

Original Research Article

Comparison of efficacy and safety profiles of rivaroxaban and aspirin versus clopidogrel and aspirin in the prevention of atherosclerotic events in Chinese dyslipidemic patients with coronary artery disease

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Sent for review: 17 January 2022

Revised accepted: 27 September 2022

Abstract

Purpose: To compare the efficacy and safety profiles of rivaroxaban (R) + aspirin (A) and clopidogrel (C) + aspirin (A) in the prevention of atherosclerotic events in Chinese dyslipidemic patients with coronary artery disease (CAD).

Methods: Coronary artery disease patients were given either R (10 mg daily) + A (100 mg daily) or C (75 mg daily) plus A (100 mg daily), with 105 subjects in each group. Each patient was followed up for 30 months. The following clinical outcomes (as aspects of primary endpoints) were assessed: percentage of patients with incidence of atherosclerotic events, and deaths due to any cause/cardiovascular causes. Hazard ratios and safety were also determined.

Results: A total of 210 enrolled patients completed the study. Compared to C + A group, patients treated with R + A had slightly lower incidence of atherosclerotic events (33.2 vs 32.6 %, $p > 0.05$) and lower death rate due to any cause/cardiovascular causes (3.1 vs 2 %, $p > 0.05$). Patients treated with R + A had significantly greater incidence of bleeding ($p < 0.05$).

Conclusion: The R + A treatment is more effective than C + A treatment in the prevention of atherosclerotic events, although this was not statistically significant different. The incidence of bleeding are significantly higher in R + A group than in C + A group.

Keywords: Aspirin, Clopidogrel, Rivaroxaban, Coronary artery disease, Atherosclerotic, Dyslipidaemia

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INTRODUCTION

Atherosclerotic diseases have a tendency to provoke arterial thrombosis which is a long-term consequence of severe atherosclerosis [1-6]. Reduction of cholesterol level is essential for the prevention of arterial thrombosis [3-9]. The role

of platelets in pathogenesis of atherothrombosis has been well documented. Low-dose aspirin is often used for heart disease patients. The use of low-dose aspirin in combination with clopidogrel as dual antiplatelet therapy is the most recommended treatment for CAD patients with heart diseases and myocardial infarction (MI),

with and without ST-segment elevation. Moreover, it has been reported that dual antiplatelet is effective among CAD patients undergoing angioplasty with stenting [5-9].

Several studies have shown significantly greater protection against CVS events in CAD patients on dual antiplatelet therapy than in patients who took only aspirin (A) or clopidogrel (C) [5-8]. There are some reports on the efficacy of rivaroxaban (R) in controlling atherothrombosis and preventing atherosclerotic events in non-Chinese patients with CAD [9-13]. The present study was designed to determine and compare the effectiveness and safety profiles of rivaroxaban + aspirin and clopidogrel + aspirin in the prevention of atherosclerotic events in Chinese dyslipidaemic patients with CAD.

METHODS

Patients and ethics

Chinese patients with history of stable atherosclerotic vascular diseases were enrolled. Written informed consent was obtained from each enrolled patient. The study received approval from the institutional ethics committee of Ningbo Women and Children's Hospital, *vide*, approval no. NWCH/20223D/MAR-20/ICE-328. The procedures used in the study were in line with the ethical principles laid down in the Helsinki Declaration and its later amendments [14]. Patients with a history of severe renal impairment, liver disease, lung disease, severe CAD and thyroid disease were excluded. Moreover, patients with any other pathology likely to affect the study outcomes, and patients who received concomitant and contra-indicated medications, as well as patients undergoing any other form of surgery, were excluded.

Treatments and procedures

Subjects who met the eligibility criteria were enrolled and were given either rivaroxaban (R) (10 mg daily via the oral route) in combination with aspirin (100 mg daily via the oral route), or clopidogrel (C) (75 mg daily via the oral route) in combination with aspirin (A) (100 mg daily via the oral route). There were 105 patients in each group. Each enrolled patient was carefully monitored and followed up for 30 months.

Assessment of efficacy and safety profiles

Baseline characteristics of each patient were assessed. The following clinical outcomes (as aspects of primary endpoints) were assessed:

incidence of atherosclerotic events, percentage of patients who died due to any cause, percentage of death from cardiovascular causes, percentage of patients with MI, percentage of patients with ischemic stroke, percentage of patients with stroke, and percentage of patients hospitalized due to heart attack. The following safety endpoints (as parts of secondary endpoints) were assessed: incidence of severe bleeding, incidence of fatal bleeding, incidence of intracranial hemorrhage, and incidence of moderate bleeding.

Statistical analysis

No formal sample size calculation was performed in this study, since it was designed as a pilot study. Appropriate method was used to analyze data based on type and distribution (normal and non-normal). The data were analyzed using Graph Pad (version 9.4.1) software. Significant difference was assumed at $p < 0.05$.

