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Safety and efficacy of rivaroxaban plus clopidogrel in atrial fibrillation patients after acute coronary syndrome

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Summary

Background

Proper antithrombotic management of patients with AF and ACS is challenging. The current ESC guidelines in 2014 recommend 'triple therapy' with OAC plus aspirin and clopidogrel for 1 or 6 months titrated to double therapy for 6 or 11 months. The effectiveness and safety of double therapy with rivaroxaban plus clopidogrel for 12 months are uncertain in such scenario.

Methods

Single-center non randomized prospective trial enrolled 100 participants with AF who had UA/NSTEMI treated either medically or underwent PCI. Fifty patients received rivaroxaban 20mg once daily plus clopidogrel (75mg) for 12 months (group:1). Another 50 patients received triple then double therapy of dose-adjusted vitamin K antagonist plus (clopidogrel and aspirin) according to ESC guidelines up to 12 months (group:2). The primary outcome was the combination of minor and major non CABG TIMI bleeding up to 12 months. The secondary outcomes were major adverse cardiovascular events (cardiac mortality, non fatal MI, stent thrombosis or stroke).

Results

Rates of both minor and major bleeding were lower in Group:1 (Rivaroxaban plus clopidogrel) but with no significant differences (OR=0.73 [95% CI=0.73to1.4]; NNT=12.5; P=0.58). RRR of bleeding rates in the rivaroxaban group was (25 to 27%). The composite rates of MACCE showed no significant differences in both groups (36% vs 30%, OR=1.14 [95% CI=0.6to2.0]; P=0.652). In subgroup analysis, patients in group:1 who treated with PCI had lower rates of non fatal MI and definite stent thrombosis in comparison to group:2 (RRR=16%; P=0.63).

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Conclusion

Rivaroxaban (20 mg OD) plus clopidogrel (75 mg) for 12 months was safe and effective in participants with AF and UA who treated medically or PCI. We recommend this regimen over standard triple therapy with a dose-adjusted vitamin K antagonist. This regimen provide better adherence and advantage that patients do not need to switch from triple to dual therapy.

Keywords

Atrial fibrillation; Unstable angina; Rivaroxaban.

Introduction

Atrial fibrillation (AF) is the most common form of arrhythmia; about 25% of AF patients have coronary artery disease (CAD). Among patients undergoing percutanous coronary intervention (PCI), approximately 5% to 21% of patients have concomitant AF [1]. For decades, oral anticoagulants (OAC) have been effectively used to decrease complications associated with medical conditions such as AF, mechanical heart valves or deep venous thrombosis. Aspirin and P2Y12 inhibitors (DAPT) discovered to be inferior to OAC for preventing stroke. Similarly, OAC are not effective as DAPT after stent implantation [2].

Combination therapy between OAC and DAPT (Triple therapy) seems like an attractive option for preventing both stroke and in-stent thrombosis but must be balanced against a suspected higher bleeding risks [3]. Generally, bleeding events with triple therapy have been found to be 3.7 times higher than that with warfarin alone and 4 times than with aspirin as a monotherapy [4]. The yearly incidence of bleeding with triple anti thrombotic therapy have been found to reach 12% compared to only 3.7% for DAPT [5].

Lack of large randomized control trials in assessing the optimal anti thrombotic regimens for high-risk patients with concurrent AF and unstable angina (UA) has resulted in divergence in medical society recommendations [6]. In clinical practice, physicians' strategies broadly vary according to self experience. The decision is usually influenced by the anticipated bleeding risk of combined pharmacotherapy. For safety purpose, it is very important to decide how many anti-thrombotic agents and at what intensity we should be treating patients [7].

Patients and methods

Study population

This single-center, prospective, non randomized trial performed from March 2016 to May 2017. Inclusion criteria was AF (prior, persistent, or >6 hrs duration); physician decision that OAC is indicated; UA-NSTEMI and/or PCI with planned DAPT. Exclusion criteria was previous ACS, PCI or CABG; absolute contraindications for OAC; patients with prosthetic valves or rheumatic mitral stenosis; discontinue of OAC during follow up or shifted in between vitamin K or non vitamin K oral anticoagulants (NOACs); any cardiac or non cardiac surgery/procedure which required OAC withhold during follow up.

Study protocol

Designed as a safety and non inferiority trial to estimate TIMI non-CABG bleeding risks of rivaroxaban 20mg once daily (OD) plus clopidogrel 75mg compared to a dose-adjusted vitamin K antagonist plus DAPT (triple therapy). Sample size of 100 AF patients none randomly divided after having recent diagnosed attack of UA/NSTEMI into two groups.

