Clinical and Applied Thrombosis/Hemostasis
Volume 25: 1-9

DOI: 10.1177/1076029619881409
journals.sagepub.com/home/cat
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Thromboprophylactic Efficacy and Safety of Anticoagulants After Arthroscopic Knee Surgery: A Systematic Review and Meta-Analysis

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Abstract

To examine the efficacy and safety of anticoagulants after knee arthroscopy (KA), PubMed, EMBASE, databases of Cochrane Central Register of Controlled Trials, and Chinese National Knowledge Infrastructure were searched up to August 2019 for randomized controlled trials (RCT). Seven RCTs including 4097 patients were demonstrated eligible according to the inclusion and exclusion criteria. The efficacy and safety of thromboprophylaxis were assessed and expressed using relative risk (RR) and 95% confidence intervals (95% CIs). The analysis of pooled data showed that anticoagulants group exhibited significant lower overall incidence of symptomatic and asymptomatic venous thromboembolism (VTE; RR = 0.35, 95% CIs: 0.22-0.55, $P < .00001$), significant higher incidence of all bleeding events (RR = 1.42, 95% CIs: 1.08-1.86, $P = .01$) compared to control group. However, no significant difference was found in terms of incidence of symptomatic VTE (RR = 0.43, 95% CIs: 0.15-1.21, $P = .11$) and incidence of major bleeding events (RR = 1.87, 95% CIs: 0.40-8.67, $P = .42$). The pooled number needed to treat to prevent one symptomatic or asymptomatic VTE was 26, while the pooled number needed to harm to cause one major bleeding event was 869. These results show that anticoagulants can effectively reduce the overall risk of VTE after KA; however, the increased risk of bleeding should be fully considered. Further studies are required to address the risk–benefit calculus and cost-effectiveness of anticoagulants after KA.

Keywords

anticoagulants, knee arthroscopy, bleeding events, venous thromboembolism

Date received: 10 June 2019; revised: 23 August 2019; accepted: 30 August 2019.

Introduction

Venous thromboembolism (VTE) is one of the most common complications of orthopedic surgeries. It is a critical health issue that related to considerable mortality and resource consumption.[1-3] The use of anticoagulants after most orthopedic surgeries has been well established, as it significantly reduces the risk of thrombosis with only slightly increased risk of bleeding.[4-8] Nevertheless, the necessity of anticoagulants after arthroscopic knee surgery is still controversial.

Knee arthroscopy (KA) has been viewed as one of the most frequently performed orthopedic surgeries. More than 4 million arthroscopic knee surgeries are conducted every year worldwide.[4] Knee arthroscopy is considered by some clinicians to be at low risk of VTE as its minimally invasive feature. However, according to the clinical studies, without intervention, the incidence of deep vein thrombosis (DVT) after KA varies from 0.6% to 18%,[9-13] and a meta-analysis reported an overall weighted incidence of DVT 9.9%.[14] A large population-based case–control study showed that there is a remarkably increased risk of VTE after KA, especially for patients with acquired or genetic risk factors.[15]

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There is the potential that clinicians may underestimate the risk of DVT after arthroscopic knee surgery. However, consistent guideline has not been reached until now by authorities to guide clinical practice due to the lack of adequate evidence. Most doctors in Germany use anticoagulants as a routine thromboprophylaxis measurement according to a questionnaire,[16] while The American College of Chest Physicians (ACCP) only recommend the use of anticoagulants after KA on patients with risk factors.[17] On the other hand, The American Academy of Orthopaedic Surgeons (AAOS) and The National Institute for Clinical Health and Excellence of United Kingdom haven't given any recommendation on the thromboprophylaxis after KA.[18]

Recently, several large sample size randomized controlled trials (RCTs) have been conducted to explore the necessity of anticoagulants after KA. We therefore performed the present meta-analysis of randomized trials by pooling the data together to seek more comprehensive evidence and hopefully provide insights into clinical practice.

