

Comparable efficacy of 100 mg aspirin twice daily and rivaroxaban for venous thromboembolism prophylaxis following primary total hip arthroplasty: a randomized controlled trial

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Abstract

Background: Aspirin has demonstrated safety and efficacy for venous thromboembolism (VTE) prophylaxis following total hip arthroplasty (THA); however, inconsistent dose regimens have been reported in the literature. This study aimed to evaluate and compare the safety and efficacy of 100 mg aspirin twice daily with rivaroxaban in VTE prophylaxis following THA.

Methods: Patients undergoing elective unilateral primary THA between January 2019 and January 2020 were prospectively enrolled in the study and randomly allocated to receive 5 weeks of VTE prophylaxis with either oral enteric-coated aspirin (100 mg twice daily) or rivaroxaban (10 mg once daily). Medication safety and efficacy were comprehensively evaluated through symptomatic VTE incidence, deep vein thrombosis (DVT) on Doppler ultrasonography, total blood loss (TBL), laboratory bloodwork, Harris hip score (HHS), post-operative recovery, and the incidence of other complications.

Results: We included 70 patients in this study; 34 and 36 were allocated to receive aspirin and rivaroxaban prophylaxis, respectively. No cases of symptomatic VTE occurred in this study. The DVT rate on Doppler ultrasonography in the aspirin group was not significantly different from that in the rivaroxaban group (8.8% vs. 8.3%, $\chi^2 = 0.01$, $P = 0.91$), confirming the non-inferiority of aspirin for DVT prophylaxis ($\chi^2 = 2.29$, $P = 0.01$). The calculated TBL in the aspirin group (944.9 mL [658.5–1137.8 mL]) was similar to that in the rivaroxaban group (978.3 mL [747.4–1740.6 mL]) ($\chi^2 = 1.55$, $P = 0.12$). However, there were no significant inter-group differences in HHS at post-operative day (POD) 30 (Aspirin: 81.0 [78.8–83.0], Rivaroxaban: 81.0 [79.3–83.0], $\chi^2 = 0.43$, $P = 0.67$) and POD 90 (Aspirin: 90.0 [89.0–92.0], Rivaroxaban: 91.5 [88.3–92.8], $\chi^2 = 0.77$, $P = 0.44$), the incidence of bleeding events (2.9% vs. 8.3%, $\chi^2 = 0.96$, $P = 0.33$), or gastrointestinal complications (2.9% vs. 5.6%, $\chi^2 = 1.13$, $P = 0.29$).

Conclusion: In terms of safety and efficacy, the prophylactic use of 100 mg aspirin twice daily was not statistically different from that of rivaroxaban in preventing VTE and reducing the risk of blood loss following elective primary THA. This supports the use of aspirin chemoprophylaxis following THA as a less expensive and more widely available option for future THAs.

Trial Registration: Chicttr.org, ChiCTR18000202894; <http://www.chicttr.org.cn/showproj.aspx?proj=33284>

Keywords: Total hip arthroplasty; Aspirin; Rivaroxaban; Venous thromboembolism; Blood loss; Complication

Introduction

Venous thromboembolism (VTE), encompassing pulmonary embolism (PE) and deep vein thrombosis (DVT), is a well-established complication associated with total hip arthroplasty (THA).^[1-3] Post-operative VTE results in substantial preventable patient morbidity and mortality. Moreover, it entails significant financial burden due to costly medical management and prolonged hospital stay.^[1] The number of THAs continues to increase globally in proportion to the estimated burden of VTE. Therefore, safe and effective VTE prophylaxis is warranted as a prerequisite for surgical success. Compelling evidence

has shown that prophylactic antithrombotic therapy following THA effectively reduces post-operative VTE risk.^[2] However, the ideal drug regimen that optimally balances insufficient antithrombotic effect with excess bleeding risk remains controversial.

