# RIVAROXABAN IN PATIENTS OF HEART FAILURE WITH REDUCED EJECTION FRACTION AND SINUS RHYTHM

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## Abstract

**Background:** The stimulation of thrombin-related pathways is linked to heart failure and predicts a bad prognosis. We expected that treating patients with deteriorating chronic heart failure and underlying coronary artery illness with rivaroxaban, a factor Xa inhibitor, would decrease thrombin production and enhance results.

**Aim and objectives:** test the hypothesis that rivaroxaban (10 mg) added to baseline anti-failure treatment is linked with decreased risks of death and cardiovascular events in individuals with chronic heart failure who have recently deteriorated, decreased ejection fraction, and sinus rhythm.

**Subjects and methods:** Patients hospitalized to the Cardiology Department at Aswan University Hospital with at least a 3-month history of chronic heart failure and a left ventricular ejection fraction of 40% or less were included in this randomized clinical trial.

**Results:** In concern with the composite efficacy outcome of rivaroxaban, 22(73.3%) of placebo group patients developed efficacy outcome events distributed as following: 9(30%) of patients died of which 6(20%) were due to cardio vascular reasons, 3(10%) developed MI and 10(33%) re-hospitalized for worsening of heart failure.

**Conclusion**: In patients with recurrent rapid deterioration of chronic heart failure and decreased ejection fraction who also had underlying coronary artery illness and were not in atrial fibrillation, small dose rivaroxaban added to guideline-based therapy was linked to a lower rate of overall mortality, myocardial infarction, or stroke than placebo.

**Keywords:** Rivaroxaban, chronic heart failure, thrombin generation, myocardial infarction, prophylactic

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## INTRODUCTION

Heart failure (HF) is a complicated medical condition where the heart's capacity to pump and/or fill with blood is impaired. HF may be described physiologically as an insufficient cardiac function to fulfill metabolic needs or a sufficient cardiac function due to compensatory neurohormonal activation (Elevated left ventricular filling pressure is the most common symptom). **(1)**

Heart failure (HF) is a global epidemic that affects 64.34 million people and is becoming more common. Health-care costs for the elderly are high and will continue to rise as the population ages. Despite major breakthroughs in treatments and protection, death and sickness are still great, and quality of life is poor **(2).**

HF affects 5.7 million individuals in the United States now, but forecasts show that by 2030, more than 8 million people would have the disease, representing a 46 percent rise in prevalence. **(3)**

Though neprilysin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, angiotensinII receptor blockers (ARBs), beta-blockers, mineralocorticoid receptor antagonists, and particular vasodilators are among the increasing list of medicines that lower death,, but Despite advances in neurohormonal control and resynchronization therapy, mortality in chronic heart failure patients remains unacceptably great.**(4)**

In patients with increasing chronic heart failure, declining left ventricular ejection fraction, coronary artery disease, and no atrial fibrillation, rivaroxaban 2.5 mg twice daily was not linked with a substantially lower risk of mortality, myocardial infarction, or stroke compared to placebo. **(5)**.

In this trial, we want to see whether rivaroxaban at a prophylactic dosage of 10 mg, along with baseline anti-failure medication, is linked to a decreased probability of death and cardiovascular incidents in patients with late deterioration of chronic heart failure, low cardiac output, and sinus rhythm.

## PATIENTS AND METHODS

This prospective research was conducted at Aswan University Hospital's Cardiology Department. Patients hospitalized to the Cardiology Department at Aswan University Hospital having a left ventricular ejection fraction of 40percent or less and

a 3-month incidence of chronic heart failure were included in this randomized clinical trial.

**Sample size:** 60 patients were split into two groups, each with 30 patients; control group and prophylactic dose (10mg) group. We used G-power program for calculation of our sample size to obtain adequate sample size making us capable of obtaining reliable significant results.
**Inclusion criteria:** Patients having a past of chronic heart failure and a left ventricular ejection fraction of 40percent or less, as well as sinus rhythm.
**Exclusion criteria:** Patients may have one or more of the following: During the index incident, patients with a glomerular filtration rate of less than 20 ml per minute per 1.73 m2 and an elevated threat of hemorrhaging, atrial fibrillation, or a further situation requiring long-term anticoagulation, acute myocardial infarction, or surgical or percutaneous coronary artery intervention. Recent stroke or cerebral bleeding, or another condition for which anticoagulants or NOACs are not recommended.