Materials and Methods

Inclusion Criteria

Only RCTs, whether double-blinded, single-blinded, or unblinded, were included in this meta-analysis. We considered RCTs of patients with all types of arthroscopic knee surgeries, comparing anticoagulants with control.

Exclusion Criteria

(1) Cross-over design studies; (2) studies without a control group; (3) studies with insufficient data; (4) nonoriginal studies such as reviews, case reports; (5) studies that use anticoagulants in the control group. No language restrictions were applied.

Search Strategy

PubMed, EMBASE database, databases of Cochrane Central Register of Controlled Trials, and Chinese National Knowledge Infrastructure were searched up to August 2019 for all publications (Online Appendix 1).

Selection of Studies and Data Extraction

Two investigators independently assessed all the studies for eligibility and extracted data. A consensus was reached through discussion when there was a dispute, using a standardized, piloted web-based data management tool for systematic reviews. We screened all titles, abstracts, and full texts to determine the final eligibility.

We extracted the first author; year of publication; trial size; details of intervention including dose and treatment duration; patient characteristics such as mean age, gender; duration of follow-up; and outcome data.

Quality Assessment

Two authors independently evaluated the methodological quality of included RCTs using the Cochrane Handbook for Systematic Reviews of Interventions. Consensus was reached through a discussion with a third author when there were disagreements.

Statistical Methods

We used RevMan version 5.1 to analyze the data, and $P < .05$ was considered significant. As the outcome was dichotomous data, we used the relative risk (RR) to evaluate the combined overall effect sizes. We used random effects mode for this meta-analyses. We quantified heterogeneity using the χ^2 heterogeneity and the I^2 statistic. Whenever 10 or more RCTs contributed to a meta-analysis, we planned to evaluate small study effects, including publication bias, with funnel plots and the Egger linear regression test.[19] We also calculated the pooled number needed to treat (NNT) to prevent one symptomatic or asymptomatic VTE event and the number needed to harm (NNH) to cause one major or fatal bleeding event. To estimate pooled NNT and NNH, random effects meta-analyses of risk difference were performed, and the pooled estimates derived from these analyses were inverted.

Results

Identification of Trials

The databases search identified 781 articles. After going through the titles and full tests, 7 RCT articles were assessed eligible according to the formulated inclusion and exclusion criteria (Figure 1).[20-26]

Characteristics of the Included Trials

All 7 retrieved articles provided information about country, sample size, average age, gender ratio, treatment measures, efficacy end points, and follow-up durations. A total of 4097 patients were involved in the 7 eligible trials. Patients in the trials went through different types of KA surgeries, including synovial resection, meniscectomy, cartilage shaving, ligament reconstruction, or combined surgeries, except one trial[20] which was conducted based on anterior cruciate ligament reconstruction patients' sample. Sample sizes of the included studies ranged from 105 to 1451. All the included trials used low-molecular-weight heparin, aspirin, or rivaroxaban as thromboprophylaxis measures in the treatment group, while different measures were used in the control groups including no treatment,[20,24,26] placebo,[21-23] or compression stockings.[25] Stockings instead of placebo were used in KANT study because of local prophylaxis policies. All the trials chose cumulative incidence of DVT and pulmonary embolism (PE; symptomatic, asymptomatic, or both) as the efficacy end point, and incidence of major bleeding as the primary safety end point. Three trials[21,23,25] defined major and minor bleeding events