The mainstay of VTE chemoprophylaxis currently includes low-molecular-weight heparin (LMWH) and new oral anticoagulants (NOACs). NOACs, such as rivaroxaban have demonstrated superior safety, thromboprophylaxis efficacy, and convenience of use than LMWH, and are now commonly prescribed following joint arthroplasty.^[3] Although rivaroxaban has proven to be an effective anticoagulant, it could potentially display

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exaggerated clinical effects with a greater risk of bleeding and incisional complications.^[4-6]

Aspirin is a widely administered antiplatelet and alternative antithrombotic for VTE prophylaxis, and has been given a grade 1B recommendation for use in orthopedic surgery by the American College of Chest Physicians 2012 Guidelines (ACCP-9).^[7] Aspirin, like other anticoagulants, is safe and effective in symptomatic VTE prophylaxis, with a potentially lower bleeding risk.^[8-10] Given that aspirin is inexpensive, orally administered, and requires minimal blood monitoring, it has been used as a part of VTE prophylaxis in 45% of total joint arthroplasties in the United States.^[11]

However, despite the evidence of utility and efficacy, the administration regimens of aspirin in VTE prophylaxis following THA still lacks consensus. ACCP guidelines recommend 325 mg aspirin administered twice daily; however, other publications have suggested comparable efficacy using lower formulations of 81 mg.^[8,12] Unfortunately, only formulations of 100 and 25 mg are available in the Chinese market, and clinical evaluations using these dosages are presently scarce. This study aimed to evaluate and compare the safety and efficacy of 100 mg aspirin administered twice daily and rivaroxaban in VTE prophylaxis following elective primary unilateral THA. We hypothesized that the efficacy of 100 mg aspirin twice daily in VTE prophylaxis would be comparable to that of 10 mg rivaroxaban once daily, with comparative perioperative blood loss and bleeding risk.

Methods

Ethical approval

This randomized controlled trial (RCT) was designed in accordance with *the Consolidated Standards of Reporting Trials Guidelines* and conducted in compliance with the *Declaration of Helsinki*. Ethical approval was obtained from the local Institutional Review Board and the China Clinical Trial Registry (No. ChiCTR1800020289). Written informed consent was obtained from all patients before the start of the study.

Study population

All patients were enrolled between January 2019 and January 2020 in the Peking Union Medical College Hospital (China) and were allocated into two groups following a 1:1 ratio. This enrollment process was conducted by two investigators with reference to the inclusion and exclusion criteria (see below). Computer randomization was used to generate the allocation sequence. The code for each patient was concealed in an envelope by an independent investigator who did not participate in patient enrollment. After surgery, the envelope was opened to assign the patient to one of the two groups and the corresponding prescription.

For sample size calculation, we used a non-inferiority clinical trial design. According to the previous research and follow-up results of our department, the predicted

response rate of aspirin was set to 80%, rivaroxaban was set to 90%, and the non-inferiority limit was set to 0.15. A sum of the calculated sample size with an anticipated loss to follow-up required at least 30 patients in each treatment group to achieve statistical power.

Eligibility criteria

We included patients with primary unilateral THA, aged between 20 and 80 years, and with at least 1 week of aspirin cessation before surgery. We excluded patients considered to have a high risk for VTE by their attending surgeon according to the established protocol for individualized VTE risk stratification.^[13] High-risk patients included those with a history of VTE, active malignancy, known prothrombotic conditions, or requiring extended antithrombotic therapy for pre-existing conditions. Additionally, we excluded patients with contraindications to aspirin or non-steroidal anti-inflammatory drugs due to intolerance, peptic ulcer disease, or other reasons.

Study design

All patients included in this study underwent cementless THA using the posterior-lateral approach under general anesthesia. Two experienced orthopedic surgeons performed the surgical procedures. Surgical techniques and prosthetics were used at the clinical discretion of the attending surgeons. Tranexamic acid was used routinely during each surgical procedure, with an adjusted dose of 15 mg/kg intravenously before incision, and another topical dose before wound closure. No drainage was used in this study.

After surgery, patients received 5 weeks of thromboprophylaxis with either an experimental aspirin regimen or rivaroxaban control. At least 6 h post-operatively, patients in the experimental group started on 100 mg of enteric-coated aspirin (Bayer S.p.A. Italia) twice daily, whereas patients in the control group were administered 10 mg rivaroxaban (Bayer AG, Leverkusen, Germany). All patients received post-operative pneumatic compression during their hospital stay.

Crutch-assisted partial weight-bearing ambulation was started on post-operative day 1 (POD 1). All patients were monitored after surgery and regularly discharged to rehabilitation centers between PODs 3 and 5. Outpatient follow-up was scheduled for PODs 30 and 90. All complications and VTE identified at follow-up were appropriately managed until complete resolution.

Data collection and outcomes

Primary outcomes

Patient demographic data including age, gender, body mass index, and medical history were all recorded on admission.