**Operational design:** From each patient the following data had been collected upon admission
**Intial assessment:** Complete full history taking, including: Age, sex, cardiovascular hazard concerns (Diabetes, high blood pressure, excessive cholesterol,…), heart Failure symptoms (Dyspnea,edema,…), history of previous stroke or distal embolization, history Of Previous Surgeries, history Of Blood Transfusion, history Of DM, history Of Other Comorbid Conditions Such As Cardiac Disease and special Habits of Medical Importance like Smoking.

**Clinical examination focusing on:**
**General examination** in the form of **Vital signs** (Temperature, Blood Pressure, Heart Rate, and Respiratory Rate), **Signs of** (Pallor, Cyanosis, Jaundice, and Lymph node enlargement)
**Cardiovascular examination: General:** Breathlessness, fatigue, swollen ankles and legs – this is induced by a build-up of fluid (oedema), an insistent cough, which may be severe at night, wheezing, loss of appetite, excess weight or losing weight, confusion and dizziness, and fainting are all signs of Heart Failure, previous stroke, or distal embolization. Cardiomyopathy symptoms seen **locally** include: Swelling of the legs, ankles, and feet, bloating of the belly owing to fluid accumulation, cough when laying down, trouble sleeping flat to sleep, weariness, fast, pounding, or fluttering heartbeats, chest pain or pressure, and dizziness, lightheadedness, and fainting
**General Inspection:** A simple visual assessment might provide several signs about the cardiac state. Cyanosis, pallor, and sweatiness may all be signals of approaching danger in an extremely ill patient.

**Palpation:** Inspection of the precordium before auscultation may reveal past surgery — for example, a midline sternotomy indicates previous bypass, whereas a lateral thoracotomy indicates previous mitral valve or minimally invasive bypass surgery (left anterior descending coronary artery to left internal mammary artery).
**Auscultation:** With the diaphragm of your stethoscope, listen across the aortic (second intercostal gap on the right) and pulmonary (second intercostal gap on the left) sections, as well as at the left lower sternal border (elevated pitches are preferable), then use the bell for the apex (reduced pitches are preferable). Use both if you're unsure.
**Investigations** Standard ECG with 12 leads A conventional ECG instrument (Page-writer, Hewlett Packard, USA) with a paper running speed of 25 mm/s was used to capture 12 lead resting ECGs. Two cardiologists blinded to the clinical data used a magnifying glass (TorQ 150 mm Digital Caliper LCD) to evaluate ECG and heart rate (HR).
**Echocardiography:** Transthoracic echocardiography was done to Evaluate LV systolic function.
**Administrative and Ethical Design :** An Official permission was obtained from Faculty of Medicine, Aswan University. An official permission was obtained from Aswan University Hospital. Approval from ethical committee in the faculty of medicine (Institutional Research Board IRB).
**Statistical Analysis and Data Management:** All data was gathered, summarize, and statistically evaluated using the SPSS version 22 statistical software for special sciences (SPSS Inc. Chicago, IL, U.S.A). The variance in quantitative variables in two groups was determined utilizing the independent t-test and the Mann-Whitney test. To compare two dependent groups of normally distributed variables, a paired t-test was performed. The difference between qualitative variables was analyzed using the Chi square test ($\chi 2$) and the Fisher exact method.

## RESULTS

In our randomized control trial, 30 patients had taken placebo and an equal time had taken rivaroxaban. In rivaroxaban group median age of the participant was 58 with (IQR)= (9.3) ranging from 50-60 with mean ±SD equal 58.73±5.27, while in the other group median age of the participant was 63 with (IQR)= (8.5) ranging from 51-70 with mean ±SD equal 60.80±5.76 with no statistically substantial variation between two groups at p value=0.517. In our study, there were 21 females in rivaroxaban group as compared to 20 females in the other group. 18(60%) of the former group were smokers as compared to 17(56.7%) in the latter group with no statistically substantial variation between two groups at p value>0.05. **Table 1**