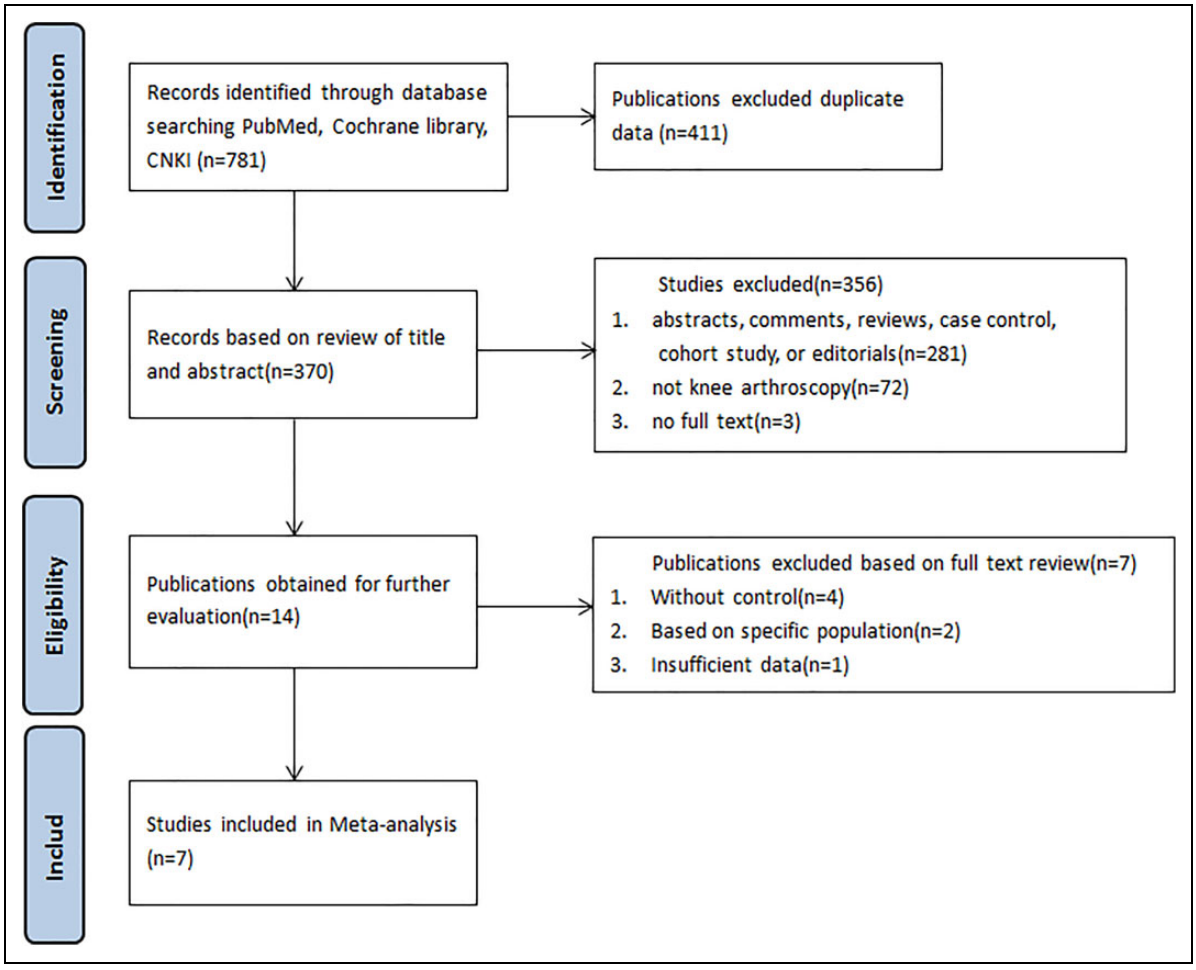

Figure 1. Selection of RCTs for inclusion in the meta-analysis. RCTs indicates randomized controlled trials.

according to the guideline of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis (ISTH).[27] The definitions of major bleeding events in the other 4 trials were not entirely consistent or not clearly mentioned, and adjustments were made according to guideline of ISTH during data extraction. All the included trials used ultrasound combined with volume of drainage to identify surgical site hematoma. Two trials[21,25] detailed DVT into symptomatic proximal DVT (SPD), symptomatic distal DVT (SDD), asymptomatic proximal DVT (APD), and asymptomatic distal DVT. These 2 trials took the cumulative incidence of mortality, SDD, SPD, and APD as the primary efficacy end point. Gastroc and soleal DVT events were not taken into account in the included trials. All the included trials mainly used ultrasonography to detect DVT and computed tomography to detect PE. Follow-up duration varied from 7 days to 3 months. Details are available in Table 1.

