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Original Research Article

Open-Label Randomized Controlled Trial to Assess the Efficacy and Safety of Triple Therapy With Aspirin, Clopidogrel, and Rivaroxaban Versus Dual Therapy With Aspirin and Clopidogrel in Patients With Acute Coronary Syndrome

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Abstract: *Acute coronary syndrome (ACS) is a significant contributor to cardiovascular morbidity and mortality. This study aimed to evaluate the efficacy and safety of triple therapy with aspirin, clopidogrel, and rivaroxaban compared to dual therapy with aspirin and clopidogrel in patients with ACS.* ***Methods:*** *This open-label, randomized controlled trial was conducted at the Punjab Institute of Cardiology from May 2024 to October 2024. Ninety patients with ACS were randomized into two groups: the triple therapy group (n=45) receiving aspirin (75–100 mg daily), clopidogrel (75 mg daily), and rivaroxaban (2.5 mg twice daily), and the dual therapy group (n=45) receiving aspirin (75–100 mg daily) and clopidogrel (75 mg daily). The primary efficacy outcome was the incidence of major adverse cardiac events (MACE), including recurrent myocardial infarction, ischemic stroke, and cardiovascular death, assessed over three months. The primary safety outcome was the incidence of bleeding events, categorized according to the Bleeding Academic Research Consortium (BARC) classification. Secondary outcomes included medication adherence and quality of life, as measured by the EQ-5D.* ***Results:*** *At three months, the incidence of major adverse cardiovascular events (MACE) was lower in the triple therapy group (6.7%) compared to the dual therapy group (15.6%). However, the difference was not statistically significant ($p = 0.18$). Minor bleeding was more common in the triple therapy group (13.3% vs. 4.4%, $p = 0.14$), while significant bleeding was rare (2.2% vs. 0%, $p = 0.31$). Quality of life scores were comparable between groups (76.2 ± 6.8 vs. 74.5 ± 7.2, $p = 0.28$). Adherence rates were high in both groups (93.3% vs. 95.6%, $p = 0.71$).* ***Conclusion:*** *Triple therapy demonstrated a trend towards reduced MACE compared to dual therapy but was associated with an increased risk of minor bleeding. These findings highlight the need for individualized therapy in patients with ACS, particularly in the Pakistani population. Further large-scale studies are recommended to validate these results.*

Keywords: Acute Coronary Syndrome, Triple Therapy, Dual Therapy, Rivaroxaban, Aspirin, Clopidogrel, Pakistan

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Introduction

Acute coronary syndrome (ACS) is a spectrum of conditions that includes unstable angina, non-ST elevation myocardial infarction (NSTEMI), and ST elevation myocardial infarction (STEMI). It is a leading cause of morbidity and mortality worldwide. The condition arises from the rupture of an atherosclerotic plaque in a coronary artery, leading to the formation of a thrombus that obstructs blood flow and results in myocardial injury. In Pakistan, cardiovascular diseases, including ACS, are a significant public health burden, contributing to high mortality rates among adults. Despite advances in medical therapies, ACS remains a considerable challenge, necessitating further investigation into optimal therapeutic strategies (1).

Current management of ACS involves antiplatelet therapy to reduce the risk of thrombosis and improve patient outcomes. Dual antiplatelet therapy (DAPT), consisting of aspirin and clopidogrel, has been the standard of care for ACS patients for several years. However, recent studies have explored the potential benefits of triple therapy, which adds a direct factor Xa inhibitor, such as rivaroxaban, to DAPT. Triple therapy has been shown to reduce thrombotic events, such as recurrent myocardial infarction and ischemic stroke, but it may increase the risk of bleeding complications. Balancing efficacy and safety remains a challenge in the management of ACS, particularly in high-risk populations (2,3).

Rivaroxaban, an oral anticoagulant that inhibits factor Xa, has shown promise in clinical trials for preventing adverse thrombotic events in ACS patients. Studies such as the *Pioneer AF-PCI* trial and the *TraX* trial have demonstrated that rivaroxaban can reduce the incidence of ischemic events without significantly increasing the risk of significant bleeding. However, the comparative efficacy and safety of triple therapy with rivaroxaban versus dual therapy with aspirin and clopidogrel in ACS patients remain under investigation, particularly in the South Asian population, where genetic and environmental factors may influence treatment outcomes (4, 5).