**Table 2 showing baseline characteristics of placebo group and rivaroxaban group n=60**

| | Placebo group n=30 | Rivaroxaban group n=30 | p-value |
|---|---|---|---|
| **Age** | | | 0.517ϕ |
| **Median(IQR)** | 58(9.3) | 63(8.5) | |
| **Mean ±SD** | 58.73±5.27 | 60.80±5.76 | |
| **Range** | 50-68 | 51-70 | |
| **Sex (n, %)** | | | |
| **Male** | 20(66.7%) | 21(70.0%) | 0.781# |
| **Female** | 10(33.3%) | 9(30.0%) | |
| **BMI** | | | 0.151 ϕ |
| **Median(IQR)** | 30.60(4) | 30.15(6.1) | |
| **Smoking (n, %)** | | | 0.793# |
| **Smokers** | 17(56.7%) | 18(60%) | |

#chi-square test was used ϕMann-whitney test was used

Regarding medical history of the Participant, 28(93.3%) of the patients who had taken rivaroxaban were having coronary artery diseases. On the other hand, 27(90%)the patients who had taken placebo were having coronary artery diseases as evidenced by the existence of at least one of the following: pathologic Q waves on electrocardiography with relating wall-motion anomalies 11(36.7%), history of coronary-artery bypass grafting 6(20%), background of percutaneous coronary intervention 16(53.3%), angiographic evidence of at least 50% stenosis in one or more coronary arteries14(46.7%) or previous myocardial infarction 21(70%).In addition 21(70%) were having chronic hypertension and 19(36.3%) were having Diabetes Mellitus (DM). no substantial distinction was foud between 2 groups regarding medical history. **Table 2**

**Table 3 showing medical history of placebo group and rivaroxaban group n=60**

| | Placebo group n=30 | Rivaroxaban group n=30 | p-value |
|---|---|---|---|
| **Coronary artery disease identified by at least one of the following (n, %)** | 27(90%) | 28(93.3%) | 0.640# |
| **aberrant wall-motion anomalies and pathologic Q waves on electrocardiography** | 11(36.7%) | 7(23.3%) | |
| **previous coronary artery bypass grafting** | 6(20%) | 5(16.7%) | |
| **previous percutaneous coronary intervention** | 16(53.3%) | 14(46.7%) | |
| **angiographic evidence of stenosis in one or more coronary arteries of at least 50%previous myocardial infarction** | 14(46.7%) | 19(63.3%) | |
| | 21(70%) | 23(76.7%) | |
| **Hypertension (n, %)** | 21(70%) | 23(76.7) | 0.559 |
| **Diabetes mellitus (n, %)** | 19(36.3%) | 12(40%) | 0.071 |

#chi-square test was used

Regarding to New york Heart Association Classification, 12(40%) of the patients who had taken placebo was classified as class 2, 15(50%) were in class 3 and 3(10%) were in class four as compared to 1(3.3%) in class 1, 13(43.3%) in class 2, 14(46.7%) in class 3 and 2(6.7%) in class four with no statistically substantial distinction between 2 groups at p value =0.735. the rivaroxaban group showed a higher mean of total cholesterol level 202.50±23.89 ranging from153-237 as compared with placebo group which showed a mean of 191.17±25.51 ranging from 153-248 with no statistically substantial distinction at p value =0.081. **Table 3**

Regarding medical history of the patients, all the patients in both groups were taking diuretics while only 27(90%) in the placebo group were taking Angiotensin converting enzyme inhibitors, 24(80%) were taking Mineralocorticoid-receptor antagonists, 25(83.3) were taking Beta-Blockers, 21(70%)were taking Aspirin or thienopyridine and 8(26.7%) were taking Dual anti-platelet therapy as compared with (28(93.3%), 20(66.7%), 24(80%), 23(76.7%) and 10(33.3%)respectively)in other group with no statistically substantial distinction at p value >0.05. **Table 4**

**Table 4 showing laboratory and clinical characteristics of placebo group and rivaroxaban group n=60**

| | Placebo group n=30 | Rivaroxaban group n=30 | p-value ϕ |
|---|---|---|---|
| **Estimated Glomerular Filtration Rate(EGFR) ml/min/1.73m2** | | | |
| **Median(IQR)** | 56.50(37.3) | 54(33.5) | 0.796 |
| **Ejection fraction %** | | | |
| **Median(IQR)** | 30.50(11.5) | 31.50(10) | 0.900 |
| **D-dimer level** | | | |
| **Median(IQR)** | 413(152.3) | 404(169.5) | 0.906 |
| **BNP level pg/ml** | | | |
| **Median(IQR)** | 840.55(404.6) | 770.75(536.6) | 0.301 |
| **NT-proBNP level** | | | |
| **Median(IQR)** | 3186.85(2848) | 4007.45(3055) | 0.302 |
| **Total cholesterol level mg/dl** | | | |
| **Mean ±SD** | 191.17±25.51 | 202.50±23.89 | 0.081 T |
| **Range** | 153-248 | 153-237 | |
| **New york Heart Association Classification (n, %)** | | | |
| **Class 1** | 0(0%) | 1(3.3%) | 0.735# |
| **Class 2** | 12(40%) | 13(43.3%) | |
| **Class 3** | 15(50%) | 14(46.7%) | |
| **Class 4** | 3(10%) | 2(6.7%) | |