The Methodological Quality of Included Trials

We utilized the criteria recommended by Cochrane Handbook for Systematic Reviews to estimate the risk of bias in the 6 included articles. Although all the trials were declared RCTs, 4 of them[20,22,24,26] did not describe the generation of the random sequence. Five trails[21-23,25,26] stated adequate use of concealment of allocation. Two trials[21,22] were double-blind while others were either single-blind or no blind design. No selective reporting was found in all 7 trials. Loss of follow-up in 4 trails[20,21,23,25] was less than 5% respectively, which we thought presents a relatively low risk of bias.[28] The methodological quality of included trials was summarized in Figure 2.

Thromboprophylactic Effects of Anticoagulants

For symptomatic VTE, as the primary effectiveness outcome, we pooled data of 4 trials[21,23-25] involving 3689 patients with a random effects model and found that anticoagulants group showed no significant difference in the incidence of symptomatic VTE compared to the control group (RR = 0.43, 95% confidence interval [CI]: 0.15-1.21, $P = .11$, Figure 3). The pooled NNT to prevent one symptomatic VTE was 107. Meanwhile, a moderate heterogeneity was found between trials ($I^2 = 40\%$). For the secondary effectiveness outcome, symptomatic and asymptomatic VTE (both proximal and distal), the pooled data of 6 trials[20-22,24-26] involving 2604 patients showed significant effects of anticoagulants in reducing the overall incidence

Table 1. Basic Characteristics of the Included Studies.

Study		Treatment Group				Control Group					
Year	Country	Sample Size	Mean Age, Year	Male Sex, %	Intervention	Sample Size	Mean Age, Year	Male Sex, %	Intervention	Outcomes	Follow-Up
van Adrichem et al (2017)[23]	Netherlands	731	48.1 ± 12.8	56.6%	2850 IU Nadroparin or 2500 IU dalteparin every day for 8 days after surgery	720	49.1 ± 12.3	55%	placebo	1. Symptomatic VTE 2. Major bleeding 3. Minor bleeding	3 months
Wirth et al (2001)[24]	Germany	117	37.6 ± 13.0	69.2%	Reviparin (1750 anti-Xa IU) every day for 7 to 10 days after surgery	122	38.5 ± 11.6	80.3%	No treatment	Symptomatic and asymptomatic VTE Major bleeding Minor bleeding	10 days
Camporese et al (2016)[21]	Italy	122	44.9 ± 12.8	63.9%	10 mg rivaroxaban for 6 days after surgery	119	45.9 ± 13.9	70.6%	Placebo	Symptomatic DVT, APD, or PE Symptomatic and asymptomatic VTE Major bleeding Minor bleeding	3 months
Michot et al (2002)[22]	Switzerland	66	42.0 ± 14.7	61.0%	2500 IU dalteparin 60 minutes before surgery; 2500 IU or 5000 IU every day for 30 days after surgery	64	46.5 ± 13.2	72%	Placebo	Symptomatic and asymptomatic VTE Major bleeding Minor bleeding	31 days
Liu (2016)[20]	China	70	UA	UA	Enoxaparin 100 Axau/kg for 7 days after surgery	35	UA	UA	No treatment	Symptomatic + asymptomatic VTE Bleeding volume	7 days
KANT (2008)[25]	Italy	1101	41.9 ± 15.1	61.8%	Nadroparin 3800 anti-Xa IU for 7 or 14 days after surgery	660	42.3 ± 14.4	62.4%	Compression stocking for 7 days	Symptomatic DVT, APD or PE Symptomatic + asymptomatic VTE Major bleeding, clinically relevant bleeding Minor bleeding	3 months
Kaye et al (2015)[26]	USA	66	46.0	58%	Aspirin 325 mg for 14 days after surgery.	104	43.4	63%	No treatment	Symptomatic + asymptomatic VTE Bleeding complications	4 weeks

Abbreviations: APD, asymptomatic proximal DVT; DVT, deep-vein thrombosis; PE, pulmonary embolism; UA: unavailable; VTE, venous thromboembolism (DVT + PE).

