%) were commonly co-prescribed drugs for comorbid conditions.

Conclusion: Usage pattern of FDC of rosuvastatin, clopidogrel, and aspirin for the treatment of ACS and in post-coronary intervention can be well defined by this study concluding rosuvastatin 10 mg plus, clopidogrel 75 mg plus, and aspirin 75 mg dose, 1–3 years treatment duration and evening time of dosing as common practice. Hypertension was common comorbid conditions, while anti-hypertensive drugs were commonly co-prescribed drugs for comorbid conditions.

Key words: Acute coronary syndromes, Clopidogrel and aspirin, Fixed-dose combinations of rosuvastatin, Observational study

INTRODUCTION

The care of patients presenting with acute coronary syndromes (ACS) has changed dramatically over the past several years, with the latest treatment guidelines adopting an aggressive approach using early coronary angiography in conjunction with the use of multiple pharmacologic agents.
ACS represents a continuum of acute myocardial ischemia, spanning from acute transmural infarction with ST-segment elevation to unstable angina (UA) characterized by minimal myocardial ischemia. Ischemic heart disease is the leading cause of death globally. India has the highest burden of coronary artery disease (CAD). The CAD has resulted in 3 million deaths annually, accounting for 25% of all mortality in India.\(^1\)

The pathophysiology of ACS in most patients involves atherosclerotic plaque rupture with superimposed thrombus development resulting in limitation or interruption of coronary blood flow. Thrombin and platelets play a fundamental role in thrombus formation, resulting in ACS.\(^2\)

The goal of health care providers in managing patients with this type of ACS is to treat within the 1st h of the onset of symptoms.\(^3\) Percutaneous coronary intervention (PCI) can restore flow of blood into the myocardium in more than 90% of patients if performed by a skilled provider at a proficient PCI facility with a “door-to-balloon” time of <90 min.\(^4\)\(^5\)

Anti-thrombotic therapy is the cornerstone of treatment for patients with ACS. It has four components: (1) Anti-platelet therapy includes oral anti-platelet agents such as aspirin, clopidogrel, ticagrelor, or prasugrel, intravenous anti-platelet drugs (glycoprotein IIb/IIIa inhibitors). (2) Anticoagulant therapy includes unfractionated heparin, low molecular weight heparins, fondaparinux, and bivalirudin. (3) Fibrinolytic drugs include streptokinase, t-PA, and reteplase tenecteplase.\(^6\)\(^7\) (4) Long-term therapy with statins (for at least 1 year) has been shown to reduce the risk of heart attack, stroke, and all-cause mortality in patients with and without established coronary heart disease (CHD).\(^7\)

ADP binding to the platelet P2Y12 receptor plays an important role in platelet activation and aggregation, amplifying the initial platelet response to vascular damage. The antagonists of the P2Y12 receptor are major therapeutic tools in ACS. Clopidogrel is an ADP receptor antagonist, selectively and irreversibly inhibits ADP receptor and prevents platelet activation. It is widely used in ACS or recent myocardial infarction (MI).\(^8\)

Several lipid-altering therapies have been shown to benefit patients at risk for CHD, lowering of low-density lipoprotein (LDL) cholesterol with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, rosuvastatin has shown the most striking results. Lowering of LDL-C levels is thought to be the main beneficial effect of statin treatment; although, effects on HDL-C and other lipoproteins also play a role.\(^9\)

Current guidelines recommend dual antiplatelet therapy that includes aspirin and the platelet P2Y12 ADP receptor antagonist clopidogrel after PCI. Statin use after PCI improves safety and effectiveness.\(^10\) A recent meta-analysis of six randomized clinical trials concluded that statin therapy reduces the risk of MI after elective PCI, but not necessarily mortality or repeat revascularization.\(^11\)

Large-scale randomized clinical trials have supported the use of early coronary angiography in high-risk patients with ACS, as well as the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) as an effective treatment in patients with CAD and especially those hospitalized with ACS.