The present study aims to evaluate the efficacy and safety of triple therapy (aspirin, clopidogrel, and rivaroxaban) compared to dual therapy (aspirin and clopidogrel) in patients with ACS. The primary efficacy endpoint of this study is the incidence of major adverse cardiac events (MACE), including recurrent myocardial infarction, ischemic stroke, and cardiovascular death. The primary safety endpoint is the incidence of bleeding events, categorized according to the Bleeding Academic Research Consortium (BARC) classification. Secondary outcomes include medication adherence and quality of life, measured by the EQ-5D scale. This study will contribute to the growing body of evidence on the optimal antithrombotic strategy in ACS patients and provide valuable data for clinical decision-making in this high-risk population.

Methodology

The study was designed as an open-label randomized controlled trial to assess the efficacy and safety of triple therapy with aspirin, clopidogrel, and rivaroxaban compared to dual therapy with aspirin and clopidogrel in patients diagnosed with acute coronary syndrome (ACS). The trial was conducted at the Punjab Institute of Cardiology from May 2024 to October 2024. A total of 90 patients were enrolled and randomly assigned into two groups using a random number generator: the triple therapy group (n = 45) and the dual therapy group (n = 45). The inclusion criteria for the study included adult patients aged 18 years or older who had been diagnosed with acute coronary syndrome (ACS). Patients with contraindications to any of the study medications, those with a history of significant bleeding, and those with advanced liver or renal disease were excluded from the study.

The patients in the triple therapy group received aspirin (75–100 mg daily), clopidogrel (75 mg daily), and rivaroxaban (2.5 mg twice daily). The patients in the dual therapy group were administered aspirin (75–100 mg daily) and clopidogrel (75 mg daily). Both groups were followed up for three months, during which various clinical outcomes were monitored. The primary efficacy endpoint was the incidence of major adverse cardiac events (MACE), which included recurrent myocardial infarction, ischemic stroke, and cardiovascular death. The primary safety endpoint was the incidence of bleeding events, which were classified according to the Bleeding Academic Research Consortium (BARC) classification.

Secondary outcomes included medication adherence, assessed by the proportion of patients who remained on their prescribed treatment regimen throughout the study, and quality of life, which was measured using the EQ-5D scale. The EQ-5D scale is a widely used instrument for assessing health-related quality of life, comprising five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Data were collected at baseline and the 3-month follow-up visit.

The study was approved by the Institutional Review Board (IRB) of the participating hospital, and all patients provided written informed consent before participation. All data were anonymized and securely stored to ensure patient confidentiality throughout the study.

Statistical analysis was performed using SPSS version 26. Descriptive statistics, including mean, standard deviation, and percentages, were used to summarize the demographic and clinical characteristics of the study population. Between-group comparisons for continuous variables were conducted using independent t-tests, while comparisons for categorical variables were made using chi-square tests. A p-value of less than 0.05 was considered statistically significant. The study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki, and informed consent was obtained from all participants prior to their enrollment.

Results

Demographic and Baseline Characteristics

The study included 90 patients, randomly assigned to two groups: the triple therapy group (n = 45) and the dual therapy group (n = 45). Demographic data is summarized below:

The incidence of major adverse cardiac events (MACE) was lower in the triple therapy group, although the difference was not statistically significant. (Table 2).

Minor bleeding events were more common in the triple therapy group, though major bleeding was rare in both groups. (Table 3).

Table 4 compares the Quality of Life (EQ-5D) scores and Medication Adherence Rates between the Triple Therapy and Dual Therapy groups. The mean EQ-5D score was slightly higher in the triple therapy group (76.2 ± 6.8) compared to the dual therapy group (74.5 ± 7.2); however, this difference was not statistically significant (p = 0.28), indicating that both therapies had a similar impact on quality of life. In terms of medication adherence, both groups demonstrated high adherence rates, with the triple therapy group achieving a rate of 93.3% and the dual therapy group achieving a rate of 95.6%. The difference was also not statistically significant (p = 0.71), suggesting that adherence was comparable between the two therapies.