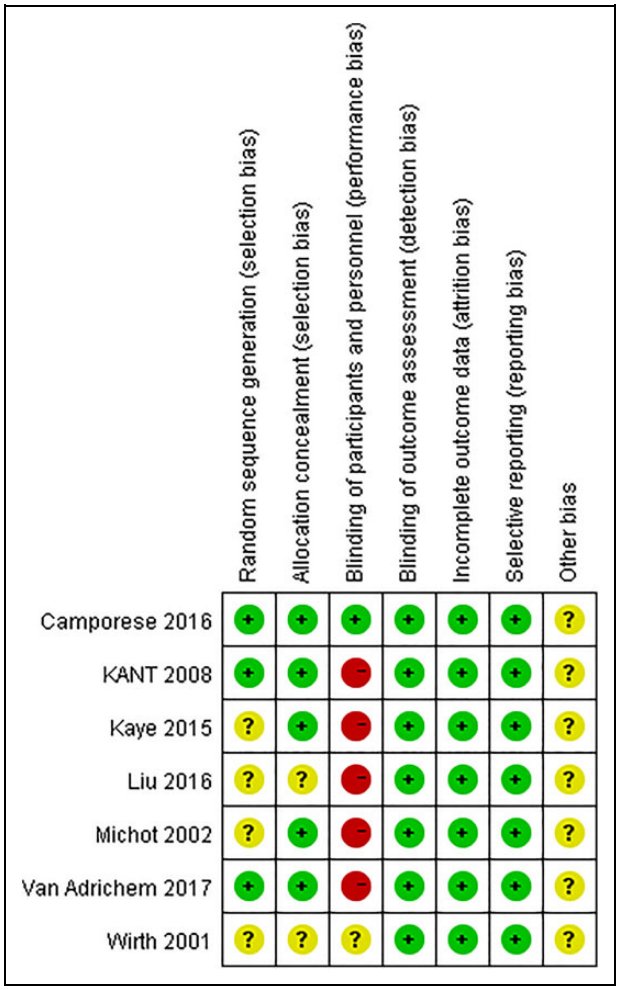

Figure 2. Risk-of-bias assessment of randomized controlled trials included in the meta-analysis.

of symptomatic and asymptomatic VTE for patients undergone KA surgery (RR = 0.35, 95% CI: 0.22-0.55, $P < .00001$, Figure 4). The pooled NNT to prevent one symptomatic or asymptomatic VTE was 26. No heterogeneity was found between the included trails ($I^2 = 0\%$).

Safety of Anticoagulants

We took the incidence of major bleeding events as the primary adverse effects outcome. After calculating the pooled data of 6 trials,[21-26] we found no significant difference between the anticoagulants group and the control group (RR = 1.87, 95% CI: 0.40-8.67, $P = .42$, Figure 5) and no heterogeneity was detected ($I^2 = 0\%$). The pooled NNH to cause one major or fatal bleeding event was 869. As 3 involved trials[21,22,24] did not report any major bleeding events, their RR were not estimable and had no effect on the calculated pooled RR.

We took incidence of all bleeding events as the secondary adverse effects outcome, and 5 trials[21-25] involving 3815 patients were included in this meta-analysis. The anticoagulants group showed significant higher incidence of all bleeding events compared to the control group (RR = 1.42, 95% CI: 1.08-1.86, $P = .01$, $I^2 = 0\%$, Figure 6). The pooled NNH to cause one bleeding event was 66.

Publication Bias

As there were limited trails involved in the present meta-analysis, small study effects were not assessed.

Discussion

The principal finding of this meta-analysis is that anticoagulants can significantly reduce the overall incidence of symptomatic and asymptomatic VTE and may reduce the incidence of symptomatic VTE compared to control in patients undergone arthroscopic knee surgery. This result is in line with recently published meta-analyses[29,30]; however, these meta-analyses only emphasized the clinical importance of SPD and ignored the clinical importance of asymptomatic DVT and SDD, thus drew a conclusion that anticoagulant is ineffective. Nevertheless, we think this conclusion is worth discussing.