Group 1 (50 patients): received rivaroxaban 20 mg OD combined to clopidogrel 75mg for 12 months.

Group 2 (50 patients): received triple therapy for 6 months (warfarin plus DAPT) if treated with PCI with at least one stent followed by double therapy (warfarin plus aspirin 75mg or clopidogrel 75mg) for another 6 months. Patients underwent PCI and were in high risk of bleeding (HAS-BLED score ≥ 3) received triple therapy for only one month followed by 11 months of double therapy. Patients who treated medically during follow up period received double therapy for 12 months [8] (Figure 1).

Methods

For all patients full history, clinical examination, 12 leads electrocardiogram , transthoracic echocardiography, laboratory investigations in form of cardiac troponins, serum creatinine, liver function test, complete CBC, HbA1C, coagulation profile including INR ratio were done to confirm diagnosis of chronic AF, assess both bleeding and stroke risks.

CHA2DS2-VASc risk score was used for stroke risk assessment at baseline, males with score ≥2 and fe-

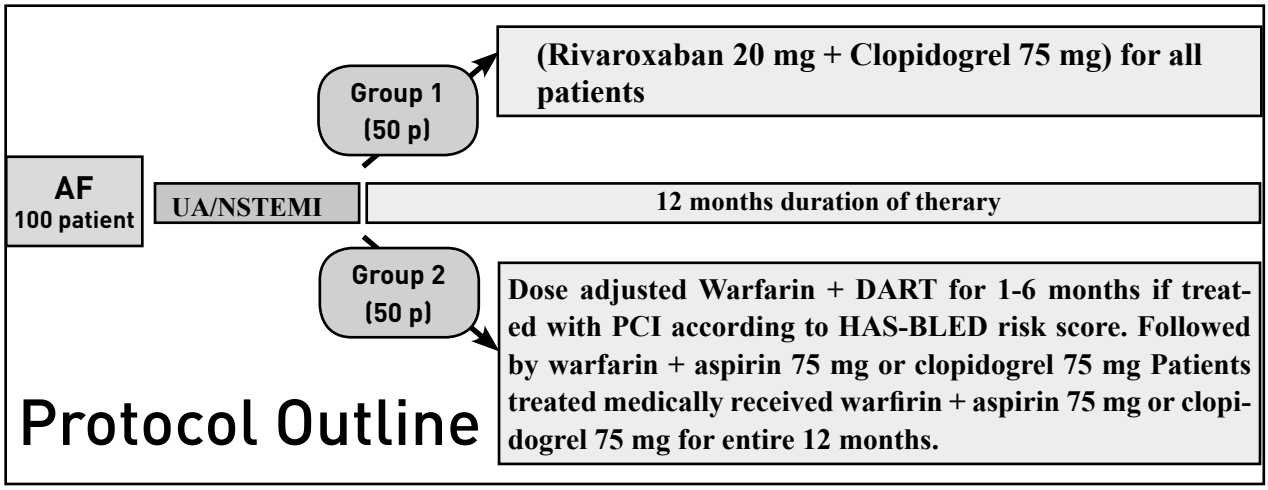

Figure 1. Protocol outline of the study.

males with score ≥3 considered high risk. Males with score ≥1 and females with score ≥2 considered low to moderate risk [9].

HAS-BLED risk score was used for bleeding risk assessment at baseline , patients in both groups had been classified into low risk of bleeding if have score ≤2 and classified into high risk of bleeding if have score ≥3 [10].

Study endpoints and definitions

- The Primary end points were composite of major or minor TIMI non-CABG clinically significant bleeding:

1. Major defined as any intracranial bleeding, any clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in haematocrit, any fatal bleeding (bleeding that directly results in death within 7 days).

2. Minor defined as any clinically overt bleeding, resulting in hemoglobin drop of 3 to <5 g/dL or ≥10% decrease in haematocrit [11].

- The secondary end points were composite of MACCE (cardiac mortality, non fatal MI, stroke/TIA or definite stent thrombosis according to ARC definition) [12].

Statistical analysis

The association between variables and treatment groups was investigated by chi-square or Fisher exact tests. Parametric unpaired Z score test was applied to evaluate differences for continuous variables between both groups. The association between type of treatment and clinical endpoints was expressed as the odds ratio (OR), and the 95% confidence interval (CI) also was reported. Relative risk reduction (RRR) analysis was applied to detect the valuable reduction of bleeding outcomes between two groups. A p value less than 0.05 were considered significant (2-sided). All analyses were carried out using Stata 12 software (StataCorp LP, College Station, Texas).