RESULTS

A total of 210 patients (105 patients in each group) were enrolled, and all patients completed the study. The demography and baseline characteristics of patients in both treatment groups were comparable, as shown in Table 1.

A summary of primary outcomes is presented in Table 2. Patients treated with R + A had slightly lower incidence of atherosclerotic events than those treated with C + A. Although death due to any cause or due to cardiovascular causes was slightly higher in patients treated with C + A than in those treated with R + A, there were no statistically significant differences between the two groups. There was a slightly higher number of patients with non-fatal MI in the group treated with C + A than in patients who received R + A, although the difference was not statistically significant. Similarly, there was a slightly higher population of patients with non-fatal ischemic stroke in the group treated with C + A than in the group that received R + A. However, the difference was also not statistically significant. Moreover, although the number of patients hospitalized due to heart attack was slightly higher in the group treated with C + A than in the group given R + A, the difference was not significant.

A summary of safety endpoints is shown in Table 3. Patients treated with R + A had significantly greater incidence of severe bleeding than patients treated with C + A.

Table 1: Baseline characteristics of patients (n = 110)

Characteristic	Rivaroxaban plus aspirin (R+A)	Clopidogrel plus aspirin (C+A)
Median age (years)	63	64
Female sex (%)	30	32
Smoking (%)	73	74
Body-mass index (obese) (%)	82	83
Body-mass index (overweight) (%)	76	79
Hypertension (%)	9	10.2
Hypercholesterolemia (%)	45	42
Congestive heart failure (%)	12	11
Prior myocardial infarction (%)	15	17
Diabetic nephropathy (%)	14	13
Diabetes (%)	18	17
Atrial fibrillation (%)	15	14
Prior stroke (%)	16	15
Peripheral arterial disease (%)	21	24
Prior percutaneous coronary intervention (%)	23	22
Prior coronary-artery bypass grafting (%)	4	3

Table 2: Summary of primary outcomes in both groups (n = 110)

Variable	R+A	C+A	P-value
Incidence of atherosclerotic events (%)	32.6	33.2	>0.05
Death due to any cause (%)	2	3.1	>0.05
Death from cardiovascular causes (%)	3	3.6	>0.05
Non-fatal myocardial infarction (%)	4	4.9	>0.05
Non-fatal ischemic stroke (%)	4.5	5.2	>0.05
Stroke (%)	3.1	3.7	>0.05
Hospitalization for unstable angina, transient ischemic attack, or revascularization (%)	5.9	6.4	>0.05

Values of *p* based on categorical variables were calculated using Chi-square test

Incidence of fatal bleeding was slightly higher in patients treated with R + A than in patients treated with C + A. The number of patients with non-fatal intracranial hemorrhage was slightly higher in the group treated with R + A than in the group given R + A. In contrast, the number of patients with moderate bleeding was significantly higher in the group treated with R + A than in those treated with C + A ($p < 0.05$). These results are presented in Table 3.

For patients aged more than 75 years, sub-group analysis showed slightly higher incidence of MI/stroke/death in patients treated with R + A than in patients treated with C + A (Table 4).

With respect to female gender, sub-group analysis showed slightly lower incidence of MI/stroke/death in patients treated with R+A than in patients treated with C + A. Moreover, sub-group analysis of patients with type 2 diabetes showed non-significant difference in incidence of MI/stroke/death between patients treated with R+A and patients treated with C + A, although the former had slightly lower incidence. Similarly, sub-group analysis revealed slightly lower incidence of MI/stroke/death in patients treated with R + A than in those treated with C + A.

Table 3: Summary of safety endpoints in the two groups (n = 110)

Variable	R+A	C+A	P-value
Incidence of severe bleeding (%)	12.8	3.2	<0.05
Incidence of bleeding (fatal) (%)	1.6	1.5	>0.05
Incidence of intracranial haemorrhage (%)	1.8	1.3	>0.05
Incidence of moderate bleeding, (%)	14.5	2.2	<0.05

Values of *p* based on categorical variables were calculated using Chi-square test

Table 4: Summary of hazard ratios for MI/stroke/death in each of the subgroups

Variable	HR	P-value
Age (>75 years)	0.92	0.05
Sex (female)	0.93	>0.05
Diabetes	0.92	>0.05
Smoking	0.89	>0.05
Body-mass index (obese)	0.92	>0.05
Body-mass index (overweight)	0.91	>0.05
Hypertension	0.90	>0.05
Hypercholesterolemia	0.87	>0.05
History of bypass surgery	0.82	>0.05
History of angioplasty	0.88	>0.05
History of infarction	0.89	>0.05
History of stroke	0.95	>0.05

Values of *p* based on categorical variables were calculated using Chi-square test

Sub-group analysis for obese and overweight patients showed slightly lower incidence of MI/stroke/death in patients treated with R + A than in patients treated with C + A, but the differences were not statistically significant. For hypertension and hypercholesterolemia, sub-group analysis showed that the incidence of MI/stroke/death was slightly higher in patients treated with R + A than in patients treated with C + A. In patients with history of bypass surgery, angioplasty, infarction and stroke, sub-group analysis revealed slightly lower incidence of MI/stroke/death in patients treated with R + A than in those treated with C + A. Bleeding was the most common adverse event in both treatment groups. The incidence of bleeding was significantly higher in patients treated with R + A than in patients treated with C + A. These results are shown in Table 5.