#chi-square test was used ϕMann-whitney test was used T t-test was used

**Table 5 showing the drug history of placebo group and rivaroxaban group n=60**

| | Placebo group n=30 | Rivaroxaban group n=30 | P-value # |
|---|---|---|---|
| **Diuretics (n, %)** | 60 (100%) | | |
| **ACIs (n, %)** | 27(90%) | 28(93.3%) | 0.640 |
| **Mineralocorticoid-receptor antagonists (n, %)** | 24(80%) | 20(66.7%) | 0.243 |
| **Beta-Blockers (n, %)** | 25(83.3) | 24(80%) | 0.739 |
| **Aspirin/thienopyridine (n, %)** | 21(70%) | 23(76.7%) | 0.559 |
| **Dual anti-platelet therapy (n, %)** | 8(26.7%) | 10(33.3%) | 0.573 |

#chi-square test was used

9 (30%) of patients died, with 6 (20%) dying from cardiovascular causes, 3 (10%) developing MI, and 10 (33%) requiring re-hospitalization owing to increasing heart failure. Only 5(16.7 percent) of patients died, with 3(10 percent) dying from cardio vascular reasons, 1(3.3 percent) developing MI, and 5(16.7 percent) re-hospitalized for worsening heart failure, with a statistically substantial distinction at the two groups regarding development of composite efficacy outcome at p value =0.004. **Table 5**

Concerning the composite safety outcome of rivaroxaban, 8(26.7%) of patients in placebo group developed safety outcome events which include the following: 3(10.0%) of patients developed fatal bleeding and 8(26.7%) had a drop in hemoglobin concentration of at least 2 g per deciliter. A variation between two groups that is substantial regarding development of composite safety outcome and a drop in hemoglobin concentration of at least 2 g per deciliter at p value =0.038. **Table 6**

Survival analysis using Kaplan-Miere curve between placebo and rivaroxaban groups showed that rivaroxaban group had a statistically significant higher survival rate without composite efficacy outcome (death from any cause, stroke, development of MI and re-hospitalization due to heart failure worsening ) as compared to placebo group with mean duration of survival equal 23.84±0.103 and 18.58±0.103 at p value <0.001. **Figure 1**

Survival analysis using Kaplan-Miere curve between placebo and rivaroxaban groups showed that rivaroxaban group had a statistically significant higher survival rate without composite safety outcome (deadly hemorrhage, bleeding into a crucial region that might result in lifelong impairment, and a hemoglobin level drop of at least 2 g per deciliter) as compared to placebo group with mean duration of survival equal 24.12±0.061 and 19.55±0.24 measured in months at p value <0.001. **Figure 2**