The prevalence rate of risk factors for CVD has been rapidly rising within India. The annual number of deaths from CVD in India is projected to rise from 2.26 million (1990) to 4.77 million (2020). As cardiovascular diseases are usually having multiple mechanisms in their pathogenesis and frequent presence of co-existing comorbidities, clinicians have to prescribe multiple drugs. Multiple drug therapy is associated with poor patient compliance and adherence to treatment, so practically, it is not a successful strategy. Thus, concomitant use of two or more drugs as fixed-dose combinations (FDC), whenever suitable, is advised with rationality. Rational use of drugs as defined by the World Health Organization (WHO) depends on making the correct diagnosis and prescribing appropriate drugs in adequate doses.\(^12\)

Globally more than 50% of drugs are prescribed, dispensed, or sold inappropriately. The market is flooded with fixed-dose ratio combinations of various drugs, though only a few FDCs are rational combinations and are approved by the world health organization. Irrational prescription of drugs has become common in clinical practice due to a lack of knowledge about drugs and also unethical drug promotion. Irrational use of drugs can lead to the high cost of medical treatment, increased incidence of adverse drug events and drug misuse.\(^12\)

Hence, this non-interventional, retrospective, cross-sectional, and observational drug utilization study was planned with an objective to assess the usage pattern of Rosuvastatin, clopidogrel and aspirin combination treatment in ACS cases undergoing elective coronary intervention from multiple sites in India.

**SUBJECTS AND METHODS**

**Review Process**

All ethical approvals for the study was obtained before the start of the trial. The protocol and data
collection form (DCF) were reviewed and approved by a central independent institutional ethics committee. Four hundred fifty-seven outpatient settings or clinics located across India participated in this observational study.

This study was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonisation—Good Clinical Practice guidelines while ensuring patient confidentiality during transcription of the patient records on the DCFs provided for the study. This was a retrospective drug utilization study conducted with the analysis of the accessed successive completed records as per the study protocol which is reviewed and approved by IEC while redacting the patient identifiers for the transcription of the data variables.

**Patient Population and Recruitment**

Patients enrolled in this study had to be at least 18 years old and alive at the time of hospital presentation, be admitted for ACS as a presumptive diagnosis (i.e., have symptoms consistent with acute ischemia), and have at least one of the following: UA, non-ST-elevation MI (NSTEMI), and STEMI who can undergo either PCI or CABG.

All patients who met all of the following criteria were considered for enrollment in the study: (A) Male or female patients 18 years and above (B) patients diagnosed with ACS and post-coronary intervention and treated with FDC of rosuvastatin, clopidogrel, and aspirin [Figure 1].

**Study Design**

This was a cross-sectional study in patients prescribed FDC of rosuvastatin, clopidogrel, and aspirin for the treatment of ACS and post-coronary intervention across India to evaluate the pattern of utilization. This study was conducted between Jan-2018 to Jul-2018 and data were collected retrospectively.

**Details of the Study Products**

Rosuvastatin 10 mg/20 mg + aspirin 75 mg + clopidogrel capsules 75 mg was prescribed for the treatment of ACS, MI, stroke, and angina.

**Data Collection**

To ensure the enrollment of an unbiased population, the first 30–50 consecutive patients (depending on each site’s patient throughput) were recruited from each site per month.

A total of 457 clinicians participated in the study from different regions of India to collect large patient population data. All participating clinicians were provided paper-based data collection form (DCF) by sponsor. All DCFs were filled by respective doctors based on the data available with their medical records and completed DCFs were collected by the sponsor. Once completed DCFs were collected, they were converted from paper to electronic form with manual data entry. With the completion of data entry, data quality checks were performed by different logic checks and extreme/missing values. After ensuring quality of the data, it was further considered for the analysis. Data transcription and analyses were carried out by an independent agency after redacting patient identifiers.

