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Comparison of rivaroxaban-based dual antithrombotic and antiplatelet therapies for symptomatic patients with lower-extremity peripheral artery disease post-revascularization: a retrospective cohort study

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Abstract

Background: Patients with symptomatic lower-extremity peripheral artery disease (LE-PAD) are prone to serious cardiovascular and limb events. Few studies have evaluated the effect of rivaroxaban-based dual antithrombotic therapy in high-risk patients with LE-PAD in Asian populations.

Objectives: To investigate the efficacy and safety of rivaroxaban-based dual antithrombotic therapy in symptomatic patients with LE-PAD.

Design: Retrospective cohort study.

Methods: This study included patients with LE-PAD treated at the Nanjing Drum Tower Hospital from 1 January 2018 to 31 December 2021. These participants were divided into antiplatelet (APT) or antiplatelet therapy combined with rivaroxaban (RAPT) groups. The efficacy outcomes in this study were the occurrence of major adverse cardiovascular events (MACE), including myocardial infarction, ischemic stroke, or death from cardiovascular causes, and major adverse limb events (MALE), including urgent revascularization, acute limb ischemia, and major amputation. The safety outcomes included major and clinically relevant non-major (CRNM) bleeding. Patients were followed up until the time of death or the end of the study (31 March 2023).

Results: We included 1144 patients with LE-PAD (APT: 502 patients; RAPT: 642 patients). The RAPT group had a lower risk of primary composite efficacy outcomes [hazard ratio (HR): 0.40] and a nonsignificant increase in major bleeding risk (HR: 2.33) than the APT group. The RATP group also had a significantly lower risk of secondary efficacy outcomes, including ischemic stroke (HR: 0.41), myocardial infarction (HR: 0.31), cardiovascular death (HR: 0.40), and MALE (HR: 0.65), than the APT group. The CRNM bleeding incidence varied between the two groups (HR: 3.96). Moreover, no significant interactions were observed between the subgroups and treatment groups in the composite efficacy analysis.

Conclusion: Rivaroxaban-based dual antithrombotic therapy significantly reduced the occurrence of MACE in patients with LE-PAD without increasing major bleeding events. High-risk patients benefited from the dual antithrombotic therapy.

Plain language summary

Comparison of rivaroxaban-based dual antithrombotic and antiplatelet therapies for symptomatic patients with lower-extremity peripheral artery disease post-revascularization: a retrospective cohort study

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Background

- Serious cardiovascular and limb events are common adverse effects in patients with symptomatic lower-extremity peripheral artery disease (LE-PAD).
- Few studies have reported the benefits of dual antithrombotic therapy with rivaroxaban in patients with high risk of LE-PAD in Asian populations.

Methods

- We collected data from in-patients with LE-PAD from January 1, 2018 to December 31, 2021.
- Depending on the antithrombotic medication administered, we classified the patients into antiplatelet therapy (e.g., aspirin and clopidogrel; APT group) and antiplatelet therapy combined with rivaroxaban (RAPT group) groups.
- The primary efficacy outcome was major adverse cardiovascular events (MACE), which was a composite of myocardial infarction, ischemic stroke or death from cardiovascular causes. The primary safety outcome was major bleeding.
- Secondary clinical outcomes included myocardial infarction, ischemic stroke, death from cardiovascular causes, clinically relevant non-major (CRNM) bleeding, and major adverse limb events (MALE), including urgent revascularization, acute limb ischemia, and major amputation.
- Follow-up continued until death or the end of the study (March 31, 2023).

Results

- The RAPT group had a lower risk of primary composite efficacy outcome and a non-significant increase in the risk of major bleeding than the APT group.
- The risk of secondary efficacy was significantly lower in the RAPT group than in the APT groups. The incidence of CRNM bleeding varied between the two groups.
- The subgroups and treatment groups had no significant interactions with the risk of composite efficacy outcomes.

Conclusions

- Rivaroxaban-based dual antithrombotic therapy has a clear therapeutic advantage over single antiplatelet therapy in Asian populations and does not increase the risk of major bleeding.
- Rivaroxaban-based combination therapy reduces the risk of serious adverse cardiovascular and limb events with an acceptable safety profile.