Results

Study population

Demographic, clinical, risk stratification, angiographic and coronary intervention variables are presented in (Table 1). There were no significant differences between the two groups regarding age, gender, diabetes mellitus (DM), hypertension, previous bleeding or stroke/TIA. High risk patients for CHA2DS2-VASc score or HAS-BLED score were equivalent in both groups (P= 0.7&0.63) (Table 1).

Table 1. **Baseline demographic, clinical, risk stratifications, angiographic, and coronary intervention characteristics by treatment Group**

	Group 1 (N=50)	Group 2 (N=50)	Z score	P value
Age, median(yrs)	66.3	66.9	0.1	0.8
Male, no. (%)	27 (54%)	27 (54%)	0	1
DM, no. (%)	20 (40%)	21 (42%)	0.1	0.89
HTN, no. (%)	29 (58%)	30 (60%)	0.1	0.91
Previous bleeding	9 (18%)	5 (10%)	0.98	0.32
Previous stroke	14 (28%)	15 (30%)	0.16	0.87
HAS-BLED score ≥3	17 (34%)	14 (28%)	0.47	0.63
CHA2DS2-VASc ≥ 2 (m), ≥3 (f)	31 (62%)	37 (74%)	0.38	0.7
Medically treated patients	18 (36%)	16 (32%)	0.29	0.7
PCI undergoing patients	32 (64%)	34 (68%)	0.19	0.8
Patients received ≥1 new generation DES	24 (48%)	24 (48%)	0	1

TIMI non CABG major or minor bleeding rates

The primary endpoint of composite major and minor TIMI non CABG bleeding occurred in 11 patients (22%) in the rivaroxaban group (Group 1) and 15 (30 %) in the Group 2, with odd ratio (OR) of 0.73 [95% CI=0.73 to 1.4]; NNT=12.5; P=0.58. (Table2 & Figure2) After adjusting for subgroup of patients with high bleeding risk at baseline (HAS-BLED ⩾3), Bleeding rates remained lower with rivaroxaban group (OR=0.66; [95% CI=0.56 to 0.76]; NNT=7.6; P=0.28). The relative risk reduction (RRR) of bleeding rates in the rivaroxaban group ranged from (25 to 27%) (Table 2).

Secondary endpoints

The secondary endpoint of composite non fatal MI, definite stent thrombosis, stroke/TIA and CV mortality occurred in 18 patients (36%) in the rivaroxaban group (Group 1) and 15 (30%) in the Group 2, with (OR of 1.14 [95% CI=0.6 to 2.0]; P=0.652) (Table 3). This non significant differences remained among subgroup of AF patients with high risk for stroke at baseline (CHA2DS2-VASc ⩾2 for males and ⩾3 for females) [14/31 (36%) vs 12/37 (30%); OR=1.2; [95% CI= 0.65-2.44]; P=0.28) (Table 4). In subgroup of patients who received stenting after UA/NSTEMI, composite rates of definite stent thrombosis and non fatal MI were lower in rivaroxaban group [6/32 (18.75%) vs 8/34 (23.5%); RRR=16%; p = 0.63] (Table 4).

Discussion

For decades, antithrombotic therapies have been effectively used to decrease complications associated with medical conditions such as AF, mechanical heart valves or deep venous thrombosis. Aspirin and clopidogrel (DAPT) is considered the standard of care to prevent stent thrombosis. For preventing stroke in AF patients with high-risk, DAPT discovered to be inferior to OAC. Similarly, oral anticoagulants are not effective as a monotherapy after stent implantation [2]. So, combined therapy of OAC and DAPT (triple therapy) seems like an attractive option for preventing both stroke and in-stent thrombosis in high-risk

Table 2. **Rates of TIMI non CABG bleeding in study groups and in subgroups with high risk of bleeding at baseline**

Primary end points	Group 1 (N=50)	Group 2 (N=50)	Odd ratio (95% CI)	RRR	NNT	Z score	P value
Composite of bleeding	11 (22%)	15 (30%)	0.73 (0.73–1.4)	-0.26	12.5	-0.911	0.5840
TIMI major bleeding	3 (6%)	4 (8%)	0.75 (0.76–3.18)	-0.25	50	-0.3919	0.696
TIMI minor bleeding	8 (16%)	11 (22%)	0.7 (0.32–1.6)	-0.27	16.6	-0.764	0.447
	HAS-BLED score ≥3 in Group 1 (N=17)	HAS-BLED score ≥3 in Group 2 (N=14)	Odd ratio (95% CI)	RRR	NNT	Z score	P value
Composite of bleeding	6(22%)	9(30%)	0.66 (0.28–1.55)	-0.26	7.66	-1.03	0.35
TIMI major bleeding	1(6%)	3(8%)	0.33 (0.03–2.7)	-0.25	8.2	-1.06	0.29
TIMI minor bleeding	5(16%)	6(22%)	0.75 (0.27–2.1)	-0.27	13.7	-0.36	0.7