**Table 5 showing composite efficacy outcome of placebo group and rivaroxaban group n=60**

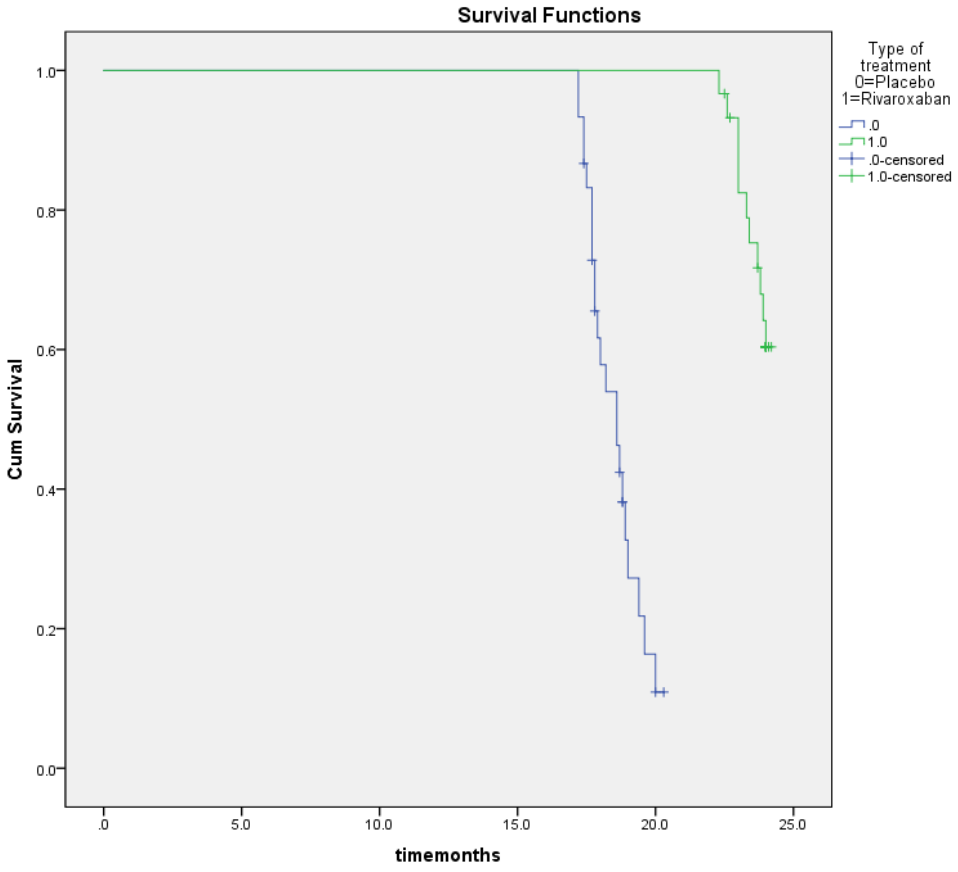
| | Placebo group n=30 | Rivaroxaban group n=30 | P- value |
|---|---|---|---|
| **composite efficacy outcome** | 22(73.3%) | 11(36.7%) | **0.004*** |
| **any cause of death** | 9(30%) | 5(16.7%) | 0.222 |
| **• Cardiovascular disease-related death** | 6(20%) | 3(10%) | |
| **Stroke** | 0(0.0%) | | |
| **Developed MI** | 3(10%) | 1(3.3%) | 0.612 |
| **Re-hospitalization for worsening of heart failure** | 10(33%) | 5(16.7%) | 0.136 |

#chi-square test was used * statistically substantial at p value<0.05

**Table 6 showing composite safety outcome of placebo group and rivaroxaban group n=60**

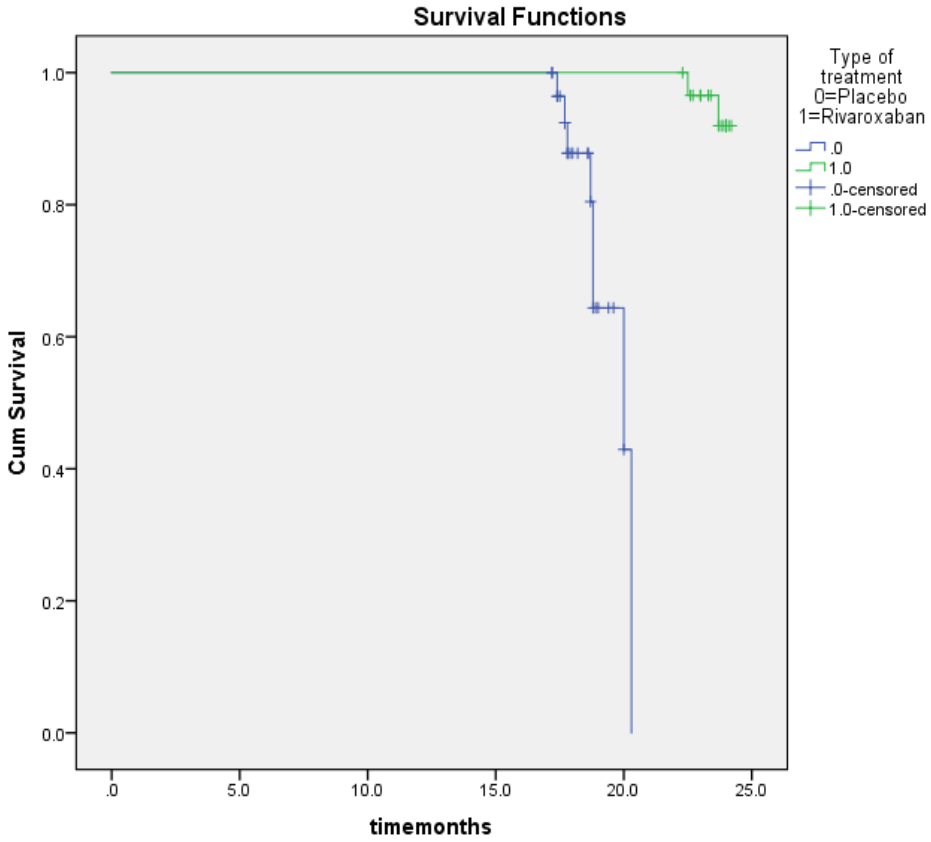
| | Placebo group n=30 | Rivaroxaban group n=30 | P- value # |
|---|---|---|---|
| **Composite safety outcome** | 8(26.7%) | 2(6.7%) | **0.038*** |
| **Fatal bleeding** | 3(10.0%) | 1(3.3%) | 0.301 |
| **Bleeding into a vital region that might result in irreversible impairment** | 0(0.0%) | | |
| **Hemoglobin level drops by at least 2 g per deciliter** | 8(26.7%) | 2(6.7%) | **0.038*** |