Keywords: dual antithrombotic therapy, efficacy, lower-extremity peripheral artery disease, rivaroxaban, safety

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Introduction

Lower-extremity peripheral artery disease (LE-PAD) is a common vascular disease in the older population in China. LE-PAD is an emerging public health burden with a prevalence of 6.6% in the general population aged ⩾35 years in China.[1,2] The underlying disease state of LE-PAD is similar to that of other atherosclerotic cardiovascular diseases. However, LE-PAD is characterized by a high risk of major adverse limb events

(MALE), including urgent revascularization, acute limb ischemia, major amputation, and major adverse cardiovascular events (MACE).[3,4]

Long-term single antiplatelet therapy is recommended for patients with LE-PAD to prevent adverse limb and cardiovascular events.[5,6] Currently, the evidence on the role of long-term dual-antiplatelet therapy with aspirin and clopidogrel as compared with aspirin alone in reducing cardiovascular events in patients with LE-PAD and increased risk of bleeding is limited.[5,7] Moreover, the optimal protocol has not been established for the administration of antithrombotic therapy after revascularization in different patients.[8] Moreover, atherosclerotic plaque rupture induces platelet aggregation, activating coagulation, increasing the local concentration of thrombin, and accelerating thrombosis.[9] Thus, in addition to antiplatelet therapy, anticoagulant therapy may inhibit fibrin formation and platelet aggregation by inhibiting thrombin bursts. The COMPASS and VOYAGER PAD trials reported that low-dose rivaroxaban and aspirin treatment significantly reduced the composite outcome incidence of acute limb ischemia, major amputation, myocardial infarction, ischemic stroke, and death from cardiovascular causes and slightly increased the risk of major bleeding compared to those of aspirin alone.[10,11] Thus, combined anticoagulation and antiplatelet therapy provide a new strategy for antithrombotic therapy in patients with LE-PAD.[12–14]

However, currently, in current clinical practice, the antiplatelet drugs prescribed for patients with LE-PAD are not limited to aspirin. Moreover, the course of the disease varies significantly among patients. To date, few studies have evaluated the effect of rivaroxaban-based dual antithrombotic therapy in high-risk patients with LE-PAD in Asian populations. Therefore, in this study, we evaluated the safety and efficacy of the combination of rivaroxaban-based anticoagulation with different antiplatelet therapies in Asian patients with symptomatic LE-PAD and various comorbidities.

Methods

Study design and patients

In this retrospective cohort study, data were extracted from the peripheral artery disease databases of Nanjing Drum Tower Hospital. We included patients with LE-PAD treated between 1 January 2018 and 31 December 2021. Patients were diagnosed with symptomatic LE-PAD based on the following criteria: (1) presence of intermittent claudication, ischemic rest pain, ischemic ulceration, or gangrene; (2) evidence of vascular occlusions revealed by computed tomography angiography or digital subtraction angiography; and (3) the ankle–brachial index.

Exclusion criteria included the following: (1) liver insufficiency (Child-Pugh class B or C); (2) renal insufficiency [creatinine clearance (CrCl) < 15 mL/min]; (3) autoimmune diseases or other diseases with symptoms overlapping with LE-PAD, including intermittent claudication, ulceration, or necrosis (e.g. arteritis); (4) any clinical condition needing systemic anticoagulation (e.g. atrial fibrillation); and (5) concomitant use of drugs with both cytochrome P450 isoenzyme 3A4 (CYP3A4) and *p*-glycoprotein inhibitors or strong inducers of CYP3A4.

Anticoagulant therapy was carefully reviewed and recorded. According to the antithrombotic strategy, patients were classified into two groups: (1) those administered only antiplatelet drugs, for example, aspirin and clopidogrel [antiplatelet therapy (APT) group] and (2) those administered antiplatelet drugs combined with rivaroxaban (RAPT group). The index date was defined as the date of hospital admission. The follow-up period started from the index date and continued until death or the end of the study period (31 March 2023), whichever occurred first. Patients were contacted *via* telephone in case of incomplete follow-up information.

Covariates

We collected data on the baseline characteristics, LE-PAD symptoms and lesions, revascularization, and drug therapy from all patients. The baseline characteristics included demographic characteristics, comorbidities, smoking history, and previous revascularization. The CrCl rate was estimated using the Cockroft–Gault formula. The lesion sites were classified as ilio-femoral-popliteal occlusion, isolated crural occlusion, or long-segment occlusion, based on the anatomical location. Patients with LE-PAD were categorized based on their symptoms according to the Rutherford classification: claudication (grade I), ischemic rest pain (grade II), and tissue loss

(grade III). The revascularization strategy included open surgery, including vascular and autovascular bypass grafting, and endovascular treatment, including percutaneous transluminal angioplasty, stent implantation, balloon dilation, drug-eluting stent implantation, drug-coated balloon dilatation, and debulking atherectomy. Concomitant use of statins, calcium channel antagonists, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers was also recorded. All these variables were considered for the inverse probability of treatment weight (IPTW) adjustment.

Study outcomes

Clinical outcomes were defined according to the relevant definitions in the COMPASS and VOYAGER PAD trials. The primary efficacy outcome was the occurrence of MACE, a composite of myocardial infarction, ischemic stroke, and death from cardiovascular causes. The primary safety outcome was major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH).[15] Secondary clinical outcomes were myocardial infarction, ischemic stroke, death from cardiovascular causes, clinically relevant non-major (CRNM) bleeding, and MALE, including urgent revascularization, acute limb ischemia, and major amputation.