Prophylactic efficacy was assessed using VTE incidence in the treatment groups. Patients were educated on how to recognize and report symptoms of VTE. DVT was

diagnosed and verified using Doppler ultrasonography performed pre-operatively and at follow-up between PODs 14 and 30, looking for emboli in the deep ascending (popliteal, femoral, common femoral, and iliac) veins. The pre- and post-operative lower limb (thigh and calf) circumferences were also recorded.

Prophylactic safety was evaluated based on the incidence of bleeding events as defined by established criteria. This included major bleeding (fatal or symptomatic), clinically significant non-major bleeding, and minor bleeding events (ecchymosis, epistaxis, hematuria, etc).^[14] Peri-operative blood loss and the need for transfusion were also monitored. Particularly, the total blood loss (TBL), calculated according to the “hemoglobin balance” theory, was also used to assess medication bleeding risk.^[15]

Furthermore, blood tests (hemoglobin [Hb], platelets, C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], and D-dimer) were performed before surgery and at PODs 1, 3, 5, and 30 to assess hemodynamic stability, along with measures of systemic wellness (partial prothrombin time [PTT], liver function [LFT], renal function tests [RFT], and vital parameters [heart rate, blood pressure, and oxygen saturation]).

Secondary outcomes

Secondary outcomes were measured and documented to further understand the medication effect. Harris hip score (HHS) was assessed pre-operatively and at PODs 30 and 90 to evaluate joint pain, range of motion, and function. Patient recovery and rehabilitation following THA were evaluated through the duration of hospital stay and at the time of post-operative walking function recovery.

All post-operative complications were recorded and categorized as surgery-related (surgical site infection, periprosthetic joint infection, hip dislocation, etc), systemic adverse events (cardiac infarction, stroke, death, etc), or gastrointestinal (GI) side effects.

Statistical analysis

All statistical tests were performed using SPSS Statistics (software version 25, IBM Corporation, Armonk, USA). The rate difference and its 95% confidence interval (CI) were used as the non-inferiority test for post-operative VTE rate. Quantitative data were reported as median and interquartile range using the Mann-Whitney *U*-test and Friedman test for inter-group and intra-group analyses, respectively. Chi-squared test are used to compare qualitative data. Univariable analysis and multivariable logistic regression analysis were performed to identify and eliminate confounding factors in terms of DVT incidence. A *P* value below 0.05 was considered as statistically significant for all tests.

Results

Patient and surgical characteristics

After screening for eligibility, 78 patients who underwent THA between January 2019 and January 2020 met the

inclusion criteria, of whom eight were excluded due to non-compliance with their antithrombotic regimen after discharge. Of the remaining 70 patients, 34 were allocated to the aspirin group (13 men and 21 women), and 36 into the rivaroxaban group (11 men and 25 women). No patients were lost to follow-up or withdrew from the study before its completion [Figure 1]. No significant inter-group differences in patient demographics or medical history were noted [Table 1].

Primary outcome analysis

In both groups, no patient was diagnosed with symptomatic VTE throughout the study. The evaluation of DVT using lower limb ultrasonography at PODs 14 to 30 identified three patients with distal DVT in both treatment groups. After statistical analysis, the 95% CI upper limit was found to be 0.119, which was lower than the previously established non-inferiority limit 0.15 (*P* for non-inferiority test = 0.01), indicating that aspirin was non-inferior to rivaroxaban DVT prophylaxis. There were no inter-group differences in pre- and post-operative limb circumferences [Table 2].

On univariable analysis, patients with identified etiological factors (non-idiopathic causes including steroid use, alcohol consumption, and immune diseases), were more likely to develop DVT than patients with idiopathic factors (odds ratio [OR] = 9.32, *P* = 0.04) [Table 1]. D-dimer levels on POD 1 was also found to significantly affect the outcome (OR = 1.09, *P* = 0.04). The choice of aspirin or rivaroxaban for medical prophylaxis was not significantly associated with DVT occurrence (OR = 1.1, *P* = 0.91) [Table 3]. Subsequently, these two risk factors (non-idiopathic and D-Dimer on POD 1) were analyzed using multivariable logistic regression, which showed that the effect of aspirin on DVT prophylaxis was comparable to that of rivaroxaban after eliminating confounding factors (OR = 0.73, *P* = 0.74) [Table 3].