#chi-square test was used * statistically substantial at p value<0.05




Log-rank test was used

**Figure 1: survival analysis using between placebo and rivaroxaban groups showing that rivaroxaban group had a statistically significant higher survival rate without composite efficacy outcome as compared to placebo group.**




Log-rank test was used

**Figure 2: survival analysis using between placebo and rivaroxaban groups showing that rivaroxaban group had a statistically significant higher survival rate without composite safety outcome as compared to placebo group.**

## DISCUSSION

The primary aim of this research was to evaluate the feasibility and security of Rivaroxaban at a prophylactic dosage of 10 mg in reducing the risk of death and cardiovascular incidents in people with chronic heart failure who have recently deteriorated, decreased ejection fraction, and sinus rhythm.

This randomized clinical trial was carried out at Aswan University Hospital's cardiac department. This research included 60 patients with chronic heart failure for at least three months and a left ventricular ejection fraction of 40% or less. Patients were randomly allocated to one of two groups: Rivaroxaban (30 patients) or Placebo (30 patients). In terms of the demographics of the groups investigated, in rivaroxaban group median age of the participant was 58 with (IQR)= (9.3) ranging from 50-60 with mean ±SD equal 58.73±5.27, while in the other group median age of the participant was 63 with (IQR)= (8.5) ranging from 51-70 with mean ±SD equal 60.80±5.76. The median (IQR) of the body mass index in the placebo group was 30.60 (4) in comparison with rivaroxaban group with median (IQR) equal 30.15(6.1). In our study, In the rivaroxaban group, there were 21 females compared to 20 females in the control group. 18(60%) of the former group were smokers as compared to 17(56.7%) in the control one. There were no substantial variations at two groups regarding age, sex, BMI and smoking.

In line with the current study COMMANDER HF trial by **Zannad et al., [6]** evaluated the effectiveness and safety of rivaroxaban 2.5 mg bid to placebo (standard therapy) in patients with decreased ejection fraction (HF-rEF) with confirmed coronary artery disease following an exacerbation of HF. In this double-blind, randomized trial, 5022 sufferers with persistent heart failure, a left ventricular ejection fraction of 40percent or less, coronary artery disease, and elevated plasma concentrations of natriuretic peptides who did not have atrial fibrillation were selected randomly rivaroxaban at a dose of 2.5 mg twice daily or placebo after recovery for an episode of rapidly deteriorating heart failure. In terms of age, sex, BMI, and smoking, there were no statistically substantial variations between the two groups.

Also, **Mega et al., [7]** In a double-blind, placebo-controlled study, researchers looked at whether low-dose rivaroxaban may improve cardiovascular outcomes in people with recent acute coronary

syndrome. 15,526 people with a recent acute coronary syndrome were given twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a median of 13 months and up to 31 months. In the study groups, the patients' baseline characteristics were well matched.

