Efficacy and Safety of Rivaroxaban versus Warfarin in Patients with Coronary Endarterectomy: A Cross Sectional Study

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Abstract

Background: Coronary endarterectomy is an adjunctive treatment to coronary artery bypass grafting (CABG) in patients with multiple coronary involvements. The aim of the present study was to compare the efficacy and safety of the rivaroxaban versus warfarin in patients undergoing CABG endarterectomy in a prospective observational study.

Methods: All the patients who had undergone CABG endarterectomy and had received rivaroxaban or warfarin during the period from January2019 until August 2021 were included in the study. Need for salvage CABG, major bleeding, and thromboembolic events were considered as primary outcomes. The secondary outcomes included all-cause mortality and minor bleeding. All patients were followed for at least six months after their hospital discharge.

Results: Out of the 73 patients recruited during the 18 months, 45 received rivaroxaban and the remaining people received warfarin along with at least one antiplatelet. During the follow-up, no salvage CABG was performed. The minor bleeding was comparable between the two groups (31.96 versus 13.27; p=0.21). There was no significant difference between warfarin and rivaroxaban in terms of major bleeding and thromboembolic events (p=0.38 and >0.99, respectively). The all-cause mortality rate was similar between the two groups (p>0.99).

Conclusion: In this preliminary real-word study, rivaroxaban was comparable to warfarin in terms of efficacy and safety in the patients undergoing CABG endarterectomy. Further larger studies are needed to clarify safety and efficacy of such approach.

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Keywords: Coronary Artery Bypass Grafting; Endarterectomy; Rivaroxaban; Warfarin

Introduction

Surgical revascularization and percutaneous intervention are two crucial procedures used for patients with complex coronary heart diseases. Cardiac surgery is an essential approach for reducing mortality, especially among patients with extensive coronary diseases. Because of the presence of diffused plaques in some patients with comorbidities, their vessels are likely to be non-graftable, and about 25% of these cases can be successfully cured by the use of the standard coronary artery bypass graft (CABG) procedure, which can lead to incomplete revascularization. To modify this process, surgeons use coronary endarterectomy (CEA) as an adjunctive treatment for CABG by removing the atherosclerotic core from the lumen of the coronary artery.

The CEA is considered as an adjunctive treatment to the CABG in patients with multiple coronary involvements. The morbidity of this surgical process lies between 2.0 - 6.5% which is greater than that of the CABG alone; for this

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reason, many surgeons have worries about the efficiency of the CEA (1). The CEA procedure was developed in 1957 by Bailey et al., The myocardium that is supplied by the peripheral branches of the diseased coronary artery can be relieved from ischemia, and more complete revascularization can be achieved by applying the CEA.

In order to maintain the patency of the CEA and because of the lack of endothelium in this procedure, which can lead to a higher risk of thrombosis, some antithrombotic protocols have been introduced. Different antiplatelet and anticoagulant protocols have been tried for this purpose. Combinations of two antiplatelets (such as aspirin with clopidogrel, aspirin and ticagrelor, aspirin and dipyridamole), anticoagulants with antiplatelets (warfarin with ticlopidine or aspirin), or anticoagulants alone are antithrombotic regimens that have previously been studied (2-6). However, the combination of aspirin with warfarin or clopidogrel were the most frequently used regimens for thrombosis prevention after CABG/CEA. Considering the fact that there are not sufficient studies conducted on the postoperative anticoagulant protocols in the CABG/CEA, we designed this study with the aim of comparing the efficacy and safety of warfarin and rivaroxaban in patients undergoing CABG/CEA following acute coronary syndrome.

Methods

This is a cross sectional study that conducted during the period from 21, January 2020 to 21, August 2021. All the patients with acute coronary syndrome who were candidate for the CABG/CEA and had received antiplatelet and anticoagulant were included in this study. All of the patients received aspirin 80 mg daily, clopidogrel 75 mg daily, and warfarin (INR: 2-2.5) or rivaroxaban 15 mg daily. For the patients with ClCr 15-50 ml/min, rivaroxaban 10 mg daily was prescribed in addition to aspirin and clopidogrel. Anticoagulant was discontinued 3-6 months after the surgery based on the surgeon's opinion.

The patients' demographic, clinical (including patients' comorbidities and hemodynamic parameters), and laboratory data (e.g. liver and kidney function, CBC, PT, PTT, INR) were recorded during their hospitalization. The follow-up was performed by telephone interview six months after the surgery. Any thromboembolic event, e.g., venous thromboembolism, myocardial ischemia, repeated revascularization, ischemic stroke, and major bleeding, were considered as a primary outcome. The secondary outcome included minor bleeding and mortality.

The HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) risk score was used in order to determine the bleeding risk among the patients. According to this score patients are categorized to four levels of bleeding risk: very low risk, low risk, moderate risk, and high risk of bleeding when the HAS-BLED score is 0, 1, 2, and ≥ 3, respectively (7, 8).