Our study evaluated medication safety using its association with bleeding. No cases of major or clinically significant bleeding were observed in this study. One minor bleeding event was reported in the aspirin group (epistaxis) and three in the rivaroxaban group (one epistaxis and two ecchymoses; *P* = 0.33). There was no inter-group difference in peri-operative TBL or intra-operative blood loss (*P* = 0.12 and 0.57, respectively); moreover, no patient in either group required transfusions post-operatively [Table 2]. The pre-operative results of laboratory blood tests of patients in both groups were statistically comparable. However, patients who received rivaroxaban demonstrated a significantly lower Hb and hematocrit (HCT) than those who received aspirin on PODs 1, 3, and 5 (Hb: *P* = 0.04, 0.04, and 0.02; HCT: *P* = 0.001, 0.001, and 0.007, respectively); however, this difference then disappeared by POD 30 (Hb: *P* = 0.79; HCT: *P* = 0.95). No significant inter-group differences were noted in any other bloodwork (platelets, CRP, ESR, and D-Dimer; see Supplementary file, <http://links.lww.com/CM9/A418>), laboratory investigations (PTT, LFT, and RFT; Supplementary Tables 1 and 2, <http://links.lww.com/CM9/A418>), or vital parameters.

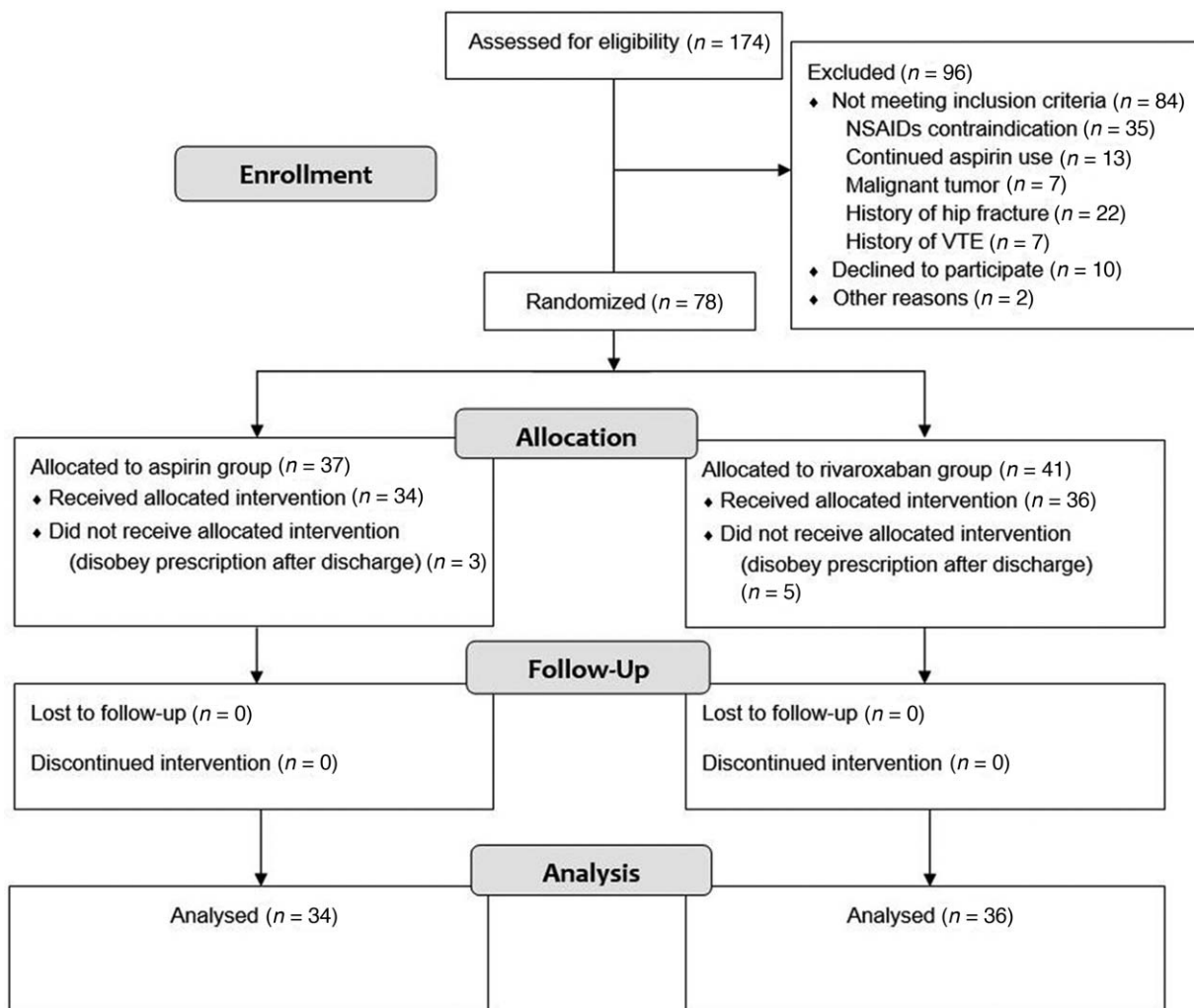


Figure 1: Flowchart showing the randomized distribution of enrolled patients into groups prescribed with aspirin or rivaroxaban.

Secondary outcome analysis

The pre-operative HHS was significantly lower than HSS at PODs 30 and 90 with intra-group comparison ($P < 0.001$). However, no inter-group difference in HHS was noted pre- or post-operatively ($P = 0.26, 0.67,$ and $0.44,$ respectively). Similar joint function and recovery between groups were supported by data measuring the duration of hospital stay and time it took for post-operative walking function recovery ($P = 0.83$ and $0.32,$ respectively) [Table 2].

There was no post-operative death or PE in this study. A total of 15 adverse events were recorded during the 90-day post-operative period investigated in the study [Table 4]. Except for the bleeding events stated previously, three cases of GI adverse events were reported: one in the aspirin group (nausea) and two in the rivaroxaban group (nausea and peptic ulcer). Nausea was tolerable in both patients, whereas the peptic ulcer was treated with proton-pump inhibitors. No significant inter-group difference was observed in the frequency of GI complications ($P = 0.29$) [Table 4]. A wound effusion was reported in one patient in the aspirin group (managed with local care), and one