As well, **Mega et al., [8]** rivaroxaban's safety and effectiveness were evaluated, with the goal of finding the best dosage and dosing schedule. The research included 3491 patients who had stabilized following acute coronary syndrome from 297 locations in 27 countries. Participants were randomized 1:1:1 within each stratum and dosage tier to have either placebo or rivaroxaban (at doses 5–20 mg) administered twice daily or the same total daily dose given once daily using a block randomization procedure. Overall, and within the treated group within each stratum, The baseline features were quite similar.

Regarding the medical history of placebo group and rivaroxaban group, we found that 28(93.3%) of the patients who had taken rivaroxaban were having coronary artery diseases as identified by at least one of the following characteristics is present: Pathologic Q waves on electrocardiography with relating wall-motion anomalies 7 (23.3%), past of coronary artery bypass grafting 5 (16.7%), past of percutaneous coronary intervention 14 (46.7%), angiographic proof of stenosis in one or more coronary arteries of at least 50% 19 (63.3 percent ),or past myocardial infarction 23 (76.7 percent). In addition, 23(76.7) were having chronic hypertension and 12(40%) were having Diabetes Mellitus (DM).

The research of **Zannad et al., [6]** which agrees with our findings, reported that there no substantial variations between two groups regarding medical history including Myocardial infarction, Stroke, Diabetes and Hypertension.

Also, the research by **Eikelboom et al., [9]** revealed that there no substantial variations between two groups regarding medical history including Myocardial infarction, heart failure, Stroke, Diabetes and Hypertension.

As well, **Mega et al., (7)** reported that there no substantial variations between two groups regarding medical history including Myocardial infarction, Hypercholesterolemia, Diabetes and Hypertension.

Similarly, **Mega et al., [8]** reported that there no substantial variations between Rivaroxaban and placebo groups regarding medical history including Myocardial infarction, Dyslipidaemia, Diabetes and Hypertension.

Regarding the laboratory and clinical characteristics of the studied groups, our results revealed that According to NYHA Classification, 12(40%) of the patients who had taken placebo was classified as class 2, 15(50%) were in class 3 and 3(10%) were in class four as compared to 1(3.3%)in class 1, 13(43.3%)in class 2, 14(46.7%)in class 3 and 2(6.7%) in class four with no substantial variations between 2 groups at p value =0.735.

In addition, the rivaroxaban group showed a higher mean of total cholesterol level 202.50±23.89 ranging from153-237 as compared with placebo group which showed a mean of 191.17±25.51 ranging from 153-248 with no statistically substantial variations at p value =0.081.

The research of **Zannad et al., [6]** which agrees with our findings, revealed that there no substantial variations between two groups in term of BNP (brain natriuretic peptide), GFR (glomerular filtration rate), NT-proBNP (N-terminal pro-brain natriuretic peptide), NYHA, Median d-dimer level, and Median ejection fraction.

Also, the study by **Eikelboom et al., [9]** revealed that there no substantial variations between two groups according Cholesterol and Estimated GFR,

As well, **Mega et al., [7] and Mega et al., [8]** revealed that there no substantial variations between two groups in term of cholesterol and Creatinine clearance.

Regarding the drug use of the studied groups, our results showed that all the patients in both groups were taking diuretics while only 27(90%) in the placebo group were taking Angiotensin converting enzyme inhibitors, 24(80%) were taking Mineralocorticoid-receptor antagonists, 25(83.3) were taking Beta-Blockers, 21(70%)were taking Aspirin or thienopyridine and 8(26.7%) were taking Dual anti-platelet therapy as compared with (28(93.3%), 20(66.7%), 24(80%), 23(76.7%) and 10(33.3%)respectively)in other group with no statistically substantial variations at p value >0.05.

In agreement with our results the study by **Mega et al., [7] and Mega et al., [8], Eikelboom et al., [9]** reported that there no substantial variations between groups according medication usage.

As regard the composite efficacy outcome of rivaroxaban, 22(73.3%) of patients in placebo group developed efficacy outcome events distributed as following: 9 (30%) of patients died, with 6 (20%) dying from cardio vascular conditions, 3(10%) developed MI and 10(33%) re-hospitalized for worsening of heart failure.

