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Efficacy and Safety of Low Dose Rivaroxaban in Patients with Anterior Myocardial Infarction

Asmaa Ahmed Abdelbaset[1], Mohammed Alamir Saber[1], Sharaf .E.D Mahmoud[2*], Alaaeldin Sedky bekhit[3], Alshimaa Lotfy Hamed[2] Hamdy Saad Mohammed[1]

[1] Internal Medicine Department Sohag University, Egypt
[2] Cardiology Department, Sohag University. Egypt
[3] Neurology Department , Sohag University. Egypt

Email: sharaf003@gmail.com **Tel**: 201122789999

Abstract

Background: Rivaroxaban has been studied extensively in various clinical settings, its efficacy and safety at low doses for patients with anterior myocardial infarction (AMI) have not been fully investigated. This gap in knowledge presents an opportunity to evaluate the potential benefits of low-dose Rivaroxaban in this highly vulnerable patient population, potentially offering a safer alternative to traditional anticoagulation therapy.

Aim of the study: The primary objective of this study is to evaluate the efficacy and safety of low-dose Rivaroxaban in patients with anterior ST-segment elevation myocardial infarction during the first month after the acute event.

Methods: This randomized interventional clinical trial was conducted at Sohag University Hospital, the study involved 150 participants with AMI received primary percutaneous coronary intervention (PCI) within the therapeutic window (12 hours from onset of chest pain) of both genders randomly divided into two distinct groups. The first group (75 patients), received a low dose of Rivaroxaban (2.5 mg twice daily orally after food) for one month following their AMI, in addition to dual antiplatelet therapy, (acetylsalicylic acid 75 mg once daily orally and Clopidogrel 75 mg once daily orally). The second (control) group (75 patients), only received the standard dual antiplatelet therapy following their AMI.

Results: Initially, both groups had comparable left ventricular functions. After one month, however, the Rivaroxaban group showed a significant improvement in left ventricular function ($p=0.048$ compared to the control group, and $p=0.001$ compared to its baseline). Left ventricular thrombus didn't occur in the Rivaroxaban group; however, there was a 4.2% incidence the control group after one month, though this was not statistically significant. The mortality rate was lower in the Rivaroxaban group (1.3%) compared to the control group (4%), even so this difference was not statistically significant. Stroke was significantly less in the Rivaroxaban group compared to the control group ($p<0.001$), indicating a protective effect. However, the rates of stent thrombosis and minor bleeding were similar and not statistically significant between groups. No cases of major bleeding were reported in both groups.

Conclusions: Low-dose Rivaroxaban, when used in conjunction with standard dual antiplatelet therapy, appears to be an effective, beneficial and safe treatment option for patients with AMI, offering improvement in cardiac function and reducing the risk of stroke without elevating the risk of bleeding or mortality.

Keywords: Anterior MI, DOAC, Efficacy, NOACs, Rivaroxaban, Safety, STEMI

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Introduction:

Even with the use of guideline directed optimal medical therapy, 12% of patients with stable coronary heart disease (CHD) and 18% of patients with recent acute coronary syndrome (ACS) experience repeated major adverse cardiovascular events (MACE) [1]. The risk of recurrent cardiovascular events may be related to persistent elevation of thrombin beyond the index result [2,3], leading to progression of cardiovascular disease by prompting inflammation, endothelial dysfunction and thrombosis [4]. The use of vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) in patients with CHD, have been evaluated as secondary prevention strategies and have shown cardiovascular benefits at the cost of higher bleeding events [5-8].

Left ventricular thrombus (LVT) usually appears within 1 month after ST-segment elevation myocardial infarction (STEMI) and mostly forms after anterior STEMI [9,10]. It complicates acute MI and is associated with a higher incidence of poor outcomes [9]. Although the prevalence of LVT after acute myocardial infarction (MI) has recently decreased dramatically due to the progress of reperfusion therapy, LVT incidence in patients with anterior STEMI remains at 4% to 26% [11,12]. Previously, conventional triple anticoagulation [combination vitamin K antagonists (VKAs) and dual antiplatelet therapy (DAPT)] was recommended to prevent LVT in patients at high risk of STEMI, although it was not supported by superior evidence [13,14]. Interest in this area was fading as a result of recognition of the prognostic relevance of major bleeding from such a therapeutic regimen [15,16].