Statistical analyses

The covariate variations between the two groups were adjusted using the stabilized IPTW approach with propensity scores calculated using logistic regression. The stabilized IPTW corrects for instability in the estimated treatment weights owing to the use of the regular IPTW for patients with a low probability of treatment. The covariates included were sex, age, body mass index (BMI), risk factors, medication use, CrCl, previous revascularization, lesion sites, Rutherford classification, and revascularization strategy. The weight for each patient was calculated and stabilized by multiplying the weight by the treatment probability. Standardized mean difference (SMD) was used to evaluate the balance of baseline characteristics, with an SMD $\leqslant 0.1$ indicating a negligible difference between the two groups. The weighted incidence rates (IRs) of clinical outcomes were calculated using the weighted number of events during the follow-up period divided by person-years (per 100 person-years). The risk of clinical outcomes for the two groups was evaluated using Kaplan–Meier survival analysis and univariate analysis with the log-rank test or multivariate analysis using weighted Cox proportional hazard regression models with IPTW. The 95% confidence intervals (CI) for hazard ratios (HR) were calculated using the APT group as the reference. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using R version 4.2.2 statistical software (The R Foundation for Statistical Computing, Vienna, Austria). The risk of clinical outcomes in specified subgroups was defined based on age (<75 years and $\geqslant 75$ years), diabetes, Rutherford classification (I, II, and III), previous revascularization, and revascularization strategy (open surgery and endovascular treatment). *p*-for-interaction of 0.1 was used to determine the significance of the interactions between the two groups and each subgroup.

BMI and CrCl data items that were missing accounted for 5.2% (60 of 1144) of the total data items and were imputed using the multiple imputation of chained equations with baseline characteristics. We used the R statistical software to create five imputed datasets and pool the outcomes. We also performed the sensitivity analysis using the complete data. The Supplemental Material provides additional details regarding the statistical analysis. The results of the secondary outcomes, subgroup, and sensitivity analyses should be considered exploratory due to the possibility of type I errors caused by multiple comparisons.

Results

Patient characteristics

Between 1 January 2018 and 31 December 2021, 1144 patients with LE-PAD were enrolled in this study. The patients were divided into two cohorts based on the antithrombotic therapy with 502 and 642 patients in the APT and RAPT groups, respectively. The baseline patient characteristics are presented in Table 1. Prior to performing IPTW, a relatively high percentage of patients in the APT group had diabetes, coronary heart disease, and cerebral infarction, and a relatively high percentage of patients in the RAPT group had a history of revascularization and statin use. There were also

Table 1. Baseline characteristics of patients in the APT and RAPT groups before and after IPTW.

Demographic and clinical parameters	Before IPTW			After IPTW		
	APT (*n* = 502)	RAPT (*n* = 642)	SMD*	APT (*n* = 483)	RAPT (*n* = 653)	SMD
Age, years	70.55 ± 10.88	71.31 ± 11.52	0.068	71.23 ± 10.84	71.08 ± 12.12	0.013
Female, *n* (%)	127 (25.3)	167 (26.0)	0.016	128 (26.5)	171 (26.2)	0.008
Body mass index, kg/m^2	22.89 ± 3.24	22.72 ± 3.29	0.052	22.94 ± 3.25	22.81 ± 3.16	0.041
Risk factors, *n* (%)						
Previous smoking	150 (29.9)	219 (34.1)	0.091	142 (29.4)	203 (31.1)	0.039
Hypertension	367 (73.1)	451 (70.2)	0.063	347 (71.8)	467 (71.5)	0.006
Diabetes	251 (50.0)	267 (41.6)	0.169	226 (46.8)	294 (45.0)	0.035
CHD	110 (21.9)	98 (15.3)	0.172	104 (21.5)	129 (19.8)	0.045
Infarction	377 (75.1)	167 (26.0)	1.127	241 (49.9)	317 (48.5)	0.027
CrCl, mL/min			0.072			0.030
⩾80	193 (38.4)	233 (36.3)		176 (36.4)	242 (37.1)	
50–80	206 (41.0)	260 (40.5)		201 (41.6)	263 (40.3)	
30–50	75 (14.9)	112 (17.4)		79 (16.4)	108 (16.5)	
15–30	28 (5.6)	37 (5.8)		27 (5.6)	39 (6.0)	
Previous revascularization, *n* (%)	21 (4.2)	67 (10.4)	0.242	45 (9.3)	52 (8.0)	0.046
Lesion sites, *n* (%)	0.123			0.039		
Ilio-femoral-popliteal	177 (35.3)	209 (32.6)		167 (34.6)	215 (33.0)	
Isolated crural	56 (11.2)	54 (8.4)		48 (9.9)	70 (10.7)	
Long segment	269 (53.6)	379 (59.0)		268 (55.5)	367 (56.2)	
Rutherford classifications, *n* (%)			0.197			0.027
Grade I	208 (41.4)	218 (34.0)		187 (38.7)	246 (37.7)	
Grade II	115 (22.9)	198 (30.8)		128 (26.5)	180 (27.6)	
Grade III	179 (35.7)	226 (35.2)		169 (35.0)	227 (34.8)	
Revascularization strategy, *n* (%)	0.083			0.022		
Open surgery	93 (18.5)	99 (15.4)		88 (18.2)	113 (17.3)	
Endovascular treatment	409 (81.5)	543 (84.6)		396 (82.0)	540 (82.7)	
Medication use, *n* (%)						
Statins	164 (32.7)	323 (50.3)	0.364	185 (38.3)	270 (41.3)	0.065
ACEI/ARB	128 (25.5)	164 (25.5)	0.001	126 (26.1)	171 (26.2)	0.005
CCB	243 (48.4)	291 (45.3)	0.062	224 (46.4)	307 (47.0)	0.013

