Observational study of ADR monitoring, safety and efficacy of clopidogrel with atorvastatin combination in cardiovascular diseases

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Abstract

Background

These days commonly used drug in cardiovascular problems is clopidogrel & atorvastatin, so the primary goal is to figure out the adequacy and any ADRs related to the treatment.

Objective

To evaluate the safety and efficacy of drugs, and also identifies the ADRs of drugs & their associated problems in cardiovascular disorder patients.

Methods

An observational study was conducted in the inpatient & outpatient unit of the cardiology department of RVM institutional, laxmakkapally for 6 months. The study shows 105 patients, including males and females diagnosed with cardiovascular disorders.

Results

The review contains 105 subjects. Out of them, 91 showed Doubtful ADRs (86.7%), 11 showed Possible ADRS (10.5%), and just 3 showed Probable ADRS (2.9%) None of them showed any Definite ADRs, and furthermore founded on the HS Troponin I mean contrast esteem (988.44) the medicine is protected and compelling in the therapy of CVS Disorder.

Conclusion

According to the Naranjo ADR probability scale and HS Troponin values the medication is demonstrated to be protected and more compelling in the treatment of CVS issues.

Keywords: ADR • CVS Disorder's • Naranjo ADR scale • HS Troponin I

Introduction

Cardiovascular Disease (CVD) is currently the leading cause of death worldwide [1]. Many CVD patients develop Acute Coronary Syndrome (ACS), a life threatening condition encompassing Myocardial Infarction (MI) with or without ST-Segment Elevation (STEMI/NSTEMI), or unstable angina [1]. Approximately 1.2 million ACS patients are being hospitalized in the United States every year for cardiovascular events [2]. Elevated platelet aggregation and subsequent thrombus formation play a critical role in the pathophysiology of these patients. As a consequence, safe and effective antiplatelet therapy is essential for reducing the high morbidity and mortality of this disease [3]. Clopidogrel is an important antiplatelet drug that is widely used to prevent vessel blockage in clinical settings such as cardiovascular and cerebrovascular diseases. Dual antiplatelet therapy with clopidogrel and aspirin has become the standard treatment for acute coronary syndrome and after Percutaneous Coronary Intervention (PCI).Additionally, clopidogrel is commonly used with statins to lower the blood lipid level and with Proton Pump Inhibitors (PPIs) to counteract gastrointestinal tract disturbances such as aspirin-induced bleeding.

The effects of clopidogrel on platelets vary among patients, with approximately 4% to 30% of patients being low responders or non responders and having an increased risk of ischemic events after stent implantation. The interaction between clopidogrel and other drugs may promote

ischemic events, as evidenced by emerging data that clopidogrel's effect on platelet function is altered by coadministration with statins or PPIs.

Clopidogrel (Plavix®), which was the second largest selling branded drug in the US in 2010 with $8.8 billion in sales, is an irreversible P2Y12 receptor antagonist indicated for reduction of arteriosclerotic events in patients with recent stroke or MI, and established peripheral arterial disease [4, 5]. Clopidogrel is a second generation thienopyridine that has largely replaced ticlopidine, a first generation thienopyridine with similar efficacy, due to improved tolerability, reduced incidence of haematological side effects, more rapid onset of action and a convenient (once-daily) dosing regimen [6]. In recent years, dual antiplatelet therapy with aspirin and P2Y12 receptor antagonists clopidogrel, prasugrel or ticagrelor has become the clinical gold standard for patients with ACS and/or undergoing Percutaneous Coronary Interventions (PCI) due to the significant improvement of long-term clinical outcome [1, 3, 7-9].

Although clopidogrel is safe and effective in many patients, there is substantial variability in treatment response between individuals [10]. Some of these patients continue to have cardiovascular events despite clopidogrel treatment [11]. This lack of efficacy has, in part, been attributed to the reduced response to clopidogrel in patients, resulting in High on-treatment Platelet Reactivity (HPR) and the development of atherothrombotic complications [3]. This relative non-responsiveness to clopidogrel therapy has been coined “clopidogrel resistance” and is thought to affect 5%-44% of patients receiving standard-dose clopidogrel treatment [11]. On the other hand, some patients also experience drug-induced bleeding due to excessive platelet inhibition [7].