In addition, the research by **Mega et al., [8]** reported that the main effectiveness objective was 5.6% (126/2331) for rivaroxaban vs 7% (79/1160) for placebo (HR 0.79, 95 percent CI 060–105; p=010) in the total cohort. (Figure 5A). For death (29/2331 [1.3 percent] vs 16/1160 [1.4 percent], HR 0.91, 0.49–1.67), myocardial infarction (67/2331 [3.0%] vs 44/1160 [4.0 percent], HR 0.75, 0.52–1.010), and stroke (6/2331 [0.3 percent] vs 6/1160 [0.5 percent], HR 0.50, 0.16–1.54), but not for severe recurrent ischaemia requiring revascularisation (44/2331 [2.0%] vs 18/1160 [1.6%], HR 1.22, 0.71–2.12).

Also, **Eikelboom et al. [9]** revealed in their investigation that A major end event of cardiovascular death, stroke, or myocardial

infarction occurred in 379 patients (4.1%) who were taken rivaroxaban + aspirin, 448 (4.9%) who were given rivaroxaban alone, and 496 (5.4%) who were given aspirin alone. When rivaroxaban (2.5 mg twice daily) was compared to aspirin alone, the relative risk for the primary result was 0.76 (95 percent confidence interval [CI], 0.66 to 0.86; P< 0.001; z=4.126). When rivaroxaban (5 mg twice day) was compared to aspirin alone, the risk ratio was 0.90 (95 percent CI, 0.79 to 1.03; P=0.12; z=1.575).

On the other hand, only 2(6.7%) of patients in group of rivaroxaban developed safety outcome events which include the following: One patient (3.3%) advanced lethal hemorrhage., and two (6.7%) experienced a drop in hemoglobin level of at least 2 g per deciliter, with a statistically substantial variation between the two groups in terms of advancement of composite safety result and drop in hemoglobin level of at least 2 g per deciliter (p value =0.038).

However, the study by **Zannad et al., [6]** reported that the main safety event of fatal hemorrhaging or hemorrhage into a critical space with the potential to cause irreversible impairment happened in 18 patients (0.7%) who were given rivaroxaban and 23 patients (0.9%) who were given placebo (risk ratio, 0.80; 95 percent CI, 0.43 to 1.49; P=0.48). There were 9 fatal hemorrhage events in each group, but the rivaroxaban group had fewer critical-space hemorrhage incidents than the placebo group (13 [0.5 percent] vs. 20 [0.8 percent]; risk ratio, 0.67; 95 percent CI, 0.33 to 1.34; P=0.25).

Survival analysis using Kaplan-Miere curve between placebo and rivaroxaban groups showed that rivaroxaban group had a statistically significant higher survival rate without composite efficacy outcome (death from any cause, stroke, Re-hospitalization due to severe heart failure and the advancement of MI) as compared to placebo group with mean duration of survival equal 23.84±0.103 and 18.58±0.103 at p value <0.001.

Based on the COMMANDER HF Trial **Greenberg et al., [5]** concluded that In individuals with HF, CAD, and sinus rhythm, thromboembolic incidents were common. Rivaroxaban may lower the hazard of thromboembolic incidents in this cohort, however thromboembolic events are not the leading cause of illness and death among patients with recent HF exacerbation for whom rivaroxaban had no benefit.

Furthermore, the recent meta-analysis by **Xie et al., [10]** which enrolled Participants taking rivaroxaban had a decreased risk of the key feasibility objective (RR, 0.86; 95 percent CI, 0.76–0.97, p =.01) but a higher risk of the primary safety endpoint (RR, 1.83; 95 percent CI, 1.10–3.05, p =.02) in five RCTs that included 43,650 patients. Subgroup studies revealed that the risk–benefit ratio seems to be more favorable in males, but it appears to be unfavorable in patients aged 65 and above, females, diabetic patients, those with mild to severe impaired renal function, and patients from Asia/other regions.

One more meta-analysis by **Ueyama et al., [11]** comprised 5 randomized controlled trials with a total of 9,390 patients, found that oral anticoagulation with or without antiplatelet medicines increased the incidence of hemorrhage in individuals with HFrEF and sinus rhythm without having a significant influence on the incidence of ischemic stroke.

## CONCLUSION:

In conclusion, In patients with recent worsening of chronic heart failure and lower ejection fraction who also had underlying coronary artery disease and were not in atrial fibrillation, small dose rivaroxaban added to guideline-based therapy was associated to a lower rate of the composite results of deaths from any cause, myocardial infarction, or stroke than placebo. More research with a bigger sample size is required to validate the present findings and determine the optimal rivaroxaban dosage.

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