Intracranial bleeding, severe gastrointestinal bleeding, hemoglobin drop of more than 2 g/dL from baseline, and life-threatening bleeding were considered major adverse events. Minor bleeding was described as hemoptysis, epistaxis and menorrhagia.

The data was analyzed using the SPSS software (V.25). The categorical variables were expressed as number and percentage. The chi-square and Fisher's exact tests were used to compare these variables between the two groups. The continuous variables were reported as mean±SD. The Shapiro-Wilk test was used in order to determine the normal distribution of the variables. The normally distributed continuous variables were compared using the student t-test, and non-normally distributed variables were compared by the use of the Mann-Whitney rank sum test. The p-values less than 0.05 were considered as statistically significant.

This study was directed according to the Helsinki Declaration, and it was approved by the Ethics Committee of Kermanshah University of Medical Sciences (ethics approval number: KUMS.REC.1398.1152).

Results

Out of the 73 patients enrolled in the study, 28 received warfarin and 45 received rivaroxaban. The baseline clinical and laboratory data of the two groups are shown in Table 1. The mean age of our patients was 62.3±10.6 years, and the majority of them were male (61.6%).

Rivaroxaban was administered in 13 patients (28.8%) at a dose of 10 mg, in 26 patients (57.7%) at a dose of 15 mg, and in 6 patients (13.3%) at a dose of 20 mg. Due to the lack of data regarding the administration of rivaroxaban in the CABG/CEA patients, this drug was administered unconfirmed in 100% of the patients. To determine the appropriate dose of this drug in the CABG/CEA patients, an equivalent dose of warfarin with INR 2 to 2.5 was used. Rivaroxaban was prescribed in 82.2% of the patients (37 people) with the correct dose and in 17.7% (8 patients) with higher dose. No kidney dose adjustment was performed in two patients with CLCr less than 50 ml/min.

The bleeding risk according the HAS-BLED risk score was similar between the two groups (p>0.99). Most of the patients in the both groups had mild bleeding risk.

Table 1. comparison of the demographic, clinical and laboratory of patients between rivaroxaban and warfarin groups.

Characteristics	Rivaroxaban(n=45)	Warfarin(n=28)	P value
Age (year, mean ±SD)	62.86±9.61	61.4±12.3	0.89*
Sex			
Male (n, %)	29/45 (64.44%)	16/28 (57.14 %)	0.53**
Female (n, %)	16/45 (35.56%)	12/28 (42.86 %)	
Height (cm, mean ±SD)	167.41±9.05	167.13±8.73	0.86*
Weight (Kg, mean ±SD)	73.79±13.21	73.56±10.45	0.69*
Heat rate (breaths/min, mean ±SD)	78.78±9.70	84.58±15.73	0.081*
Systolic blood pressure (mmHg, mean ±SD)	128.50±14.70	120.77±18.15	0.031*
Diastolic blood pressure (mmHg, mean ±SD)	77.26±9.51	77.77±10.09	0.94*
Respiratory rate (breathe/min, mean ±SD)	17.40±1.12	17.56±1.39	0.48*
Creatinine (mg/dl, mean ±SD)	1.11±0.28	1.18±0.37	0.65*
BUN (mg/dl, mean ±SD)	18.09±6.55	24.31±12.76	0.067*
Hb (g/dl, mean ±SD)	13.00±2.22	12.52±1.87	0.31*
Platelet (*10^3 cells/microliter, mean ±SD)	219.48±80.34	205.39±68.29	0.51*
AST (u/lit, mean ±SD)	43.11±46.85	65.47±60.55	0.019*
ALT (u/lit, mean ±SD)	51.97±79.65	36.00±27.59	>0.99*
ALP (u/lit, mean ±SD)	224.20±145.01	154.66±35.85	0.005*
PT (s)	15.59±2.72	19.93±5.84	0.003*
INR	1.39±0.38	2.06±0.92	0.003*
Diabetes (n, %)	17/45 (37.78%)	4/28 (14.28%)	0.023**
Heart failure (n, %)	13/45 (28.88%)	13/28 (46.43 %)	0.17**
Prior MI (n, %)	8/45 (17.78%)	1/28 (3.57%)	0.078***
Hypertension	25/45 (55.56%)	9/28 (32.14%)	0.032**
History of smoking (n, %)	15/45 (33.33%)	8/28 (28.57%)	0.62**
Opium user (n, %)	16/45 (35.56%)	16/28 (57.14%)	0.58**
Metformin (n, %)	3/45 (6.67%)	0/28 (0 %)	0.003***
Sulfonylurea (n, %)	3/45 (6.67%)	1/28 (3.57%)	0.28***
Clopidogrel (n, %)	24/45 (53.33%)	4/28 (14.28%)	>0.001**
Aspirin (n, %)	39/45) 86.67%)	22/28 (78.57%)	>0.99
Statin (n, %)	36/45 (80%)	20/28 (71.43 %)	0.39**
b-blockers (n, %)	39/45 (86.67%)	22/28 (78.57 %)	0.52***
Diltiazem (n, %)	1/45 (2.22%)	1/28 (3.57 %)	>0.99***
CCB (n, %)	3/45 (6.67%)	0/28 (0 %)	0.28***
Insulin (n, %)	2/45 (4.44%)	1/28 (3.57 %)	>0.99***
Amiodarone (n, %)	2/45 (4.44%)	2/28 (7.14 %)	0.64***
Digoxin (n, %)	0/45 (0%)	4/28 (14.28 %)	0.019***
ARB (n, %)	11/45 (24.44%)	4/28 (14.28 %)	0.29**
Diuretic (n, %)	5/45 (11.11%)	8/28 (28.57 %)	0.069***
ACEIs (n, %)	21/45 (46.67%)	14/28 (50 %)	0.78**