CYP3A4 and CYP2C19 are the most important isozymes of cytochromeP450 (CYP450), which activates clopidogrel. Fat-soluble statins are mainly metabolized by CYP3A4, and most PPIs are metabolized by

CYP2C19. When clopidogrel is coadministered with fat-soluble statins or PPIs, a drug interaction may occur because of binding site competition. Our study is a prospective, randomized, controlled trial that assesses platelet function and the platelet activation index in plasma to evaluate drug interactions when clopidogrel is simultaneously coadministered with fat-soluble statins and PPIs, providing a reference for clinical practice.

Clopidogrel is an inactive pro-drug that requires enzymatic conversion into its active metabolite by a series of cytochrome P450 (CYP) enzymes [12]. Clinical evidence suggests that patients with deficient CYP2C19 activity (e.g. poor metabolizers or as a result of drug-drug interactions) have remarkably higher on-treatment platelet reactivity, which puts them at an increased risk of ischemic events following the standard dosing regimen, prompting the U.S. FDA to issue a boxed warning [13-16]. However, the results from a multivariate analysis of the Pharmacogenomics of Antiplatelet Intervention (PAPI) study revealed that CYP2C19 polymorphisms are responsible for about 12% of the between-subject variability in response to clopidogrel treatment, whereas age or Body Mass Index (BMI) accounted for 3.8% and 2.3% of the variability, respectively [14]. Similar findings have been reported from other studies, which all indicate that, in addition to CYP2C19 polymorphism, multiple demographic and disease risk factors contribute to the interindividual variability in response to clopidogrel treatment [15–19]. However, the underlying mechanisms related to each of these intrinsic and extrinsic factors are not yet fully understood. It should be noted at this point though that the also the assays that have been used to determine the response to clopidogrel treatment are subject to substantial between-assay variability.

This prospective, randomized, nonblind, controlled trial evaluated the effects of clopidogrel on platelet function upon coadministration with atorvastatin and lansoprazole.

One hundred four adult patients with non-ST-segment elevated acute coronary syndrome (NSTE-ACS) who underwent Percutaneous Coronary Intervention (PCI) with drug-eluting stent implantation were included. All patients were treated with standard Dual Antiplatelet Therapy (DAPT) plus rosuvastatin 10mg daily after the operation. On the sixth day after PCI, patients were randomly divided into 4 groups, Group A: DAPT+atorvastatin 20 mg daily (a change from rosuvastatin to atorvastatin)+lansoprazole 30 mg daily, Group B: DAPT+atorvastatin 20 mg daily (a change from rosuvastatin to atorvastatin), Group C: DAPT+lansoprazole 30 mg daily (continuing to take rosuvastatin), Group D is the control group.

Additional drugs were used according to the situation of patients. Platelet function and concentrations of platelet activation markers (granular membrane protein 140 (P-selectin), Thromboxane B2 (TXB2), and human soluble

cluster of differentiation 40 ligand (sCD40L)) were assessed before randomization and at 15- and 30-day follow-up visits. All patients were maintained on treatment for 6 months and observed for bleeding and ischemic events.

A total of 104 patients were enrolled, 27 patients in group A, 26 patients in Group B/C, 25 patients in Group D separately, and all the patients were analyzed. There were no differences in platelet function and the levels of platelet activation markers (P-selectin, TXB2, and sCD40L) among or within the 4 groups at the 3 time points of interest (P>0.05). In the subsequent 6 months, no significant bleeding events occurred, and 12 patients experienced ischemic events, these results were also not significantly different among the groups (P>0.05).