Prophylactic VKA anticoagulant therapy combined with DAPT, in the latest practice, is not recommended in patients with potential risk factors for LVT formation [17]. Clinicians continue to face doubt in decision making for left ventricle thromboprophylaxis in this high risk subgroup of patients. However, the advent of direct oral anticoagulants DOACs, which attenuate fibrin formation by selective inhibition of factor Xa or thrombin has renewed the interest in inhibition strategies that combine DAPT with an anticoagulant drug in this area. Rivaroxaban, as one of the most widely used DOACs, has achieved positive results in atrial fibrillation (AF) thromboprophylaxis, which may hypothetically provide a new strategy for the prevention of LVT.

With the absence of randomized data evaluating the contemporary role of Rivaroxaban prophylactic anticoagulation on LVT formation in patients with anterior STEMI, we designed a randomized clinical trial (RCT) to investigate the

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effect of Rivaroxaban and DAPT on LVT formation in patients with anterior STEMI.

Patients and Methods:

This prospective, randomized interventional clinical trial was conducted in **S**ohag University Hospital on patients presented with anterior STEMI including 150 patients received primary percutaneous coronary intervention (PCI) within the therapeutic window (12 hours from onset of chest pain) randomly assigned into two equal matched groups. The first group, included 75 patients, received a low dose of Rivaroxaban (2.5 mg twice daily orally after food) for one month following their AMI, in addition to DAPT, which included acetylsalicylic acid (75 mg once daily orally) and Clopidogrel (75 mg once daily orally). The control group, also included 75 patients, had an anterior STEMI but only received the standard DAPT. The trial was conducted after the ethical approval of the Sohag University Hospital ethical committee in Egypt (OHRP#: IRB00013006 . IRB registration # : Soh-Med-23-01-09). Informed written consent was obtained from the patients.

The exclusion criteria were patients with liver cirrhosis, severe mitral stenosis, bleeding tendency (HASBLED score ≥ 3), severe renal impairment (creatinine clearance < 30 ml/min), prosthetic valve, on Ticagrelor treatment, or AF.

All patients were subjected to full history taken and clinical examination**.** We assessed cardiac Troponin ,lipid profile, CBC , INR, Creatinine, ECG, and echocardiography. All patients were followed up for MACE, Left ventricular function, LVT formation, development of transient ischemic attacks or cerebrovascular stroke.

Statistical analysis

Data were analyzed using IBM SPSS software package version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Shapiro-Wilk test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level. The used tests were; Chi-square test: For categorical variables, to compare between different groups, Fisher's Exact test:

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Correction for chi-square when more than 20% of the cells have expected count less than 5, Mann Whitney test: For abnormally distributed quantitative variables, to compare between two studied groups, and Wilcoxon Rank test : To compare two related samples, matched samples, or to conduct a paired difference test of repeated measurements on a single sample to assess whether their population mean ranks differ.

Results:

Rivaroxaban group had a mean age of 54.77± 7.12 years with most of them (88%) were males while control group had a mean age of 57.41± 13.90 years with most of them (82.7%) were males. There was no statistically significant difference between the two groups regarding gender and age (p>0.05).