Values are presented as % or mean ± SD.
*SMD ⩽ 0.1.
ACEI, angiotensin-converting enzyme inhibitor; APT, antiplatelet therapy; ARB, angiotensin receptor blocker; CCB: calcium channel blocker; CHD, coronary artery heart disease; CrCl, creatinine clearance; IPTW, inverse probability of treatment weighting; RAPT, rivaroxaban plus antiplatelet therapy; SMD, standardized mean difference.

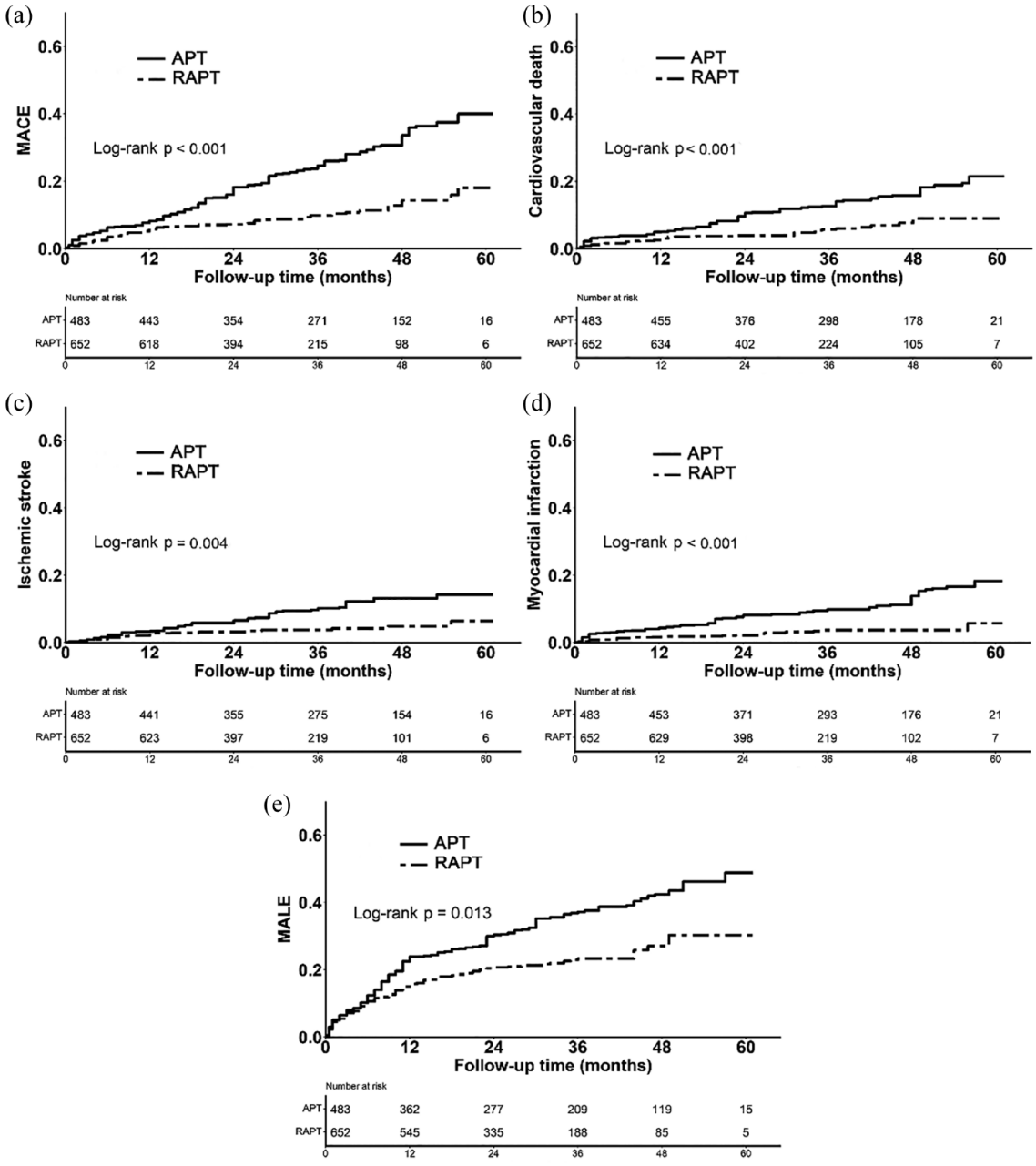

Figure 1. The weighted cumulative incidence curves of MACE (a), cardiovascular death (b), ischemic stroke (c), myocardial infarction (d), and MALE (e) in the APT and RAPT groups.
APT, antiplatelet therapy; MACE, major adverse cardiovascular events; MALE, major adverse limb events; RAPT, rivaroxaban plus antiplatelet therapy.

statistically significant differences in the distribution of lesion sites, Rutherford classification, and revascularization strategies between the two groups. After the IPTW, the baseline characteristics of the two groups were balanced.

Clinical outcomes

The weighted cumulative incidence curves and relative risks of efficacy outcomes are presented in Figures 1 and 2, respectively. The Kaplan–Meier curves revealed a clear separation of event curves