In patients diagnosed with NSTE-ACS who have had drug-eluting stent implantation, simultaneously administering clopidogrel, atorvastatin, and lansoprazole did not decrease the antiplatelet efficacy of clopidogrel or increase adverse event frequency over 6 months.

Methodology

Study design

It is a proposed research study and the subjects involved are the patients visiting RVM hospital, diagnosed with CVS disorder and are on treatment with antiplatelets along with statins class of drugs for the disease and related symptoms.

Study protocol

It's a proposed review study conducted for a period of months and about 105 patients, who met the study criteria were incorporated into the research. The required data was poised from the patients through respective case sheets, patient caregivers, and patients. The acquired data was estimated o the respective data collection form.

Inclusion criteria

- Patients who are diagnosed (old and new cases) with CVS disorders.
- Either gender of all categories objects are considered.
- Patients with other chronic diseases.
- Patients started with a drug (as a monotherapy in combination) are considered.
- Patients on regular follow-ups.

Exclusion criteria

- Patients not had given their consent.
- Lactating and pregnant women.
- Patients with diagnosis uncertainty.

Materials

- To assess the acuteness of ADRs in patients associated with CVS disorders on therapy with atorvastatin and clopidogrel.
- We are using the standard scale. Naranjo Algorithm or ADR probability scale.

Collection of data

Case sheets, patient caregiver, and patients.

Ethical committee approval

The ML was diagnosed using the USG abdomen and Wong Bakers' pain scale.

The Institutional Human Ethical Committee of GCPK approved the study. The code is given-GCPK/IEC/NOV2021-22/B05.

Results & Statistical Analysis

Descriptive statistics and graphical presentation of data analysis on "Observational Study of ADR Monitoring, Safety and Efficacy of Clopidogrel with Atorvastatin Combination in Cardiovascular Diseases." Values are stated as Frequency, percentage, mean and SD. Comparison of mean HST values Before and study groups by using the paired Student t-test. P<0.05 was contemplated significant in results. SPSS statistical software, version 22, was used for all statistical analyses.

Discussion

An Aggregate of 105 cardiovascular disorder patients was monitored when taking a mixture of clopidogrel and atorvastatin. Out of 105 patients, 91 doubtful adverse reactions were identified and the remaining patients showed 11 possible and 3 probable adverse reactions no definite adverse reactions information was gathered by using the Naranjo Adverse reaction scale. The HS-Troponin I t-value shows a crucial variance allying prior to following the use of medication within the patients.

Cardiovascular disorders distribution

The most widely recognized CVD determined is CAD to have HTN (46) trailed by the AWMI (23) though the least CVD analyzed is CAG (5).

Gender Distribution

Out of 105 cases, males were more affected with

TABLE 1. Cardiovascular disorders distribution.	
Diagnosis	**Frequency**
CAD(HTN, DM)	46
CAD(VD)	16
CAD(ACS)	18
MI	15
AWMI	23
CAG	5