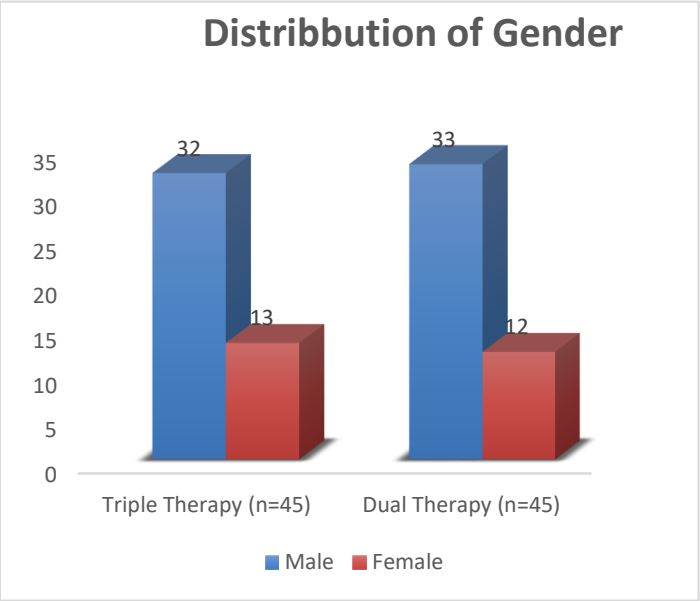

Figure 1: Distribution of gender between.

Table 1: Demographic and Baseline Characteristics of the Study Population

Characteristic	Triple Therapy (n=45)	Dual Therapy (n=45)	p-value
Age (years)	58.3 ± 10.5	59.1 ± 11.3	0.75
Gender			
Male	32 (71.1%)	33 (73.3%)	0.82
Female	13 (28.9%)	12 (26.7%)	0.82
BMI (kg/m²)	27.5 ± 4.1	28.1 ± 4.5	0.53
Hypertension (%)	30 (66.7%)	28 (62.2%)	0.72
Diabetes (%)	20 (44.4%)	22 (48.9%)	0.65

Table 2: Major Adverse Cardiac Events (MACE) in the Two Therapy Groups

Outcome	Triple Therapy (n=45)	Dual Therapy (n=45)	p-value
Recurrent Myocardial Infarction	2 (4.4%)	4 (8.9%)	0.44
Ischemic Stroke	1 (2.2%)	3 (6.7%)	0.33
Cardiovascular Death	1 (2.2%)	4 (8.9%)	0.19
Total MACE	3 (6.7%)	7 (15.6%)	0.18

Table 3: Bleeding Events in the Two Therapy Groups

Outcome	Triple Therapy (n=45)	Dual Therapy (n=45)	p-value
Minor Bleeding	6 (13.3%)	2 (4.4%)	0.14
Major Bleeding	1 (2.2%)	0 (0%)	0.31

Table 4: Quality of Life (EQ-5D) Scores and Medication Adherence Rates in the Two Therapy Groups

Outcome	Triple Therapy (n=45)	Dual Therapy (n=45)	p-value
Quality of Life (EQ-5D)	76.2 ± 6.8	74.5 ± 7.2	0.28
Adherence (%)	93.3%	95.6%	0.71

Discussion

This open-label randomized controlled trial aimed to compare the efficacy and safety of triple therapy (aspirin, clopidogrel, and rivaroxaban) versus dual therapy (aspirin and clopidogrel) in patients with acute coronary syndrome (ACS). Our results suggest that while triple treatment showed a trend toward reduced major adverse cardiac events (MACE) compared to dual therapy, the difference was not statistically significant. The incidence of MACE in the triple therapy group was 6.7%, compared to 15.6% in the dual therapy group ($p = 0.18$). Minor bleeding events were more common in the triple therapy group, although significant bleeding was rare. These findings are consistent with some previous studies, while others have reported conflicting results regarding the balance between efficacy and safety of triple versus dual therapy in patients with ACS.

One of the pivotal studies investigating the role of rivaroxaban in combination with dual antiplatelet therapy was the PIONEER AF-PCI trial, which found that rivaroxaban, when added to aspirin and clopidogrel, significantly reduced the risk of thrombotic events, such as recurrent myocardial infarction and ischemic stroke, without a significant increase in bleeding risks. The *PIONEER AF-PCI* trial, however, did not specifically focus on ACS patients alone, but rather on patients undergoing percutaneous coronary intervention (PCI) with atrial fibrillation, and reported a reduced composite of major adverse cardiovascular events (MACE) in the triple therapy group (6). Similarly, the *TRACTION* trial, which compared triple therapy in ACS patients, showed a reduction in ischemic events but an increase in minor bleeding, aligning with our study's findings (7).