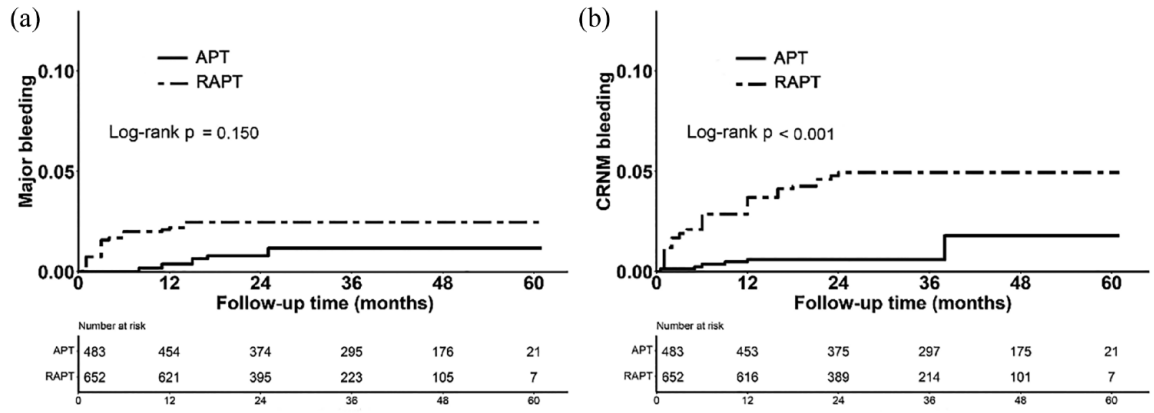

Figure 2. Weighted IR, HR, and 95% CI of clinical outcomes in the APT and RAPT groups.
APT, antiplatelet therapy; CI, confidence interval; HR, hazard ratio; IR, incidence rate; RAPT, rivaroxaban plus antiplatelet therapy.

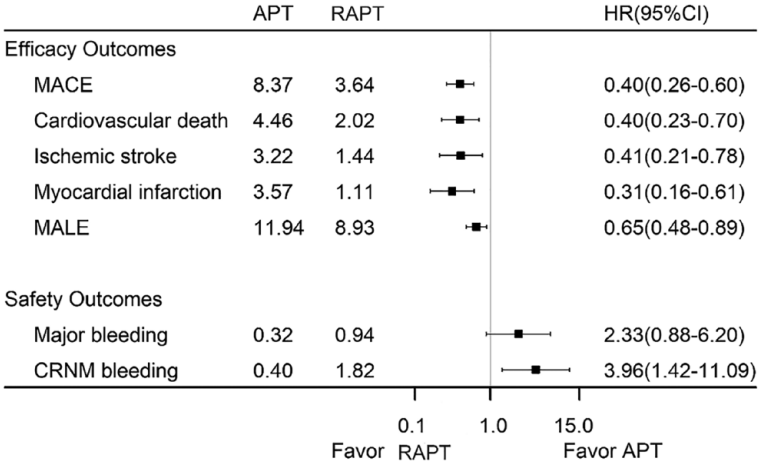

Figure 3. The weighted cumulative incidence curves of major bleeding (a), and CRNM bleeding (b) in the APT and RAPT groups.
APT, antiplatelet therapy; CRNM, clinically relevant non-major; RAPT, rivaroxaban plus antiplatelet therapy.

for each clinical outcome in the two groups. RAPT was associated with significantly reduced risk for composite MACE outcome (HR: 0.40, 95% CI: 0.26–0.60) compared to that of APT. Similarly, a significantly lower risk was observed for each secondary efficacy outcome, including ischemic stroke (HR: 0.41, 95% CI: 0.21–0.78), myocardial infarction (HR: 0.31, 95% CI: 0.16–0.61), cardiovascular death (HR: 0.40, 95% CI: 0.23–0.70), and MALE (HR: 0.65, 95% CI: 0.48–0.89), in the RAPT group than in the APT group.