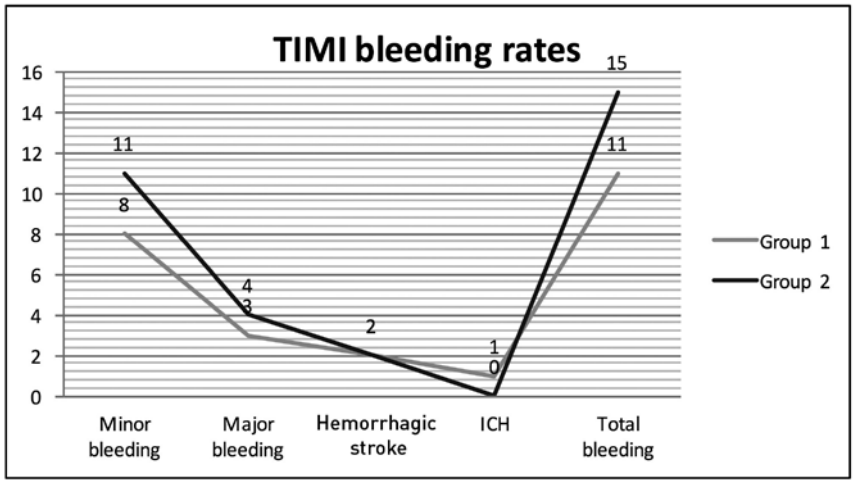

Figure 2. TIMI bleeding rates in both groups

Table 3. **Secondary endpoints in study groups**

Secondary endpoints	Group 1 (N=50)	Group 2 (N=50)	Odd ratio (95% CI)	Z score	P Value
Composite of MACCE	18(36%)	15 (30%)	1.14 (0.62–2.0)	0.45	0.652
CV mortality	4 (8%)	3 (6%)	1.3 (0.3–5.5)	0.361	0.696
Non fatal MI	3 (6%)	2 (4%)	1.43 (0.2–8.4)	0.458	0.65
Stroke/TIA	5 (10%)	5 (10%)	1 (0.9–1.1)	0	1
Definite stent thrombosis	4 (8%)	3(6%)	1.3 (0.3–5.5)	0.39	0.696

Table 4. **MACCE in subgroups of high risk of stroke and composite of coronary events in subgroups treated with PCI in both groups**

	CHA2DS2-VASc score ≥2 for males and≥3 for Females in Group 1 (N=31/50)	CHA2DS2-VASc score ≥2for males and≥3 for females inGroup2 (N=37/50)	OR (95% CI)	Z score	P Value
Composite of MACCE	14/31(36%)	12/37 (30%)	1.2 (0.65–2.44)	1.07	0.28
CV death	4/31 (8%)	3/37 (6%)	1.3 (1.4–1.2)	0.64	0.51
MI	3/31 (9.7%)	2/37 (4%)	1.5 (1.6–1.4)	0.67	0.5
Stroke/TIA	3/31(9.7%)	3/37 (8%)	1 (0.9–1.1)	0.22	0.88
Definite stent Thrombosis	4/31 (8%)	4/37 (10%)	1.3 (1.41.2)	0.26	0.78
	Patients in Group1 PCI treated (N=32/50)	Patients in Group2 PCI treated (N=34/50)	RRR	Z score	P value
Composite of coronary events	6/32 (18.75%)	8/34 (23.5%)	16%	-0.47	0.638
Non fatal MI	2/32 (6.25%)	2/34 (5.8%)	17%	0.062	0.952
Definite stent thrombosis	4/32 (12.5%)	6/34 (17.6%)	16%	-0.526	0.56

patients with concurrent AF and unstable angina but must be balanced against a suspected higher bleeding risks [3]. Generally, bleeding events with triple therapy have been found to be 3.7 times higher than that with warfarin alone and 4 times than with aspirin as a monotherapy [4]. Similarly, adding warfarin to DAPT increases the relative risk for bleeding up to 2.2, and the yearly incidence of bleeding up to 12% compared to 3.7% for DAPT [5].