The first question is whether asymptomatic DVT make clinical sense, especially when used to evaluate the efficacy of anticoagulants. One of our involved trials had raised similar question, considering that asymptomatic thrombosis events led to overestimation of the incidences, and could not provide implication for clinical practice.[23] In addition, there is a sense that clinical practice should be based on clinical end points, should not be disguised by combination with surrogate end points.[31] It is assumed that most clinical silent thrombi can be resolved spontaneously, leading to no clinical complications, so there is no need for preventive measures. However, literature is not conclusive in this area. Firstly, studies have revealed the clinical significance of asymptomatic DVT, showing that reduction in asymptomatic DVT by anticoagulants was associated with a reduction in symptomatic events, indicating that, without intervention, some asymptomatic DVT events might turn to be symptomatic eventually.[32] From a retrospective study, 14.5% of the patients with asymptomatic DVT developed symptomatic VTE in 5 years.[33] Secondly, certain asymptomatic thrombi can get involved in the proximal veins, which usually draw attention of most clinicians, as they may have the potential to cause fatal PE. In a retrospective cohort study of consecutive patients with clinically suspected DVT, proximal DVT was found in the asymptomatic leg.[34] One of the involved trials in our meta-analysis calculated the proportion of proximal DVT events in the overall asymptomatic DVT events in the control group was 41% (7/17). This result is consistent with findings of previous studies showing that 37% of asymptomatic DVT in medical patients involved the proximal veins.[35-37] In addition, it was found that asymptomatic DVT was associated with increased all-cause mortality in patients with an acute medical disease.[38] To date, there have been no RCTs exploring the necessity of treatment for asymptomatic DVT, and the prognosis of asymptomatic DVT remains

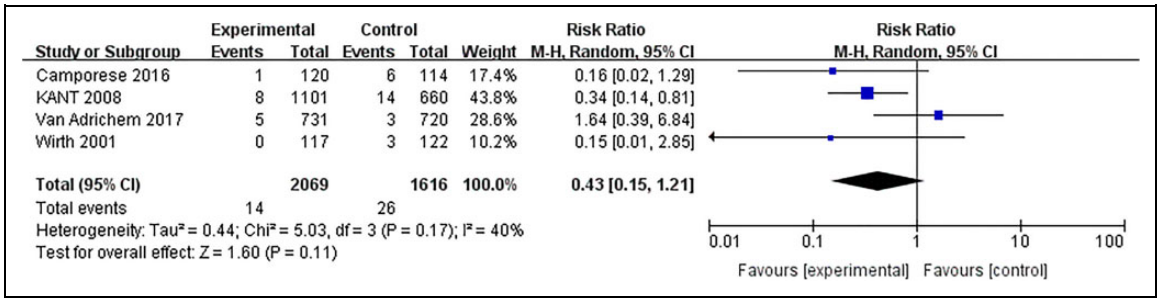

Figure 3. Forest plots for comparison of symptomatic VTE between treatment group and control group. VTE indicates venous thromboembolism.