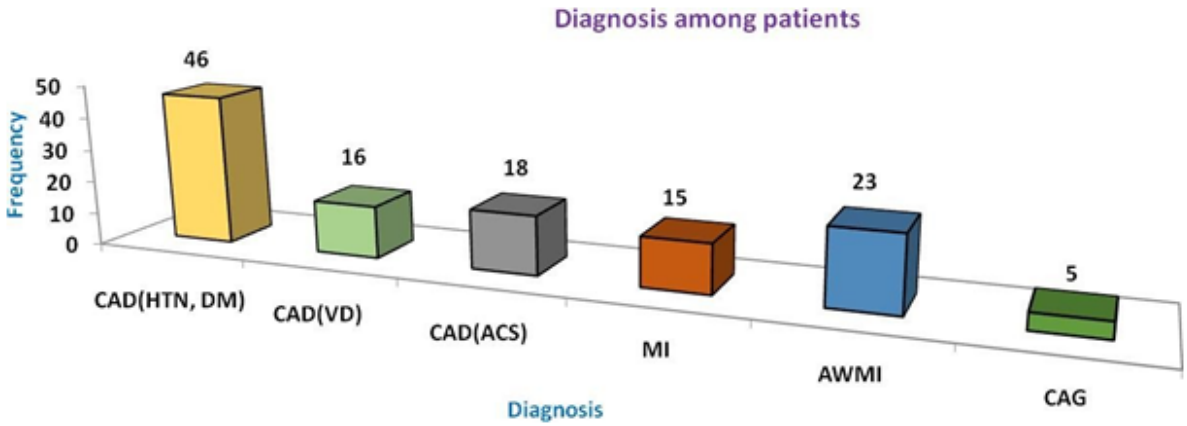

FIGURE 1. Diagnosis among patients

TABLE 2. Gender distribution.		
Gender	**Frequency**	**Percent**
Male	56	53.3
Female	49	46.7
Total	105	100

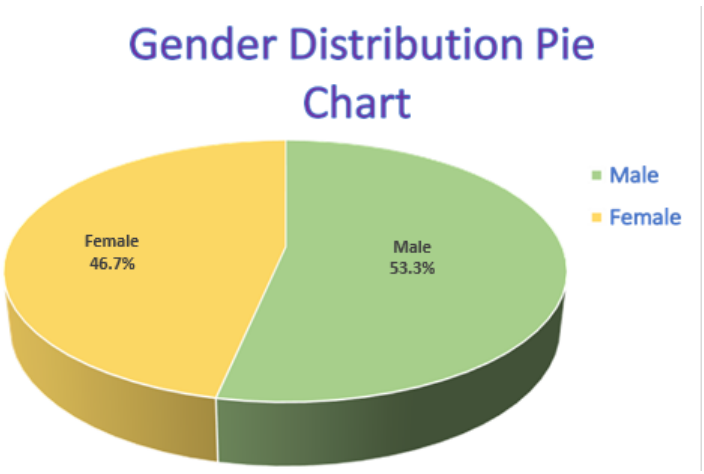

FIGURE 2. Gender distribution pie-chart

cardiovascular disorders compared with females.

■ Age distribution

Inside the gathered 105 cases, we have observed higher cases are falling in the age group over 60 years, following that between 51 years-60 years age group. The least cases kept in ages between 20 years-30 years.

■ Lab parameter distribution

Outlook of Lab parameter, We uncover that the Age group equivalent to or more 53 years is impacted the most. Additionally parameters like HST, UR, and K+ are showing tremendous changes in impacted cases.

■ HS-Troponin I distribution

TABLE 3. Age distribution		
Age(years)	**Frequency**	**Percent**
20 – 30	7	6.7
31 – 40	19	18.1
41 – 50	15	14.3
51 – 60	28	26.7
>60	36	34.3
Total	105	100

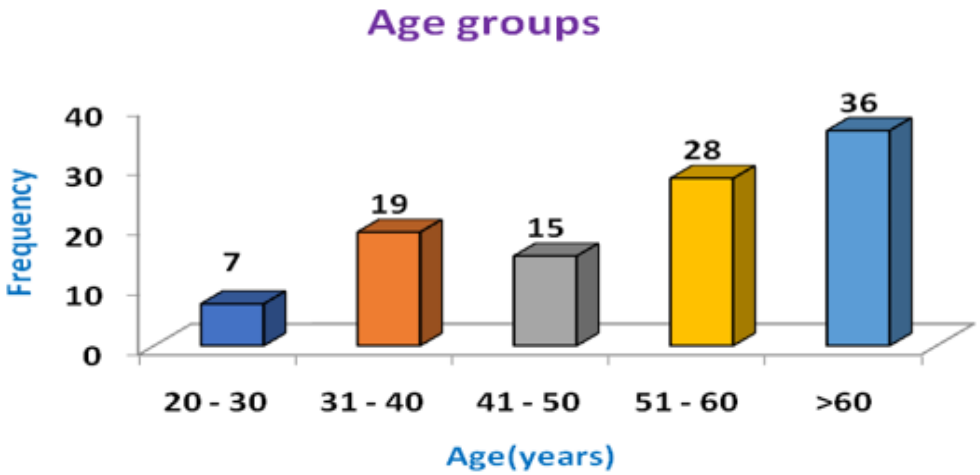

FIGURE 3. Age groups.