The cumulative incidence and relative risk of bleeding outcomes are presented in Figures 2 and 3, respectively. In the RAPT group, a nonsignificant trend was observed for an increased risk of major bleeding as per the ISTH criteria (HR: 2.33, 95% CI: 0.88–6.20). CRNM bleeding also had a higher event rate in the RAPT group than in the APT group (HR: 3.96, 95% CI: 1.42–11.09).

Subgroup analysis

Subgroup analysis was performed based on age, comorbidities, Rutherford classification, previous revascularization, and revascularization strategy to evaluate the difference in the risk of MACE or MALE among the different patient populations (Figure 4).

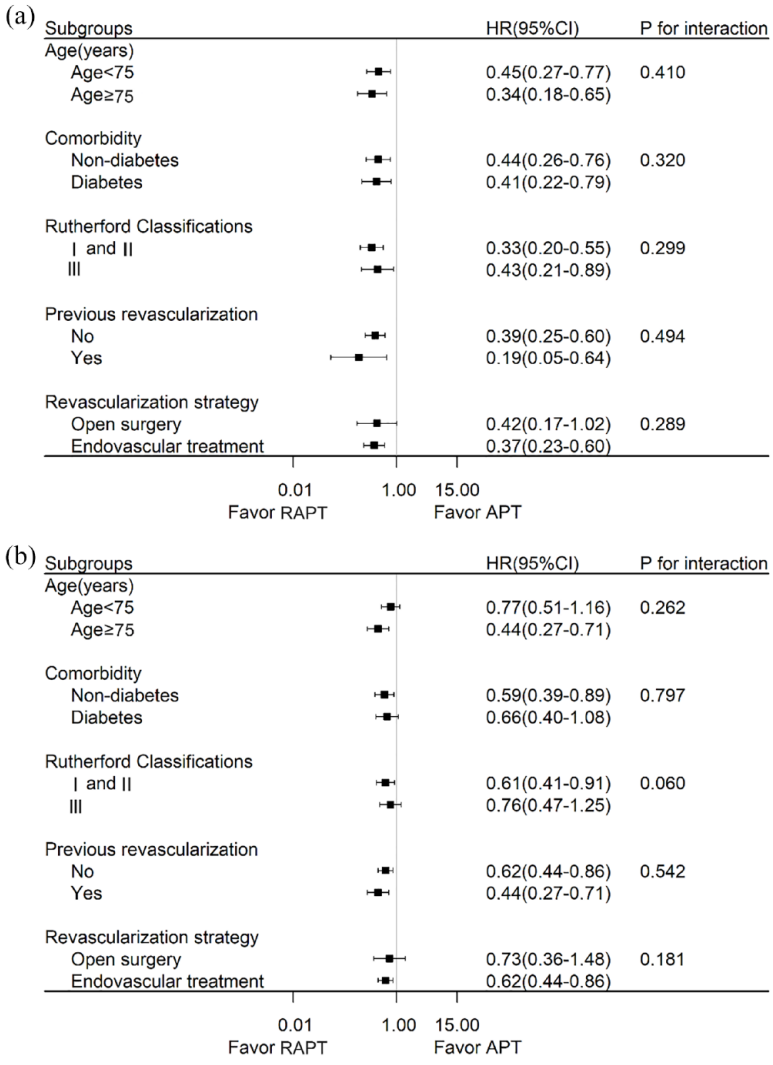

Figure 4. Risk of MACE (a) and MALE (b) in patients with APT *versus* RAPT based on various subgroups.
APT, antiplatelet therapy; MACE, major adverse cardiovascular events; MALE, major adverse limb events; RAPT, rivaroxaban plus antiplatelet therapy.

When 75 years was used as a cutoff to define age subgroups, RAPT reduced the risk of MACE in different age subgroups (HR: 0.45, 95% CI: 0.27–0.77 *versus* HR: 0.34, 95% CI: 0.18–0.65; *p*-for-interaction = 0.410). However, the risk of MACE did not vary significantly in the comorbidity subgroup (HR: 0.44, 95% CI: 0.26–0.76 *versus* HR: 0.41, 95% CI: 0.22–0.79; *p*-for-interaction = 0.320). Furthermore, RAPT was associated with a low risk of MACE regardless of the Rutherford classification stratification or history of revascularization. Unlike patients who underwent open surgery, a significant difference in the risk of MACE was observed between the APT and RAPT groups in patients who underwent endovascular treatment (HR: 0.37, 95% CI: 0.23–0.60). Overall, no significant interactions were observed in the incidence of composite MACE between the various subgroups and antithrombotic therapy. The subgroup analysis findings matched those of the entire study population.