**Statistical Analysis**

This drug utilization surveillance study was conducted with a sample size of 15,000 cases as retrospective cohort analyses of the prescription records containing FDC of rosuvastatin, aspirin, and clopidogrel from 457 centers across India. Per protocol analyses for 13,410 cases were carried out while assessing the records for complete details on baseline demographics, rosuvastatin/aspirin/clopidogrel FDC posology, common adverse drug reaction rate, and clinical indication as UA, NSTEMI, and STEMI before undergoing intervention as PCI or CABG.

Descriptive statistics were employed to describe the demographic variables while the continuous and categorical

![Figure 1: Patient disposition chart for cases receiving fixed-dose combination of rosuvastatin/aspirin/clopidogrel with diagnosis of stable acute coronary syndrome](image-url)
variables were analyzed with appropriate statistical methods utilizing Students’s T and Fischer’s exact test.

All statistical analyses were performed using validated SPSS software (version 20, SPSS Inc., Chicago, Ill., USA.

RESULTS

A total of 13,410 patients with a diagnosis of UA or NSTEMI or STEMI were included in this analysis. However, missing values for a particular parameter were excluded and hence sum of all categories of any one characteristic may not come up to this number. As missing values vary with variables, total number will be different for different variables. Percentage mentioned in the results is valid percentages (excluding missing values).

Usage Pattern
Five thousand eight hundred sixty-eight (41.9%) patients were prescribed FDC of rosuvastatin, clopidogrel, and aspirin for UA, while 4836 (32.0%) and 2706 (13.8%) patients were prescribed it for NSTEMI and STEMI, respectively. Nine thousand five hundred five (77.6%) patients were prescribed 10 mg+75 mg+75 mg dose of FDC of rosuvastatin, clopidogrel, and aspirin, while 2738 (22.4%) patients were prescribed 20 mg+75 mg+75 mg dose of FDC of rosuvastatin, clopidogrel, and aspirin. Five thousand four hundred forty-four (41.8%) patients were having a treatment duration of 1–3 years, while 4756 (36.5%), 2146 (16.5%), and 680 (5.2%) patients were having treatment duration of <1 year, 3–5 years and >5 years, respectively. Six thousand five hundred nineteen (51.2%) patients were prescribed FDC of rosuvastatin, clopidogrel, and aspirin at evening, while 4036 (31.7%) and 2182 (17.1%) patients were prescribed it at morning and at afternoon, respectively. Summary of the usage pattern of FDC of rosuvastatin, clopidogrel, and aspirin is mentioned in Table 1 and Figure 2.

Demographic distribution
A total of 13,410 patients were enrolled in the study, of which 3068 (23.3%) were female and 10,112 (76.7%) were male. 0.5% patients were below 30 years of age while the frequency of patients in 30–44 years, 45–60 years, and >60 years age category was 10.5%, 50.8%, and 38.2%, respectively, and mean age, weight, and height of the study population were 57.7 years, 73.1 kg, and 163.9 cm, respectively. Summary of demographic distribution is shown in Table 2.

Patient Characteristics
Seven thousand eight hundred (66.6%) patients had a family history of ACS. Seven thousand four hundred ninety-eight (55.9%) patients had high blood cholesterol as a risk factor, while 5398 (40.3%), 4228 (31.5%), and 3475 (25.9%) patients had a risk factor of smoking, alcohol, and physical inactivity, respectively. Summary of the distribution of patient characteristics is mentioned in Table 3.

Prevalence of Other Comorbid Conditions
Nine thousand seven hundred forty-two (72.6%) patients were having hypertension as comorbid conditions, while 6950 (51.8%), 4505 (33.6%), and 324 (2.4%) patients were having diabetes, obesity, and chronic kidney disease CKD, respectively. Summary of distribution of comorbid conditions is mentioned in Table 4.