In Rivaroxaban group, (56%) of cases were smokers, (41.3%) had hypertension, and (50.7%) were diabetics. In control group, (66.7%) of cases were smokers, (50.7%) had hypertension, and (50.736%) were diabetics. There was no statistically significant difference between Rivaroxaban group and control group regarding smoking, hypertension and DM (P > 0.05) as shown in table (1)

Table 1: Comparison between the two groups regarding comorbidities

		Group (A) Rivaroxaban group (N= 75)		Group (B) Control group (N= 75)		*Chi- Square test*	
		No.	**%**	**No.**	**%**	**Test value** (X^2)	**P-value**
Comorbidities	**Smoking**	42	56.0%	50	66.7%	1.377	0.241 (NS)
	Hypertension	31	41.3%	38	50.7%	0.966	0.326 (NS)
	DM	38	50.7%	27	36.0%	2.715	0.099 (NS)

p≤0.05 is significant, p≤0.01 is high statistically significant, X2:Chi- Square test

No significant difference was observed between Rivaroxaban group and control group regarding serum troponin, Serum creatinine, WBCs, hemoglobin, platelets count as well as serum LDL and INR (p>0.05) at admission.

There was no statistically significant difference between Rivaroxaban group and control group as regards left ventricular function at presentation (p>0.05). While after 1 month, left ventricular function was significantly increased in Rivaroxaban group compared to control group (p=0.048). In Rivaroxaban group, there was high statistically significant increase in left ventricular function after 1

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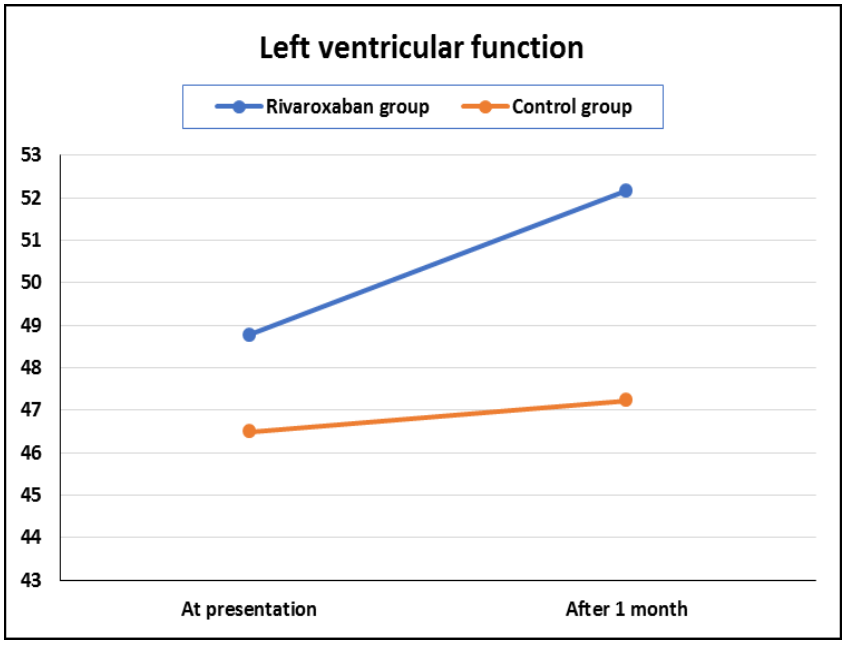
month compared to its measurement at presentation (p=0.001) while in control group, no statistically significant difference in left ventricular function at presentation & after 1 month (p>0.05). figure (1)

Figure (1): Comparison between study groups regarding left ventricular function at presentation and after 1 month.



In Rivaroxaban group, none of cases had LVT neither at presentation nor after 1 month while in control group none of cases had LVT at presentation while after 1 month; three cases (4.2%) were reported. The Rivaroxaban group showed none statistically significant reduction in left ventricular thrombus formation after 1 month more than control group (P > 0.05) as shown in table (2).

Table (2): Left ventricular thrombus of the two studied groups at presentation and after 1 month.

		Group (A) Rivaroxaban group (N= 75)		Group (B) Control group (N= 75)		*Chi- Square test*	
		No.	%	No.	%	Test value (X^2)	P-value
Left ventricular thrombus	At presentation	0	0.0%	0	0.0%	-	-
	After 1 month	0	0.0%	3	4.2%	3.190	0.115^{FET} (NS)

p≤0.05 is significant, p≤0.01 is high statistically significant,
X^2: Chi- Square test, FET: Fischer Exact Test

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There was no statistically significant difference between Rivaroxaban group and control group regarding SWMA at presentation (P > 0.05).