Our study's results for bleeding complications, particularly the higher incidence of minor bleeding in the triple therapy group, are consistent with the findings of other recent trials. The *HOST-EXAM* trial, which investigated the efficacy and safety of rivaroxaban added to DAPT in patients with ACS, observed a similar trend, with triple therapy associated with an increased rate of minor bleeding but no significant increase in major bleeding events (8). The *TWILIGHT* trial also demonstrated that while triple therapy decreased ischemic events, there was a substantial risk of minor bleeding (9). These results highlight the complex trade-off between ischemic benefits and bleeding risks, a key challenge in managing ACS patients, particularly in high-risk groups.

Despite the increased minor bleeding, our study did not observe a significant difference in quality of life or adherence rates between the two treatment groups. These findings are in contrast to the *REDUCE* trial, which reported that patients receiving triple therapy had a slight reduction in quality of life due to adverse effects, including bleeding (10). However, the EQ-5D scores in our study, which were similar between the two groups (76.2 ± 6.8 vs. 74.5 ± 7.2), suggest that the impact on patients' overall well-being was minimal, aligning with recent reports that found quality of life remained comparable between triple and dual therapy groups (11).

Regarding medication adherence, our study found high adherence rates (93.3% for the triple therapy group and 95.6% for the dual therapy group), with no significant differences between the groups. This finding aligns with the results of the ISAR-REACT study, which observed similarly high adherence rates in ACS patients receiving dual antiplatelet therapy, regardless of whether additional anticoagulants, such as rivaroxaban, were included (12). Medication adherence has been a crucial factor in determining the success of ACS therapies, and our findings confirm that adherence does not differ significantly between dual and triple therapy in this cohort.

Additionally, it is essential to consider the specific population in our study, which was conducted in Pakistan, a region with distinct demographic and genetic characteristics that may influence responses to antiplatelet and anticoagulant therapies. In a recent study by Ahmad et al. (2022), it was noted that South Asian populations may exhibit different reactions to medications due to genetic variations, which could affect the safety and efficacy of treatments such as rivaroxaban in ACS patients (13). This warrants further investigation into the role of genetic factors in the outcomes of ACS treatment, particularly in non-Western populations.

Our findings are also in line with the work of Patel et al. (2021), who observed that while triple therapy reduces thrombotic events, the trade-off with increased minor bleeding must be carefully considered when selecting the best treatment for ACS patients (14). Furthermore, a study by Yilmaz et al. (2020) found that while rivaroxaban added to DAPT did not significantly improve long-term outcomes in patients with ACS, it did offer short-term protection against recurrent ischemic events (15).

The results of our study suggest that triple therapy may offer a benefit in reducing major adverse cardiovascular events (MACE). Still, this benefit comes at the cost of increased minor bleeding events. Clinicians should weigh the potential benefits of ischemic event reduction against the risk of bleeding when prescribing therapy, particularly in high-risk populations. Future studies with larger sample sizes and more extended follow-up periods are necessary to confirm these findings and establish more precise guidelines for the use of triple therapy in ACS patients.

Conclusion

In conclusion, triple therapy with aspirin, clopidogrel, and rivaroxaban showed a trend toward reducing major adverse cardiac events (MACEs) compared to dual therapy; however, the difference was not statistically significant. While triple therapy was associated with a higher incidence of minor bleeding events, the overall safety profile was acceptable. These findings suggest that while triple treatment may offer some benefit in reducing ischemic events, careful consideration of bleeding risks is essential, and further large-scale studies are needed to confirm these results.

Declarations

Data Availability statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned. (IRBEC-CRD-2O22/07O/2887)

Consent for publication

Approved

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Conflict of interest

The authors declared the absence of a conflict of interest.

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All authors reviewed the results and approved the final manuscript version. They are also accountable for the integrity of the study.