Lack of large randomized control trials in this area has resulted in divergence in medical society recommendations. ESC guidelines in 2014 recommended that high-risk patients with concurrent AF and unstable angina treated with PCI should receive triple therapy for one month up to 6 months depending on their bleeding risk. Patients treated medically should receive double therapy of warfarin and clopidogrel or aspirin for 12 months [13, 14]. Different scenarios could be noticed in ACC/AHA and other international guidelines! In clinical practice, physicians' strategies broadly vary according to self experience! The decision is usually influenced by the anticipated bleeding risk of combined pharmacotherapy [15].

In Meta analysis of large randomized trials (RELY, ROCKET-AF, ARISTOTLE, ENGAGE-AF) included 42411 patients, NOACs significantly reduced stroke or systemic embolic events by 19% compared with VKA with lower rates of ICH and hemorrhagic strokes. However, there are few randomized studies in which triple therapy including rivaroxaban with DAPT in patients with ACS [16].

Single P2Y12inhibitor or DAPT in AF patients after ACS and/or PCI

Aiming to reduce bleeding risks in combined anti thrombotic regimens, The Option to omit aspirin from the regimen and treat only with an (N)OACs and a single P2Y12 inhibitor was first studied in WOEST trial, which showed that warfarin plus clopidogrel reduced bleeding risk and improved efficacy versus triple therapy. In the most recent study PIONEER AF PCI, Rivaroxaban with reduced doses 15 mg once-daily plus one P2Y12 inhibitor (clopidogrel) reduced the rates of TIMI minor and major bleeding (16.8%; HR) versus triple therapy included warfarin plus DAPT [17].

In correlation with WOEST & PIONEER AF PCI results , this study showed lower rates of composite major and minor TIMI non CABG bleeding in the group received rivaroxiban 20mg once daily plus clopidogrel (OR=0.73; NNT = 12.5; p value = 0.58). These rates remained lower with rivaroxiban group even in subgroup of patients with high bleeding risk (OR=0.66; NNT= 7.6; p = 0.28) with RRR of bleeding rates ranged from (25 to 27%) (Tables 2).

The reduced versus full dose of NOACs

The efficacy and safety of optimal reduced doses of NOACs in Patients with AF and ACS or PCI was only

powered in few trials [18]. In the PIONEER AF PCI trial, Rivaroxaban with reduced doses included in two arms (15 mg once-daily plus clopidogrel) or (2.5 mg twice-daily plus DAPT). The rates of TIMI minor and major bleeding were lower in first arm (16.8%; HR) and second arm (18.0%; HR) versus 26.7% in the warfarin arm. Risk of MACCE included stroke did not differ between the three arms [17]. Rivaroxaban 2.5 mg BID is approved in Europe for the prevention of atherothrombotic events in adult patients after ACS but it has not been tested for stroke prevention in patients with AF. Rivaroxaban 15 mg OD is approved for stroke prevention in patients with AF [19]. According to stroke risk reduction in AF, our study showed non inferiority of rivaroxiban with standard full dose 20mg OD plus clopidogrel in comparison to triple therapy with dose adjusted VKA (10% in both groups). (Table 3) This non inferiority remained among subgroup of AF patients with high risk for stroke at baseline (CHA2DS2-VASc ≥2 for males and ≥3 for females) [36% versus 30%; OR=1.2; P=0.28] (Table 4).

The novelty of current study

The novelty of current study that rivaroxiban with full dose (20mg) plus clopidogrel was effective in reduction of both stroke and stent thrombosis risks and also was completely safe in reduction of major and minor bleeding in comparison to triple therapy including warfarin with RRR = 25-27%. (Tables 2&3)

The ongoing trials on NOACs versus warfarin in patients with AF and ACS or PCI

The ongoing RE-DUAL PCI phase 3b randomized trial will evaluate dual therapy with dabigatran 150 mg or 110 mg twice daily vs. triple therapy with warfarin in AF patients undergoing PCI with stenting (elective or due to an ACS) [20].

The ongoing AUGUSTUS phase 4 randomized trial will evaluate dual therapy with Apixaban Versus Warfarin in patients with AF and ACS and/or PCI [21].

Study limitation

The statistic analysis of study results could be affected with the relative small sample size.

Conclusion

Rivaroxaban OD plus single P2Y12 inhibitor regimen was associated with improved safety compared with a standard VKA-based triple therapy strategy in patients with AF and UA and/or PCI. Furthermore, the simple dosing regimen of the rivaroxaban 20 mg OD strategy may be associated with better adherence and also provides the practical advantage that patients do not need to switch from triple to dual therapy. Considering both safety and practical use, the single full dose of rivaroxaban 20 mg plus single antiplatelet therapy (clopidogrel) could become the approach of choice once approved.

Conflict of interest: None declared

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