patient in the rivaroxaban group experienced systematic complications of acute coronary syndrome at POD 2 that was treated with antiplatelets with an uneventful recovery.

Discussion

The VTE is an unexpected and health-threatening complication of THA. The peri-operative administration of anticoagulant prophylaxis has proven to reduce death rates and post-procedural VTE-associated complications. Rivaroxaban, an oral anticoagulant, can provide effective thromboprophylaxis after elective hip arthroplasty,^[16] and was used for extending prophylaxis beyond hospital discharge because of its efficacy, safety, and convenience of use.^[17] In the literature, the RECORD trial series have demonstrated that the symptomatic and total VTE risk reduction by NOACs was relatively lower than that of LMWH, with an absolute risk reduction of 2.6% to 9.3%.^[16,18-20] Rivaroxaban was recommended for about 10 to 14 days after total joint arthroplasty in the ACCP-9 guideline.^[7]

Recent studies have reported the efficacy of aspirin, which was formally used to treat arterial diseases, in preventing post-operative lower extremity venous thrombosis and

Table 1: Comparison of demographic characteristics between the two study groups for venous thromboembolism prophylaxis following primary total hip arthroplasty.

Items	Aspirin group (n = 34)	Rivaroxaban group (n = 36)	Statistics	P
Sex				
Male	13 (38.3)	11 (30.6)	0.46	0.49
Age (years)	54.5 (40.8–62.3)	50.0 (36.8–57.0)	–1.21	0.23
BMI (kg/m ²)	23.6 (20.7–25.5)	23.5 (20.3–26.0)	–0.27	0.79
Etiological factors				
Idiopathic ONFH	15 (44.1)	12 (33.3)	0.86	0.35
Non-idiopathic				
Steroid-related	5 (14.7)	7 (19.4)	0.28	0.59
Alcohol-related	4 (11.8)	1 (2.8)	2.13	0.14
Immune disorder	3 (8.8)	0	3.31	0.07
OA secondary to trauma	3 (8.8)	6 (16.7)	0.96	0.33
OA secondary to DDH	3 (8.8)	10 (27.8)	3.33	0.06
Others	1 (2.9)*	0	1.07	0.30
Comorbidity				
Hypertension	5 (14.7)	6 (16.7)	0.05	0.82
Diabetes	3 (8.8)	1 (2.8)	1.19	0.28
Hyperlipemia	2 (5.9)	2 (5.6)	0.01	0.95
CAD	1 (2.9)	0	1.07	0.30
Immune disease	4 (11.8)	6 (16.7)	0.34	0.56
Drinkers	8 (23.5)	4 (11.1)	1.89	0.17
Smokers	8 (23.5)	5 (13.9)	1.07	0.30
Arteriosclerosis findings in arterial ultrasound [†]	6 (17.6)	4 (11.1)	0.61	0.43