For MALE, no meaningful relationships were observed between the treatment groups and subgroups, except for the Rutherford classification stratification. Patients with grade I and II LE-PAD in the RAPT group had a reduced risk of MALE compared to that of the patients in the APT group (HR 0.61, 95% CI: 0.41–0.91). In addition,

patients with grade III LE-PAD had the same outcomes in the APT and RAPT groups (p-for-interaction = 0.060).

Sensitivity analysis

Overall, 1084 of the 1144 patients had complete data for all variables in the main analysis. In the sensitivity analysis, regression analysis using complete data revealed results similar to those obtained using multiple imputed datasets (Supplemental Table 1 and Figure 1).

Discussion

The COMPASS study led clinicians to attempt rivaroxaban treatment in patients with LE-PAD in 2017, and the VOYAGER PAD trial further confirmed the applicability of rivaroxaban in combination with antiplatelet agents in patients with LE-PAD in 2020. Despite the extensive research, these studies have not identified LE-PAD types compatible with rivaroxaban treatment. Therefore, some clinicians use rivaroxaban in combination with antiplatelet agents for patients with LE-PAD, while others are likely to adhere to traditional antiplatelet agent therapies. In the monocentric hospital, in addition to the guidance of authoritative research, rivaroxaban is used depending on the attending physician's understanding of the guidelines and the patient's condition. Therefore, this study compared the safety and efficacy of different antithrombotic therapies (antiplatelet therapy *versus* rivaroxaban-based dual antithrombotic therapy) in Asian patients with LE-PAD. Previous studies have primarily investigated the effect of aspirin, with or without rivaroxaban, in patients with LE-PAD. However, clinicians may choose other antiplatelet therapies based on the patient's tolerance and preferences. Therefore, we specifically evaluated the effects of clinically established antiplatelet agents, including aspirin, clopidogrel, and cilostazol, in combination with rivaroxaban.

Our results revealed majority of the patients with LE-PAD at our medical center were administered RAPT. Patients with LE-PAD administered with RAPT had a significantly lower incidence of composite outcomes of myocardial infarction, ischemic stroke, and cardiovascular death than those administered APT, even when the clinical outcomes were analyzed separately. No significant difference was observed in the incidence of major bleeding between the groups as defined by the ISTH criteria. However, CRNM bleeding occurred more frequently in the RAPT group than in the APT group. In the subgroup analysis, no significant interaction was observed between the different subgroups and antithrombotic therapy for the composite MACE outcome, consistent with the analysis of the overall study population.

LE-PAD is a manifestation of atherosclerosis in the arteries of the lower extremities. LE-PAD treatment is focused on improving arterial patency, thus preventing intravascular thrombosis and reducing the risk of cardiovascular and limb-related events.[16] Previously, antiplatelet therapy formed the basis for the antithrombotic treatment of LE-PAD.[5] Moreover, anticoagulant therapy is associated with an increased bleeding risk and results in minimal benefit in patients with PAD as compared with antiplatelet therapy alone. Nonetheless, the COMPASS and VOYAGER PAD trials provided robust data supporting the use of anticoagulant therapy in patients with PAD.[10,11] Our study provides further evidence that rivaroxaban-based antithrombotic therapy can significantly reduce the risk of MACE in patients with PAD, without increasing the risk of major bleeding.

One of the major challenges of LE-PAD treatment is the significant variability in patient presentation, ranging from asymptomatic to presenting with intermittent claudication, skin ulceration, or gangrene.[16,17] Moreover, the pattern of disease progression is complicated by several comorbidities. Several clinical studies have provided evidence of the benefits of antithrombotic therapy for patients with PAD and have proposed management strategies for them. However, further research is needed to identify the subset of patients who would benefit the most from these therapies while minimizing the risk of major bleeding.

Patients with LE-PAD with comorbid diabetes are considered a high-risk group with a high rate of vascular events despite several advances in different treatment modalities, including lipid, blood pressure, and glycemic management.[18] Thus, patients with LE-PAD and diabetes require a more aggressive antithrombotic therapy than patients without diabetes.[19] We verified that patients with LE-PAD and diabetes had a similar absolute risk reduction in MACE when treated

with dual antithrombotic therapy. In a prespecified analysis of the COMPASS trial, the combination of rivaroxaban with aspirin provided similar relative benefits in reducing coronary, cerebrovascular, and peripheral events in patients with or without diabetes.[11] Due to their higher baseline risk, patients with LE-PAD and diabetes obtained a greater absolute benefit from this combination therapy. Our subgroup analysis yielded similar results.