ACEI: Angiotensin-converting enzyme inhibitors; ALT: Alanine transaminase; ALP: Alkaline phosphatase; ARB: Angiotensin receptor blocker; AST: Aspartate aminotransferase; BUN: blood urea nitrogen; CCB: Calcium channel blockers; Hb: hemoglobin; INR: International Normalized Ratio; MI: Myocardial infarction; PT: Prothrombin Time
*Mann–Whitney U
**Chi-square test
***ficher's exact test

Table 2. Comparison of the HAS-BLED risk score between rivaroxaban and warfarin groups

HAS-BLED risk score	**Rivaroxaban**(n=45)	**Warfarin**(n=28)	P value
Very Low-low risk (n,%)	40/45 (88.8%)	25/28 (85.7%)	
Moderate-High risk (n,%)	5/45 (11.1%)	3/28 (14.2%)	>0.99*

*fisher's exact test

The efficacy and safety of warfarin and rivaroxaban were similar in the patients (Table 4). The major bleeding was similar between the two groups (p=0.38). There was no significant difference between the two groups in terms of thromboembolic events (p>0.99).

One patient from each group died and the mortality rate was similar between the two groups (p>0.99). Minor bleeding occurred in 6 patients from each group. The characteristics of these patients are summarized in Table 3. There was no significant difference about minor bleeding between the two groups (p=0.21). During the follow up period, no patients needed any surgery.

The mean INR and PT in the patients who were receiving warfarin at the time of admission were 2.1 ± 0.9 and 19.9 ± 5.8 seconds, respectively. About 10% of the patients in the warfarin group showed out of range INR during the follow up.

The mean INR and PT in patients who were receiving warfarin during the follow-up period were 2.26 ± 0.35 and 18.6 ± 0.58 seconds, respectively. During of the follow-up, the INR was less than the therapeutic range in two patients (7.14%).

Out of the 45 patients who were receiving rivaroxaban, 2 (4.4%) did not adhere to the regimen due to the high cost of rivaroxaban.

Table 3. Characteristic of the CABG/Endarteractomy patients with minor bleeding.

No	Age	Sex	Group	Bleeding score	Type of minor bleeding	Medical history	Concurrent medications
1	43	M	Warfarin	1	Nose	HTN	ASA
2	46	F	Warfarin	1	Petechia	HTN	ASA
3	74	M	Warfarin	2	Petechia Hemoptysis	--	ASA
4	42	F	Warfarin	0	Nose	DM	ASA
5	51	F	Warfarin	2	Nose	HTN	ASA
6	77	F	Warfarin	1	Petechia	CHF	ASA
7	61	M	Rivaroxaban	2	Hematuria	CHF, DM	ASA, clopidogrel
8	67	F	Rivaroxaban	3	Nasal bleeding	HTN, DM	ASA
9	57	F	Rivaroxaban	2	Petechia	--	ASA, clopidogrel
10	55	M	Rivaroxaban	2	Petechia	HTN, DM	ASA, clopidogrel
11	57	M	Rivaroxaban	0	Hematuria	---	ASA, clopidogrel
12	46	M	Rivaroxaban	1	Petechia	HTN	--

ASA: Aspirin; CHF: Congestive Heart Failure; DM: diabetes mellitus; F: Female; HTN: hypertension; M: Male

Table 4. Comparison the efficacy and safety of the rivaroxaban and warfarin in patients undergoing CABG endarterectomy.