Data was presented as median (interquartile range) or *n* (%). * Induced by synovial chondromatosis of the hip joint. [†] Positive findings except for thrombosis, such as atherosclerosis, thickening of the intima, arteriostenosis, and so on. BMI: Body mass index; ONFH: Osteonecrosis of femoral head; OA: Osteoarthritis; DDH: Developmental dysplasia of hip; CAD: Coronary arterial disease.

Table 2: Primary and secondary results of study group for venous thromboembolism prophylaxis following primary total hip arthroplasty.

Items	Aspirin group (n = 34)	Rivaroxaban group (n = 36)	Statistics	P
Primary outcomes				
Doppler DVT	3 (8.8)	3 (8.3)	0.01	0.91
Bleeding results				
Blood loss in surgery (mL)	300.0 (200.0–300.0)	300.0 (200.0–375.0)	0.57	0.57
Intra-operative transfusion,*	3 (8.8)	2 (5.9)	0.01	0.95
TBL (mL)	944.9 (658.5–1137.8)	978.3 (747.4–1740.6)	1.55	0.12
Circumference of lower limb (cm)				
Thigh circumference before surgery	40.0 (37.0–42.0)	42.0 (39.0–43.9)	1.85	0.06
Thigh circumference after surgery	40.3 (37.1–42.1)	42.0 (39.4–44.1)	1.86	0.06
Calf circumference before surgery	33.0 (31.0–35.1)	33.5 (32.1–37.0)	1.19	0.23
Calf circumference after surgery	33.6 (31.4–35.7)	33.9 (32.5–37.6)	1.15	0.25
Secondary outcomes				
Joint function				
Harris score before surgery	54.5 (45.0–61.0)	56.5 (49.3–63.0)	1.12	0.26
Harris score at POD 30	81.0 (78.8–83.0)	81.0 (79.3–83.0)	0.43	0.67
Harris score at POD 90	90.0 (89.0–92.0)	91.5 (88.3–92.8)	0.77	0.44
Rehabilitation				
Post-operative day to stand up (days)	1.0 (1.0–1.0)	1.0 (1.0–1.7)	–0.22	0.83
Hospital stay after surgery (days)	5.0 (4.0–7.0)	5.0 (4.0–6.0)	–0.99	0.32

Data was presented as median (interquartile range) or *n* (%). * Type of transfusion: suspended red blood cell. DVT: Deep venous thrombosis; ROM: Range of motion; TBL: Total blood loss; POD: Post-operative day; ANOVA: Analysis of variance.

PE.^[8-10,14] In previous studies, the administered dose of aspirin in VTE prophylaxis has been widely variable, with a maximum of 650 mg twice daily.^[21] In the primary

American Academy of Orthopedic Surgeons guidelines, panelists recommended a dosage of 325 mg twice a day.^[22] Moreover, several previous pieces of literature have

Table 3: Univariable analysis and multivariable logistic regression analysis for VTE.

Variable	Univariable analysis			Multivariable analysis		
	OR (95% CI)	Statistics	P	OR (95% CI)	Statistics	P
Medical intervention						
Rivaroxaban	Ref			Ref		
Aspirin	1.10 (0.21–5.87)	0.01	0.91	0.73 (0.11–4.76)	0.11	0.74
Sex						
Male	Ref			Ref		
Female	0.50 (0.09–2.69)	0.65	0.42	7.95 (0.83–76.22)	3.23	0.07
BMI						
<24 kg/m ²	Ref			1.07 (0.98–1.17)	2.47	0.12
24–30 kg/m ²	2.93 (0.45–18.95)	1.27	0.26			
>30 kg/m ²	4.88 (0.36–66.41)	1.41	0.24			
Age						
<40 years	Ref					
40–49 years	2.67 (0.22–32.96)	0.59	0.45			
50–60 years	0.94 (0.05–16.35)	0.01	0.97			
>60 years	1.78 (0.15–21.51)	0.21	0.65			
Etiological factors						
Idiopathic	Ref			Ref		
Non-idiopathic	9.32 (1.02–84.82)	3.92	0.04	7.953 (0.83–76.22)	3.23	0.07
Comorbidities						
None	Ref					
Systematic	2.15 (0.4–11.61)	0.76	0.37			
Arterial ultrasound						
Negative	Ref					
Positive	1.20 (0.13–11.50)	0.03	0.87			
CRP POD1	1.00 (0.98–1.03)	0.05	0.83			
ESR POD1	0.97 (0.89–1.06)	0.45	0.51			
D-Dimer POD1	1.09 (1.00–1.19)	3.99	0.04	1.073 (0.983–1.171)	2.47	0.12