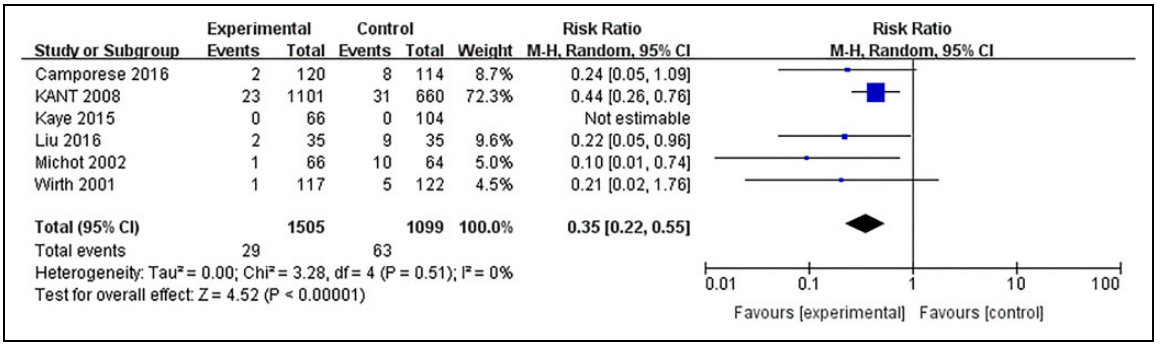

Figure 4. Forest plots for comparison of symptomatic and asymptomatic VTE between treatment group and control group. VTE indicates venous thromboembolism.

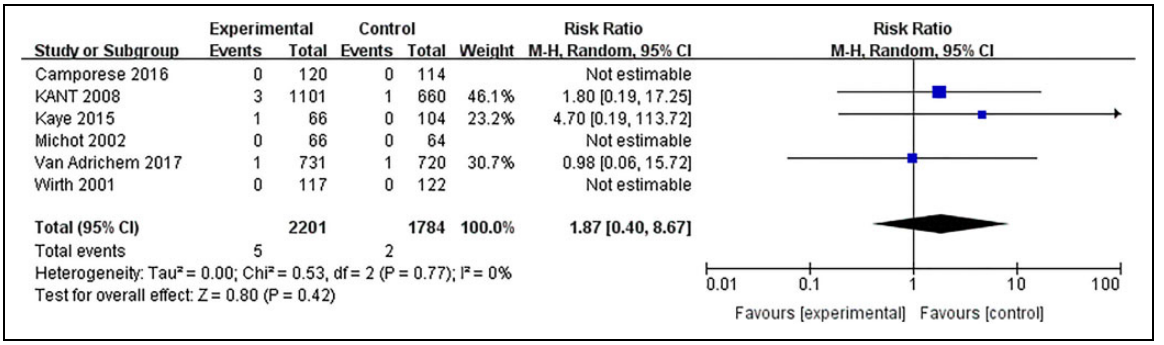

Figure 5. Forest plots for comparison of major bleeding events between treatment group and control group.

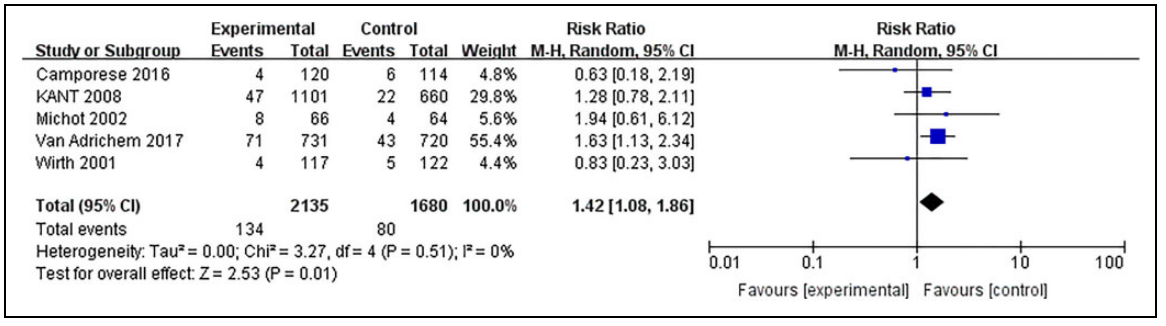

Figure 6. Forest plots for comparison of all bleeding events between treatment group and control group.

uncertain. Therefore, further researches are needed to foster consensus on this issue.