Drugs Co-prescribed with Rosuvastatin, Clopidogrel, and Aspirin FDC
Ten thousand one hundred nineteen (75.5%) patients were prescribed anti-hypertensive drugs for comorbid condition, while 6295 (46.9%), 5548 (41.4%), and 1659 (12.4%) patients were prescribed anti-diabetic drugs, lipid-lowering drugs, and anti-coagulants, respectively. Summary of distribution of co-prescribed drugs is mentioned in Table 5.

DISCUSSION

In 2000, Wald et al. first proposed the use of FDC therapy for CVD prevention in the form of polypill. FDCs have many potential advantages like improved patient compliance and adherence to treatment as well as more efficacy, minimal side effects, and low cost of therapy. A meta-analysis by Bangalore et al. showed that FDCs improve medication compliance.
Another study also supports the use of FDCs in the treatment of CVD, combination pharmacotherapy at low doses is likely to be more efficacious than high dose with a monotherapy. FDCs treat different ailments in the same patient at the same time and with one pill.

Another study published by Gari et al. in 2019 in Indian population shows that rosuvastatin+aspirin+clopidogrel combination is prescribed in 23% of CAD/diabetes, 33.33% CAD/diabetes/hypertension, 19% for CAD/hypertension, and 13% in CAD patients.

This observational study was the first of its kind in India to analyze the utilization pattern of FDC of rosuvastatin, clopidogrel, and aspirin for the treatment of ACS and post-coronary intervention. Demographic distribution, prevalence of other comorbid conditions, and co-prescribed drugs were also evaluated in this study. Higher proportion of male patients (76.7%) as compared to
females (23.3%) was observed in this study. Most patients (61.3%) were between 30 and 60 years of age with mean age, weight, and height for the study population of 57.7 years, 73.1 kg, and 163.9 cm, respectively.

Most patients were having a family history of ACS (66.6%) and risk factor of high blood cholesterol (55.9%). Most patients (41.9%) were prescribed FDC of rosuvastatin, clopidogrel, and aspirin for the treatment of UA. Rosuvastatin 10 mg+ clopidogrel 75 mg+ aspirin 75 mg dose (77.6%), 1–3 years (41.8%) of treatment duration, and evening time of dosing (51.2%) of FDC of rosuvastatin, clopidogrel, and aspirin were observed to be common among study patients.

Hypertension (72.6%), diabetes (51.8%), and obesity (33.6%) were common comorbid conditions, while anti-hypertensive drugs (75.5%), anti-diabetic drugs (46.9%), and lipid-lowering drugs (41.4%) were commonly co-prescribed drugs for comorbid conditions.

Strength and Limitation of Study
This was a cross-sectional observational study to understand the clinical role, usage, or positioning for the FDC of rosuvastatin/ aspirin/ clopidogrel in real-world outpatient settings for patients with stable post-ACS or UA cases wherein the use of FDC with a low-intensity statin can be explored further following at least 3 months of the intervention can be explored further through confirmatory randomized trials.

CONCLUSION
Multifactorial etiology of CVD justified the use of FDCs to increase treatment adherence as well as improve medication compliance by reducing the pill burden of patients. Usage pattern of FDC of rosuvastatin, clopidogrel, and aspirin for the treatment of ACS and in post-coronary intervention can be well defined by this study concluding usage of rosuvastatin 10 mg plus, clopidogrel 75 mg plus, and aspirin 75 mg dose, 1–3 years treatment duration, and evening time of dosing as common practice. Dyslipidemia was common comorbidity in only half of the cases, thereby highlighting the benefit or clinical role of statin for their complementary effects with the recommendation to reach new lipid targets or goal in such a high-risk population.

Further studies are needed to validate the efficacy and safety of FDCs involving low-intensity statin in stable cases of ACS patients who may have undergone elective surgery or intervention for revascularization, which is not included in the current study.

DISCLOSURE
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AUTHORSHIP
All named authors meet the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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