VTE: Venous thromboembolism; OR: Odds ratio; CI: Confidence interval; Ref: Reference variable; BMI: Body mass index; CRP: C-reaction protein; ESR: Erythrocyte sedimentation rate.

Table 4: Complications within POD 90 following total hip arthroplasty in the two study groups.

Complications	Aspirin group (n = 34)	Rivaroxaban group (n = 36)	Statistics	P
GI adverse events, n (%)	1 (2.9)*	2 (5.6)†	1.13	0.29
Bleeding events, n (%)	1 (2.9)‡	3 (8.3)§	0.96	0.33
DVT events, n (%)	3 (8.8)	3 (8.3)	0.01	0.91
Systematic complication, n (%)	0	1 (2.8)	0.96	0.33
Wound complication, n (%)	1 (2.9)	0	1.07	0.30

* One case of post-operative nausea during hospital stay. † One case of post-operative nausea during hospital stay, and one case of stomachache diagnosed with peptic ulcer. ‡ One case of epistaxis. § One case of epistaxis and two cases of ecchymosis. GI: Gastrointestinal; DVT: Deep venous thrombosis.

suggested that aspirin showed similar antithrombotic efficacy and lower bleeding risk at this dose when compared with anticoagulants.^[14,23] However, the administration of the aforementioned dose was considered high and became controversial over relevant disadvantages, which were associated with the internal antithrombotic process through the vascular-derived prostacyclin mechanism^[24] and a dose-related GI side effect.^[25] In the field of carotid endarterectomy, the use of a lower dose (81 mg) might even be more effective than that of a high dose.^[26]

Therefore, the study to explore new modalities for the appropriate dosage of aspirin for VTE prophylaxis in total

joint replacement has emerged. The Pulmonary Embolism Prevention trial was among the first clinical trials to examine the effect of low-dose aspirin (160 mg daily) for either hip fracture surgeries or elective hip or knee arthroplasty compared with placebo,^[27] and suggested that aspirin reduced the incidence of both symptomatic DVT and non-fatal or fatal PE. Colwell *et al*^[28] adopted a compression device with a lower dose, 81 mg per day, to compare its safety and efficacy with LMWH after total hip replacement, suggesting that a lower incidence of major bleeding but equal VTE risk under aspirin-combined therapy. More recently, investigators reported that comparative experiments using two different doses of aspirin to study the efficacy of low-dose use.^[18,29] In two

single-center studies, patients were assigned to two groups receiving high-dose (325 mg twice a day) or low-dose (81 mg twice a day) aspirin. They found similar VTE occurrence and bleeding risk in the high- and low-dose groups; however, a significant reduction in GI side effects was noted in the low-dose group. These studies cast new light on antithrombotic treatment for orthopedic surgeons and showed compelling support for low-dose aspirin use in VTE prophylaxis following total joint replacement.

Recently, some RCTs have attempted the use of low-dose aspirin for joint replacement surgeries in China. The most commonly used dosage of aspirin in these RCTs was 100 mg once daily. In two studies, the authors concluded a similar post-operative incidence of VTE and bleeding risk between aspirin and other anticoagulants.^[30,31] However, another study comparing aspirin with rivaroxaban and subcutaneous LMWH, found a higher DVT rate in patients receiving aspirin than that in rivaroxaban.^[32] Few studies have investigated that the role of aspirin in VTE chemoprophylaxis in patients post-THA in China.