The Rivaroxaban group showed a non-significant reduction in mortality rate than control group (1.3% vs. 4%, respectively) (P > 0.05) as shown in table (3)

Table (3): Comparison between the two groups regarding outcome.

		Group (A) Rivaroxaban group (N= 75)		Group (B) Control group (N= 75)		*Chi- Square test*	
		No.	%	No.	%	Test value (X^2)	P-value
Outcome	**Alive**	74	98.7%	72	96.0%	3.061	0.245^{FET} (NS)
	Died	1	1.3%	3	4.0%		

p≤0.05 is significant, p≤0.01 is high statistically significant

X^2: Chi- Square test, FET: Fischer Exact Test

As one case dies in Rivaroxaban group and three cases died in control group during follow up, so the final number after one month was 74 and 72 respectively cases. In Rivaroxaban group, one case reported stroke and 5 cases had minor bleeding and three cases had stent thrombosis within one month. In control group, two cases reported stent thrombosis, three cases reported minor bleeding and 5 cases had stroke within one month. No cases of major bleeding in both groups. Stroke was significantly higher in control group compared to Rivaroxaban group (p<0.001) meanwhile there was no statistically significant difference between the two groups regarding stent thrombosis or bleeding (P > 0.05) as shown in table (4)

Table (4): Complications in the two groups after 1 month.

Complications within 1 month		Group (A) Rivaroxaban group (N= 74)		Group (B) Control group (N= 72)		*Chi- Square test*	
		No.	%	No.	%	Test value (X^2)	P-value
Stroke	**No**	74	98.6%	67	93.1%	13.611	**<0.001**
	Yes	1	1.4%	5	6.9%		
Stent thrombosis	**No**	72	96.0%	70	97.2%	0.002	1.00^{FET}
	Yes	3	4.0%	2	2.8%		
Bleeding	**Minor**	5	6.8%	3	4.2%	0.536	0.464
	Major	0	0.0%	0	0.0%	-	-

p≤0.05 is significant, p≤0.01 is high statistically significant,

X^2: Chi- Square test, FET: Fischer Exact Test

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Discussion

The anterior myocardium receives vascular supply via the left anterior descending (LAD) coronary artery. Sustained ischemia due to LAD artery occlusion leads to AMI. Atherosclerotic plaque rupture, followed by thrombus formation is the most common cause of AMI [18-20].

The prevalence of CHD has not decreased; nevertheless the mortality from MI has been decreasing due to advanced treatment strategies and better management. One study determined that the incidence of anterior STEMI is approximately 33% of all STEMIs [21, 22].

Rivaroxaban is an oral direct factor Xa inhibitor that reduces thrombin generation [23, 24]. In doses of 10 to 20 mg daily, this agent is approved for a variety of indications, including the treatment and prevention of venous thromboembolism and the prevention of stroke or systemic embolism in patients with AF [25, 26].

Lower doses of Rivaroxaban (e.g., 2.5 mg twice daily), in combination with antiplatelet agents, have been found to reduce the risk of death from cardiovascular causes, myocardial infarction, and stroke in patients with ACS or stable coronary artery disease [27, 28].

The main aim of this study was to study the efficacy and safety of low dose Rivaroxaban in patients with anterior STEMI during the first month after the acute event.

The main results of this study were as follows:

In the current study, we found that Rivaroxaban group had a mean age of 54.77± 7.12 years with most of them (88%) were males while control group had a mean age of 57.41± 13.90 years with most of them (82.7%) were males. There was no statistically significant difference between the two groups regarding gender and age ($p>0.05$).