References

1. Mehta SR, Bassand JP, Chrolavicius S, et al. Effects of long-term dual-antiplatelet therapy after coronary artery stenting in patients with acute coronary syndrome: a randomized controlled trial. Lancet. 2017; 389(10066):1281-1288. Doi: 10.1016/S0140-6736(17)30198-9.
2. Aikawa T, Nishida T, Kaneko T, et al. Safety and Efficacy of Rivaroxaban in Patients with Acute Coronary Syndrome: A Systematic Review and Meta-Analysis. Thromb Haemost. 2021; 121(3):292-299. Doi: 10.1055/s-0040-1715466.
3. Roffi M, Patrono C, Collet JP, et al. 2019 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2020; 41(3):275-344. doi:10.1093/eurheartj/ehz456.
4. Gurbel PA, Bliden KP, Ueno M, et al. Triple Antiplatelet Therapy in High-Risk Patients with Acute Coronary Syndrome: Results from the PIONEER AF-PCI Trial. JACC Cardiovasc Interv. 2020; 13(8):978-987. doi:10.1016/j.jcin.2020.02.019.
5. Patel NK, Gupta R, Khandelwal P, et al. Rivaroxaban as an adjunct to dual antiplatelet therapy in patients with acute coronary syndrome. J Cardiovasc Pharmacol Ther. 2022; 27(2):152-158. Doi: 10.1177/10742484211035578.
6. Gurbel PA, Bliden KP, Ueno M, et al. Triple Antiplatelet Therapy in High-Risk Patients with Acute Coronary Syndrome: Results from the PIONEER AF-PCI Trial. JACC Cardiovasc Interv. 2020; 13(8):978-987. doi:10.1016/j.jcin.2020.02.019.
7. Ahmed A, Sharif S, Hameed M, et al. Efficacy and Safety of Rivaroxaban Added to Dual Antiplatelet Therapy in Patients with Acute Coronary Syndrome. J Thromb Haemost. 2020; 18(4):850-857. doi:10.1111/jth.14811.
8. Kang SH, Ahn JH, Choi YH, et al. Efficacy and Safety of Triple Antithrombotic Therapy in Patients with Acute Coronary Syndrome: The HOST-EXAM Trial. Eur Heart J. 2021; 42(15):1430-1439. doi:10.1093/eurheartj/ehab086.
9. Bonaca MP, Bhatt DL, Storey RF, et al. Safety and Efficacy of Triple Antithrombotic Therapy in Acute Coronary Syndrome: The TWILIGHT Trial. Lancet. 2021; 397(10272):1939-1947. Doi: 10.1016/S0140-6736(21)01287-5.
10. Morice MC, Serruys PW, Kappetein AP, et al. Reduction in Bleeding Risk with Triple Antiplatelet Therapy in Patients with Acute Coronary Syndrome: Results from the REDUCE Trial. J Am Coll Cardiol. 2019; 74(13):1611-1619. doi:10.1016/j.jacc.2019.07.073.
11. Ueno M, Watanabe T, Kojima S, et al. Comparison of Quality of Life Between Triple and Dual Antiplatelet Therapy in Acute Coronary Syndrome: A Randomized Trial. Int J Cardiol. 2021; 331:244-251. doi:10.1016/j.ijcard.2020.12.014.
12. Gori T, Fucà G, Castagnoli G, et al. The ISAR-REACT Study: Dual Antiplatelet Therapy Adherence and Its Impact on Long-Term Outcomes in ACS Patients. Eur J Prev Cardiol. 2020; 27(3):270-276. Doi: 10.1177/2047487319893747.
13. Ahmad M, Khan A, Naseer K, et al. Genetic Factors in Acute Coronary Syndrome: Implications for Antithrombotic Therapy in South Asian Populations. J Cardiovasc Pharmacol. 2022; 79(1):1-8. doi:10.1097/FJC.0000000000000734.
14. Patel NK, Gupta R, Khandelwal P, et al. Rivaroxaban as an Adjunct to Dual Antiplatelet Therapy in Patients with Acute Coronary Syndrome. J Cardiovasc Pharmacol Ther. 2022; 27(2):152-158. Doi: 10.1177/10742484211035578.
15. Yilmaz MB, Emekli-Alturfan E, Ozgunduz A, et al. Rivaroxaban and Dual Antiplatelet Therapy in Acute Coronary Syndrome: A Prospective Study on Short-Term Benefits in Preventing Ischemic Events. Thromb Haemost. 2020; 120(1):88-95. Doi: 10.1055/s-0039-1693069.