Our study is one of the first prospective RCT comparing the efficacy of aspirin and rivaroxaban following THA with a dose of 100 mg twice daily, which was different from previous RCTs in China. No symptomatic DVT or PE was detected in our study, and the patients in the two groups had low and very similar rates of asymptomatic DVT during follow-up. Our results indicated that the inexpensive and widely available generic agent aspirin was not significantly different from the more expensive, direct oral anticoagulant rivaroxaban in VTE prophylaxis after THA. Through multivariable logistic analysis, we excluded the influence of other confounding factors, and the comparable prophylactic effect of these two drugs was further confirmed ($P = 0.74$). The incidence of VTE in this study was relatively lower than that reported in the literature.^[33] Multiple aspects of the post-operative regimen may play a role in addition to chemoprophylaxis, including early mobilization and supplemental use of sequential compression devices. Despite this, there were no significant inter-group differences in terms of peri-operative treatment.

Surgeons have been concerned about the increased risk of post-operative bleeding associated with the use of aspirin, especially after orthopedic surgery. Previous literature has compared the clinical outcomes of NOACs with those of LMWH^[16,18-20]; however, there are relatively limited data comparing aspirin with NOACs in THA. Lindquist *et al*^[34] compared rivaroxaban, LMWH, and aspirin for chemoprophylaxis of VTE following total knee arthroplasty (TKA) and THA. Other studies compared rivaroxaban with aspirin for VTE chemoprophylaxis following TKA,^[30,32] showing a significantly lower bleeding risk of aspirin compared to that of rivaroxaban. In this study, there was no significant inter-group difference in peri-operative TBL and average post-operative Hb, suggesting the safety of aspirin use. Surgeons still need to be attentive to post-operative hidden blood loss because of the high proportion of TBL. The hidden blood loss may be related to hemolysis, bleeding in the interstitial space, and other factors, which

could be exacerbated following anticoagulant treatment.^[35] Furthermore, two patients in the rivaroxaban group developed obvious subcutaneous ecchymosis in our study, which implies more bleeding after anticoagulant prophylaxis with rivaroxaban. The results in this study corroborated with those in the literature^[9,10,16,18-20,31-33] and extended to different doses of aspirin for chemoprophylaxis.

The GI adverse effects are a major concern for NOACs^[16,35,36] as well as aspirin. By affecting the platelet activity and inhibiting prostacyclin production, aspirin might cause mucosal ulceration and bleeding.^[37] The risk of aspirin-related GI adverse effects is dose-dependent,^[38] even with a low-dose (75 mg) of aspirin exposure.^[39] In this study, there was one case of post-operative nausea in the aspirin group, and one case of nausea with one case of peptic ulcer symptom in the rivaroxaban group ($P = 0.29$). All three patients did not withdraw from the study. No GI bleeding occurred in our study. It is recommended that gastro-protective strategies could be utilized to minimize the GI risk associated with aspirin treatment for high-risk patients, such as the adoption of enteric-coated formulations and the co-administration of proton pump inhibitors.^[8]

This prospective clinical trial has several limitations. First, this was a single-center study, and the current research involved a relatively small number of cases. Since the incidence of symptomatic DVT is relatively low, from 0.1% to 4.6%,^[8,14,30] we chose to observe the asymptomatic DVT event, which was less clinically important than symptomatic DVT. First, future multicenter studies with more cases and different doses of aspirin are needed to analyze the effect of aspirin on the chemoprophylaxis of symptomatic VTE following THA in China. Second, this study was not powered to detect the superiority of 100 mg aspirin twice daily over rivaroxaban for chemoprophylaxis. The main objective of this study was to determine the non-inferiority of 100 mg aspirin in the prevention of asymptomatic VTE following THA. Third, post-operative Doppler ultrasonography was performed between PODs 14 and 30, which indicated that we might have missed some thrombotic events thereafter. Fourth, this study was underpowered to detect the inter-group difference in the secondary outcomes. Finally, given that the risk factors overlap, patients with VTE are at increased risks for arterial thrombotic events.^[40] In addition to VTE prophylaxis, aspirin might be superior to NOACs in the prevention of arterial thrombotic events following THA. However, this study excluded patients with cardiovascular risk, and the limited number rendered it underpowered to analyze the co-effect of aspirin.

In conclusion, this prospective study demonstrated that 100 mg aspirin twice daily extended to POD 35 was not inferior to the NOAC rivaroxaban for VTE prophylaxis following primary selective THA. Using aspirin for chemoprophylaxis could lead to similar TBL as that in rivaroxaban use following THA. Aspirin use might be a safe and effective modality for VTE prophylaxis following THA in the future; thus, future studies are warranted to determine its eligibility in our country.

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Conflicts of interest

None.

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