In agreement with our results, Zhang et al., [29] who aimed to investigate the effects of Rivaroxaban on left ventricle thromboprophylaxis in patients with anterior STEMI. They found that in 279 patients with anterior STEMI who had undergone primary percutaneous coronary intervention to receive, in a 1:1 ratio, low-dose Rivaroxaban (2.5 mg twice daily for 30 days) and DAPT or only DAPT. In Rivaroxaban (n=139) group, Age, was 56.0 (49.0-64.0) with most of them were males 115 (82.7%) while in No Rivaroxaban (n=140) group, age was 59.0 (52.0-66.0) with most of them were males 108 (77.1%).

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Also, Mega et al., in ATLAS ACS-2–TIMI-51 trial [30] who their study focuses on the results of Rivaroxaban versus placebo in the pre-specified subgroup of patients following a STEMI, in whom long-term anticoagulant therapy has been of particular interest. They reported that in Rivaroxaban 2.5 mg Twice Daily group, Age, was 61.5±8.8 years with most of them were males (79.2%).

As well, Zhang et al., [31] B who aimed to observe differences in efficacy between Rivaroxaban plus DAPT therapy and VKA plus DAPT in patients who developed LVT after STEMI. They found that in Rivaroxaban (n=33) group, as regard baseline characteristics, there were 24 (72.7%) males and Age, years was 60.3±14.7. While in Warfarin (n=31) group, there were 23 (74.2%) males and Age, years was 61.3±9.0. There was no significant difference as regard age and gender between the two groups (Rivaroxaban group and Warfarin group).

In our study, we revealed that in Rivaroxaban group, 42 (56%) cases were smokers, 31 (41.3%) cases had hypertension, and 38 (50.7%) cases were diabetics. In control group, 50 (66.7%) cases were smokers, 38 (50.7%) cases had hypertension, and 27 (50.736%) cases were diabetics. There was no statistically significant difference between Rivaroxaban group and control group regarding smoking, hypertension and DM ($P > 0.05$).

Similarly , Zhang et al., [29] found that in Rivaroxaban (n=139) group, Hypertension in 45 patients (32.4%), Diabetes mellitus in 22 patients (15.8%) and Current smoker in 78 patients (6.1%) was found . While in No Rivaroxaban (n=140) group, there was hypertension in 55 (39.3%) patients, hyperlipidemia in 68 (48.6%), Diabetes mellitus in 31 (22.1%) and Current smoker in 65 (46.4%) patients.

Also, Mega JL et al., in ATLAS ACS-2–TIMI-51 trial [30] found that in Rivaroxaban 2.5 mg Twice Daily group, there was Hypertension in (57.9%), Diabetes in (29.3%) and Hypercholesterolemia in (41.0%).

As well, Zhang Z et al., [31] B revealed that in Rivaroxaban (n=33) group, Hypertension in 23 patients (69.7%), diabetes mellitus in 10 patients (30.3%) and Current smoker in 11 patients (33.3%) was found. While in Warfarin (n=31) group, there was hypertension in 11(33.5%), diabetes mellitus in 5 (16.1%) and current smoker in 17 (54.8%). There was no significant difference as regard hypertension, diabetes mellitus and smoking between the two groups (Rivaroxaban group and Warfarin group).

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Interestingly we found that after 1 month of therapy , left ventricular function was significantly increased in Rivaroxaban group compared to control group (p=0.048). In Rivaroxaban group, there was high statistically significant increase in left ventricular function after 1 month compared to its measurement at presentation (p=0.001) while in control group, no statistically significant difference in left ventricular function at presentation & after 1 month (p>0.05) this finding may be owing to improvement in coronary microcirculatory function. Also we noticed a non-significant reduction in LVT formation after 1 month in the Rivaroxaban group compared to control group (P > 0.05).