Characteristics	Rivaroxaban (n=45)	Warfarin (n=28)	P value*
Thrombotic events	1 (2.22%)	1 (3.57%)	>0.99
Major bleeding	0 (0%)	1 (3.57%)	0.38
Minor bleeding	6 (13.27%)	6 (31.96%)	0.21
Mortality rate	1 (2.22%)	1 (3.57%)	>0.99

*fisher's exact test

Discussion

The efficacy and safety of warfarin/aspirin and rivaroxaban/aspirin were similar in the present study. Thrombosis, as one of the major causes of graft dysfunction, could worsen the patients' outcomes (9). In the recent years, the CABG/CEA has been considered due to the importance of complete revascularization in patients with diffuse and extensive coronary artery diseases.

After coronary endarterectomy, the lack of endothelium can lead to coagulation cascade activation via the subendothelial material exposed to blood flow. Therefore, proper antiplatelet or anticoagulation management is required. Different antithrombotic treatment modalities, including short-term therapeutic doses of heparin, aspirin, clopidogrel or warfarin, have been used by clinicians after the CABG/CEA; however, no standard anticoagulation regimen is available for this indication (10).

Subsequently, a meta-analysis of 19 cohort studies and one randomized controlled trial with a high risk of bias showed a higher risk of hospitalization, myocardial ischemia and 30-day mortality, ventricular arrhythmia, acute renal failure, need for ionotropic support, and blood products transfusion in the patients who had undergone the CABG/CEA versus the CABG alone (1). Therefore, to reduce the thrombosis risk after surgery, the clinicians used different antithrombotic regimens. For example, Abid et al. used aspirin 75 mg and clopidogrel 150 mg 2 hours before the procedure and 75 mg of aspirin and clopidogrel for 3 months (2). Other studies used warfarin, combination of aspirin and dipyridamole, combination of warfarin and ticlopidine, and warfarin and aspirin for different treatment durations (3-6). Indefinite anticoagulants therapy with warfarin was used by some authors (6).

The results of our study are similar to those of the recent studies (11, 12). In one study, the authors compared the dual antithrombotic therapy (aspirin plus one following clopidogrel, ticagrelor, or warfarin) vs. aspirin alone (11). Finally, the authors concluded that there was no difference between the single antithrombotic therapy vs. the dual antithrombotic therapy in terms of graft patency (11). In addition, Russo et al., compared single vs dual antiplatelet therapy in the patients who were undergoing coronary endarterectomy (12). 20 patients received 100 mg aspirin and 52 patients received 100 mg aspirin and 75 mg clopidogrel. In the hospital, the mortality, myocardial infarction, and bleeding were similar between the two groups. Finally, the authors recommended the dual antiplatelet therapy for patients undergoing CE. It seems that combination of aspirin with either clopidogrel or ticagrelor can lead to similar outcomes (13). The current guideline by The European Association for Cardio-Thoracic Surgery recommends the use of the dual anti-platelet therapy in the selected patients with stable ischemic heart disease after the CABG/CEA (14).

Platelet inhibitory of clopidogrel may vary, and less than 15% of parent drug may be biologically available (15). In addition, up to 25% of the patients undergoing PCI with stenting may be clopidogrel resistant (16). Therefore, some authors recommended the use of anticoagulants (warfarin at target INR of 2 for 3 months) and antiplatelet (aspirin 100 mg daily indefinitely) in order to minimize graft dysfunction (17, 18). However, safety and efficacy this approach are not well clarified.

Hua Yan et al., compared the dual antiplatelet regimens (aspirin with clopidogrel or ticagrelor) in the patients with the CABG/CEA. During the one-year follow-up, ischemic events and overt bleeding were observed in 5% and 3% of all the patients, respectively. The efficacy and safety of the regimens containing clopidogrel and ticagrelor were similar (19).

The efficacy of the two antithrombotic regimens in the patients who were undergoing the CABG/CEA was reviewed. In this clinical trial, the authors recommended that aspirin/clopidogrel can be considered as a preferred alternated regimen for aspirin/warfarin (20).

The efficacy of aspirin/acenocoumarol and aspirin/clopidogrel were compared in a retrospective study by Kyuchukov et al. Aspirin/clopidogrel was considered as the alternate regimen because of the similar efficacy and lower bleeding compared to the other regimen (21).

Although our study provides real-world data on the safety and efficacy of rivaroxaban use in CABG/CEA patients. However, the study has limitations. First, this was an observational study and the limitations of observational studies should not be neglected. For example, rivaroxaban was not covered by most insurance companies at the beginning of the study, and therefore; some patients were unable to fill their prescriptions for longer periods of time. Second, the small sample size was not large enough to draw definitive conclusions. And finally, some patient data was lost due to telephone follow-up.

Although there are limited data about the best antithrombotic regimen after the CABG/CEA, most of the authors prescribe the dual antiplatelet regimens.

Further studies should be conducted to assess whether the dual antiplatelet regimen is sufficient to reduce risk of thrombosis after the CABG/CEA, or a regimen containing anticoagulant should be prescribed.

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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