TABLE 4. Lab parameter distribution					
Parameter	**No. Of Cases**	**Minimum**	**Maximum**	**Mean**	**SD**
Age	105	20	87	53.28	15.77
SBP	105	80	200	121.82	22.32
DBP	105	40	890	89.58	80.46
PR	105	35	134	81.47	13.59
HB	105	5	19	11.94	2.49
BHST	105	0	26678	1511.73	4555.6
AHST	105	0	8562	523.3	1395.28
CR	105	0	11	1.52	1.1
UR	105	0	118	37.45	22.25
Na+	105	112	190	138.05	10.91
K+	105	2	45	7.44	10.4
CL	105	88	190	104.64	11.66

TABLE 5. HS-Troponin I distribution.				
HST	**Mean**	**Mean difference**	**t-value**	**Significance**
Before	1511.73±4555.60	988.44	3.17	0.002*
After	523.3±1395.28			

The HS-Troponin I mean qualities show the viability of the medication. P<0.05; mean ADR values are statistically significant between prior and After by using paired Student t-test.

■ Naranjo ADR scale distribution

In view of the Naranjo, Adverse reactions Scale score the greater number of the cases fall under Doubtful Adverse reactions however no Definite Adverse reactions were recorded.

The study enrolled 105 participants who met the trial's requirements.

- Cases with Hypertension and Type 2 Diabetes mellitus are sure to develop a coronary artery disease than those with myocardial infarction, with coronary angiography being the least common **(TABLE 1 and FIGURE1)**.
- Gender based on Pie graphical portrayal Males is overwhelmed by cardiovascular disorders than females **(TABLE 2 and**

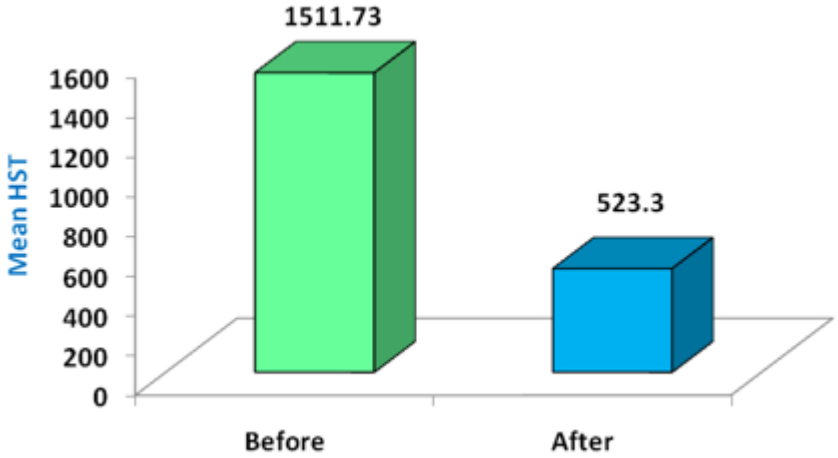

FIGURE 4. Mean HST.

TABLE 6. Adverse reactions of individual drugs.		
Clopidogrel	**Atorvastatin**	**CLOPINOL-AT(clopidogrel+atorvastatin)**
Nose bleeds	nasopharyngitis, arthralgia.	bleeding, rash, diarrhea
itching	diarrhea, pain, UTI.	Insomnia
tarry stools	Among the most solemn adverse effects include myopathy,	loss of appetite
pain swelling	liver enzyme abnormalities	abdominal pain.
vomiting	rhabdomyolysis.	In some instances, it is feasibly possible. Bruising.