Similarly, the COMPASS subgroup analysis demonstrated a 26% reduction in MACE and 45% reduction in MALE in patients with LE-PAD and comorbid PCI/acute coronary syndrome or a history of CHD when treated with 2.5 mg of rivaroxaban and aspirin compared to those in patients treated with aspirin alone. Previous studies have also that reported low-dose rivaroxaban and aspirin dual antithrombotic therapy are beneficial in patients with LE-PAD, regardless of their history of stroke, particularly those with low bleeding characteristics. Thus, rivaroxaban-based antithrombotic therapy may be effective in patients with LE-PAD with or without multivessel disease. Moreover, we performed a partial assessment of the multivessel disease in our subgroup analysis, and in the future, we aim to further characterize patients with LE-PAD and multivessel disease.

Overall, patients with LE-PAD were at high risk of both cardiovascular and adverse limb events. The COMPASS trial subgroup analysis revealed that symptomatic patients with severe symptoms had the highest 30-month incidence risk of MACE or MALE, especially resting pain or tissue ulceration.[20] Symptom severity usually represents a reliable method for stratifying the risk associated with LE-PAD, which could guide the selection of antithrombotic therapy and risk reduction strategy.[21] The Rutherford classification is a widely used system for classifying the severity of LE-PAD, based on symptom severity and clinical findings.[22] This classification includes the presence and severity of pain, the extent of skin changes, and the presence of ulcerations or gangrene. In our study, among patients with symptomatic LE-PAD categorized based on the Rutherford classification, dual antithrombotic therapy reduced the risk of MACE in different patient categories. However, the reduction of risk of MALE was associated with Rutherford Grades I and II and not Rutherford Grade III. This may be because patients with advanced disease (Rutherford grade III) have severe gangrene or tissue loss, which often cannot be treated or controlled by drugs and can only lead to limb events, including amputation. Moreover, these patients have severe gangrene or tissue loss endangering a part of or the entire lower extremities with significantly high rates of revascularization failure and amputation. Therefore, the rivaroxaban-based dual antithrombotic therapy did not have the expected limb efficacy in this patient population. However, the consistent efficacy and safety of rivaroxaban and aspirin in patients who underwent revascularization were confirmed in a subgroup analysis of VOYAGER PAD, and the role of rivaroxaban in preventing acute limb ischemia was particularly robust (absolute risk reduction of 6.3% at 2 years; HR, 0.67; 95% CI, 0.55–0.82). Moreover, previous revascularization surgery in patients with LE-PAD increases the risk of cardiovascular and limb events. This study also revealed that dual antithrombotic therapy was effective in reducing the risk of MACE and MALE in patients with a history of prior revascularization.

Symptoms in patients with LE-PAD range from claudication to critical limb ischemia requiring revascularization to maintain blood flow and prevent further tissue damage. Patients who undergo revascularization, including open surgery or endovascular treatment, are at high risk of subsequent vascular complications, particularly acute limb ischemia. The risk of limb ischemia is approximately fourfold higher in patients requiring revascularization than in those who have never undergone revascularization.[23] Patients treated with open surgery had advanced ischemia, whereas those who underwent endovascular treatment had a high rate of technical failure.[23] Both treatments had similar rates of postprocedural cardiovascular events. In the subgroup analysis of this study, dual antithrombotic therapy significantly reduced the risk of MACE and MALE in patients undergoing endovascular treatment, while the risk reduction was not significant in the open surgery group.

This study has some imitations. First, as this was a retrospective observational cohort study, despite the use of inverse probability weighting to balance the covariates, the results should be interpreted with caution, particularly the subgroup analysis results. Second, the actual patient adherence to antithrombotic medication in this study was

challenging to assess. Considering the possibility of change in the antithrombotic therapy during the treatment course, we grouped the patients based on the intention-to-treat principle using the initial antithrombotic therapy. Finally, in the subgroup analysis, except for the risk of major bleeding, we only analyzed the risk of MACE and MALE in the different subgroups. This was due to the limited sample size and the low incidence of major bleeding. Regardless of baseline vascular risk, this study revealed the clinical potential of dual antithrombotic therapy in MACE and MALE reduction, outweighing the risk of major bleeding.

Conclusion

In patients with symptomatic LE-PAD, rivaroxaban-based anticoagulants combined with antiplatelet therapy reduced the incidence of composite MACE, without increasing the risk of major bleeding. Furthermore, the study revealed that patients with high-risk LE-PAD can be treated with dual antithrombotic therapy to reduce the risk of adverse MACE or MALE.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. Approval for the study was obtained from the Ethics Committee of Nanjing Drum Tower Hospital (Approval Number: 2021-198-03). The requirement for participant informed consent was waived by the ethics board. All methods were carried out in accordance with relevant guidelines and regulations. For this study, the raw data were first extracted from HIS, and patients' identities, including names, screening IDs, patient IDs, and mobile phone numbers, were de-identified.

Consent for publication

Not applicable.

Author contributions

Ye Ji: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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