In agreement with our results, Zhang Z et al., [29] revealed that at baseline echocardiography findings in Rivaroxaban (n=139) group, LVEF % was 55.0 (46.8-60.0) and LVDD, mm was 44.0 (42.4-48.9) while after one month LVT was 1 (0.7%). In No Rivaroxaban (n=140) group, LVEF % was 53.0 (44.0-60.0) and LVDD, mm was 46.0 (42.7-49.6) while after one month LVT was 12 (8.6%). There was significant difference as regard LVT after one month between Rivaroxaban group and No Rivaroxaban group which may be underestimated in our study due to small number

Also, Mega JL et al., [30] they reported that in Rivaroxaban 2.5 mg Twice Daily group, LVEF % was 50.7±10.6.

As well, Zhang Z et al., [31] B they found that in Rivaroxaban (n=33) group, as regard echocardiography findings at baseline, LVEF, % was 42.9±13.1, LVEDD (mm) was 51.1±7.4 while during the follow-up period LVT resolution was 26 (78.8%). In Warfarin (n=31) group, baseline LVEF, % was 41.4±10.8, LVEDD (mm) was 52.5±6.5 while during the follow-up period LVT resolution was 23 (74.2%). With no significant difference in LVEF % at baseline between the two groups.

In our outcomes, the Rivaroxaban group showed a non-significant reduction in mortality rate than control group (1.3% vs. 4%, respectively) (P > 0.05).

In agreement with our results, Zhang Z et al., [29] found that after one month in Rivaroxaban (n=139) group, All-cause mortality was 2 (1.4%) while in No Rivaroxaban (n=140) group, All-cause mortality was 3 (2.1%). There was no significant difference in all-cause mortality between the two groups.

As well, Zhang Z et al., [31] B revealed that in Rivaroxaban (n=33) group, the all-cause mortality in 1 (3.0%). While in Warfarin (n=31) group, the all-cause mortality in 4 (12.9%). With no significant difference between the two groups.

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In our study Stroke was significantly higher in control group compared to Rivaroxaban group ($p<0.001$) meanwhile there was no statistically significant difference between the two groups regarding stent thrombosis or bleeding ($P > 0.05$). No major bleeding was detected in both groups.

In consistent with our results, Zhang Z et al., [29] found that after one month in Rivaroxaban (n=139) group, there was systemic embolism in 1 (0.7%), Rehospitalization for cardiovascular events in 2 (1.4%) and Bleeding events in 4 (2.9%); Major bleeding in 1 (0.7%) and Minor bleeding in 3 (2.2%). In No Rivaroxaban (n=140) group, there was systemic embolism in 4 (2.9%), Rehospitalization for cardiovascular events in 1 (0.7%) and Bleeding events in 2 (1.4%); there was no reported cases with Major bleeding while there was minor bleeding in 2 (1.4%). With no significant difference after one month between the two groups regarding systemic embolism, rehospitalization for cardiovascular events and bleeding events.

As well, Zhang Z et al., [31] B revealed that in Rivaroxaban (n=33) group, there was Re-hospitalization for Cardiovascular events in 7 (21.2%) patients and Bleeding events in 2 (6.1%); no cases with major bleeding while Minor bleeding was present in 2 (6.0%) cases. While in Warfarin (n=31) group, there was Re-hospitalization for Cardiovascular events in 12 (38.7%) patients and Bleeding events in 3 (9.7%); there were 1 (3.2%) with major bleeding while Minor bleeding was present in 2(6.4%) cases. With no significant difference as regard bleeding events between the two groups.

Conclusions:

We studied the efficacy and safety of low dose Rivaroxaban in patients with anterior STEMI during the first month after the acute event.

Accordingly, we found that in Rivaroxaban group there was significant improvement in LVF and non-significant improvement in LVT . Stroke was significantly higher in control group compared to Rivaroxaban group meanwhile there was no statistically significant difference between the two groups regarding stent thrombosis or bleeding.

Accordingly, low dose Rivaroxaban is effective, beneficial, and safe to use in recent anterior STEMI patients

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None

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Data availability

No datasets were generated or analyzed during the current study.

Conflict of Interest

None

Limitations

1- Limited number of the patients
2- No extended follow up
3- Selected patients of very low bleeding risk

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