TABLE 7. Naranjo ADR scale distribution		
ADRS	**Frequency**	**Percent**
Doubtful	91	86.7
Possible	11	10.5
Probable	3	2.9
Definite	0	0
Total	105	100

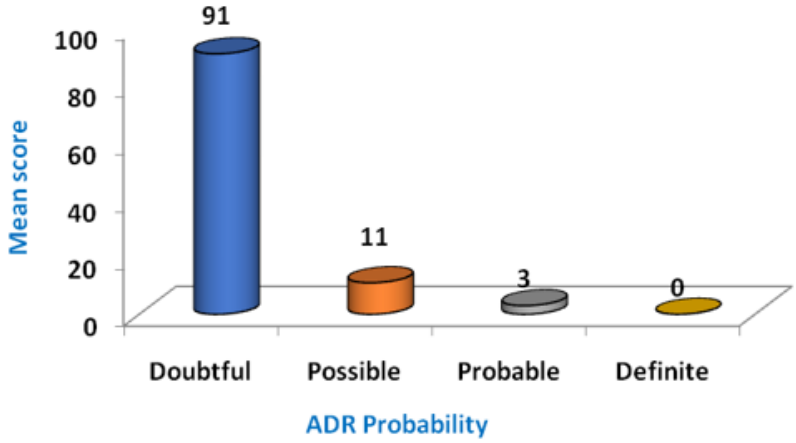

FIGURE 5. ADR probability.

FIGURE 2).

- With a 10-year class intervals, patients with separate age groups. Cardiovascular issues are greater familiar in people over 60 years old, followed by 51years-60 years and 20 years -30 years at least has the lowest risk **(TABLE 3 and FIGURE 3)**.
- Using laboratory parameters The cardiac biomarker HS-Troponin I shows a high sensitivity when diagnosing cardiac damage **(TABLE 4)**.
- In impacted situations, additional indicators like Urea Potassium and Creatinine show significant alterations.
- HS-TROPONIN I in a short time after a cardiac attack, the foremost extensively

utilized biomarker with the best-known sensitivity enters the bloodstream. Troponin I is present only in cardiac muscle, whereas Troponin T can be detected in both cardiac and skeletal musculus **(TABLE 5 and FIGURE 4)**.

- TROPONIN I relates to the cardiac muscle in a very precise way and remains significantly higher than creatinine kinase for a long time (CK-MB). Creatinine kinase (CK-MB) is found in cardiac muscle, brain (CK-BB), and skeletal musculus (CK-MM). Vigorous exercise and deep intramuscular injections can cause CK levels to rise. CK-MB occasionally generates false-positive results.
- ADRS of individual drugs like Clopidogrel – Nose bleed, itching, vomiting, swelling, etc. Atorvastatin- nasopharyngitis, arthralgia, diarrhea, pain, UTI. Clopinol-AT- Insomnia, bleeding, rash, diarrhea, abdominal pain **(TABLE 6 and FIGURE 5)**.
- ADRS were documented and formed on the NARNJO SCALE. Taking age and habits into account, we discovered that the symptoms the patients had coalesced to other cases such as chest discomfort and jaw pain owing to a stomach condition, in addition to trauma, which were the most typical reasons in ADR DOUBTFUL cases. Other than age and habits, only PROBABLE instances of ADRs are reported when patients are prescribed medicines for insomnia, lack of appetite, heartburn, or abdominal pain.

Conclusion

- The study reveals the evaluation of ADRs associated with Clopinol-AT
- Based on HS-TROPONIN I values obtained by using paired student t-test the Drug Clopinol-AT (Clopidogrel + Atorvastatin) Combination therapy manifests to be peculiarly implicit in the therapy of cardiovascular issues.
- Clopinol-AT (clopidogrel + Atorvastatin) show extremely less Adverse Reactions.
- In light of our survey Clopidogrel and atorvastatin in combination turned out to be intimate and further productive in the therapy of Cardiovascular problems with a less unfavorable response

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