Table 5: Summary of treatment emergent adverse events (n = 110)

Variable	R+A	C+A
Severe bleeding (%)	47	32
Abdominal pain (%)	12.5	11.4
Abdominal burning (%)	14	15
Cramping (%)	12	11.4
Gastritis (%)	13	12
Stomach ulcers (%)	17	15
Nausea (%)	11	12
Ringling in the ears (%)	5	03
Rash (%)	1	1.3
Dizziness (%)	2	2.3

DISCUSSION

In China, there are no studies on comparison of safety and efficacy profiles of R + A and C + A in the prevention of atherosclerotic events in Chinese dyslipidaemic patients with CAD thereby making this the first of such study. The

findings are consistent with those reported in previous studies in which R + A produced lower CVS-related death than aspirin monotherapy [10-13]. However, the risk of bleeding associated with R + A was higher than that in aspirin monotherapy. In the published studies, the risk of bleeding associated with R + A was 50 % higher than the corresponding risk associated with aspirin monotherapy [9-13].

In the present study, the risk of severe bleeding in R + A was 13 %, which was significantly higher than 3 % risk in C + A group. In a previous study, R + A produced 25 % lower clinically beneficial outcomes than aspirin monotherapy (4.7 vs. 5.9 %). In an earlier published study, R + A did not significantly differ from aspirin monotherapy in terms of clinical outcomes. However, the incidence of bleeding was higher with rivaroxaban alone. In contrast to findings in an earlier study, the present study has demonstrated that patients treated with R + A and those who received C + A did not differ significantly. Furthermore, subgroup analysis showed slightly lower incidence of MI/stroke/death in R + A group than in R + A group.

Overall, the results of the present study suggest that R + A is as effective as C + A in preventing atherosclerotic events in Chinese dyslipidaemia patients. Incidents of atherosclerotic events were slightly lower in patients treated with R + A than in those treated with C + A. Overall, both study drugs were statistically similar with respect to primary endpoints. In numerical terms, R + A was more effective than C + A in prevention of atherosclerotic events. The possible reason for the non-significant differences in clinical outcomes between the two groups may be due to the low sample size used in the study. However, there was higher incidence of bleeding in R + A than in C + A.

Limitations of the study

The results of this study may not be generalized to the Chinese population due to the low sample size used. Thus, a study with a large sample size is required to validate the results reported here.

CONCLUSION

This study has demonstrated that R + A is slightly more effective than C + A in preventing atherosclerotic events in Chinese dyslipidemic patients with CAD. However, there is higher incidence of bleeding in patients treated with R +

A than in those given C + A. Therefore, the use of R + A may be a better alternative for Chinese CAD patients for whom C + A combined treatment is not suitable.

DECLARATIONS

Acknowledgements

Authors would like to thank patients and study staff for their support in conducting this study.

Funding

None provided.

Ethical approval

The study was approved by the institutional Ethics Committee of Ningbo Women and Children's Hospital, China (approval no. NWCH/20223D/MAR-20/ICE-328).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors have made substantial contributions to the conception and design of this work; or the acquisition, analysis, or interpretation of data for the work; and drafted the work or revised it critically for important intellectual content; and gave final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REFERENCES

- Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999; 340: 115–126.
- Ruggeri ZM. Platelets in atherothrombosis. *Nat Med* 2002; 8: 1227–1234.
- Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque. I. Evolving concepts. *J Am Coll Cardiol* 2005; 46: 937–954.
- Lopez AD, Murray CC. The global burden of disease, 1990–2020. *Nat Med* 1998; 4: 1241–1243.
- Bhatt DL, Steg PG, Ohman EM. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006; 295: 180–189.
- Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. *BMJ* 2002; 324: 71–86.
- Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. The clopidogrel in unstable angina to prevent recurrent events trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; 345: 494–502.
- Chen ZM, Jiang LX, Chen YP. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005; 366: 1607–1621.
- Turpie AG, Lassen MR, Eriksson BI. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty: pooled analysis of four studies. *Thromb Haemost* 2011; 105: 444–453.
- The EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; 366: 1287–1297.
- The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; 363: 2499–24510.
- Patel MR, Mahaffey KW, Garg J. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365: 883–891.
- Mega JL, Braunwald E, Wiviott SD. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012; 366: 9–19.
- World Medical Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. *JAMA* 1997; 277: 925–926.