The second question is whether SDD deserves clinical attention and is it appropriate to ignore the SDD when assessing the necessity of anticoagulants. To date, there has been considerable debate about this issue. The trial by Righini (CACTUS trial)[39] indicated that nadroparin did not significantly reduce the risk of proximal extension in outpatients with symptomatic calf DVT, but significantly increased bleeding events. It seems anticoagulation in isolated SDD does harm rather than good. However, there was a 10% venous thromboembolic event rate at 3 months for untreated symptomatic calf DVT in the placebo group of CACTUS trial, which is not negligible.[40] In addition, it was proposed that lower doses of heparin rather than nadroparin, which was used in CACTUS trial, might exhibit a better safety profile.[39] In addition, it is worth mentioning that the ACCP 2012 and 2016 guidelines still recommend initial use of anticoagulation in patients with acute isolated distal DVT.[41,42] Besides, a recent meta-analysis favored the use of anticoagulants for isolated distal DVT,[43] revealing that anticoagulants significantly reduce the proximal extension of distal DVT. Collectively, it is not precise to neglect asymptomatic DVT and SDD, especially considering that the overall incidence of VTE in treatment group and control group were 1.8% and 6.3% respectively from our study.

Anticoagulants cause significantly higher incidence of all bleeding side effects compared to placebo in patients undergone arthroscopic surgeries from this meta-analysis, but there was no significant difference in terms of incidence of major bleeding side effects. This result is in line with previous studies. The overall incidences of major bleeding events in treatment group and control group were 0.22% and 0.11% respectively, and the overall incidences of all bleeding events in treatment group and control group were 6.3% and 4.8%, respectively. Although most of the bleeding events were minor bleeding events, which were not life-threatening and needed no extra intervention, the risk of major bleeding events cannot be excluded based on the CI (RR = 1.87, 95% CI: 0.40-8.67), so it requires thoughts to weigh the advantage of reducing the thrombogenic risk and the disadvantage of more minor bleeding complications when using anticoagulants after arthroscopic surgeries.

Aspirin has been considered an adequate chemoprophylaxis following orthopedic surgery with advantages of low cost, high efficacy, and easy administration.[44,45] One included RCT[26] in our meta-analysis used aspirin for thromboprophylaxis. No symptomatic or asymptomatic VTE event was found in the treatment group, indicating a high efficacy of aspirin. However, it should be noted that this RCT was conducted in a low-risk population with stricter exclusion criterion compared to the other included RCTs, especially no smokers were included. More studies are needed to explore the thromboprophylactic efficacy and safety of aspirin after KA.

A number of limitations of this study should be considered. Firstly, there was a mild heterogeneity ($I^2 = 40\%$) in the pooled data of incidence of symptomatic VTE. In the identification of symptomatic VTE after KA, in van Adrichem's study,[23] VTE-related signs and symptoms were determined by the patients themselves with the help of an informative brochure. Researchers collected the results by telephone, and ultrasonography was conducted on suspected participants to confirm a symptomatic VTE event, which they thought reflected a general clinical practice. Whereas, in the other included trials, signs and symptoms were determined by nurses or doctors in an interview before ultrasonography was conducted on all the participants at a fixed time. In addition, 2800 IU nadroparin was implemented in treatment group of Van Adrichem's study[23] while 3800 IU nadroparin was implemented in treatment group of KANT study.[25] The included trials differed in patient population, type and dosage of anticoagulants, duration of treatment, and follow-up durations. Those might be sources of heterogeneity. Secondly, although a protocol had been made before we started this meta-analysis, it has not been registered at PROSPERO or elsewhere, therefore possible bias may exist. However, we followed the steps of systematic evaluation strictly to minimize possible bias.

This study provides some implications for clinical practice. The AAOS has not published a position statement on thromboprophylaxis after KA as the lack of adequate evidence, and many clinicians choose not to routinely treat patients undergone KA with anticoagulants based on individual experience. But our meta-analysis of recent RCTs confirmed the benefit of anticoagulants on reducing the overall incidence of symptomatic and asymptomatic VTE after KA. If asymptomatic VTE and SDD should be taken seriously, then the efficacy of anticoagulants after KA seems doubtless. Meanwhile, as a side effect, the increased risk of bleeding is worthy of consideration. Although acknowledging the limitations of this meta-analysis, our findings may provide insights into clinical practice.

This study also provides some implications for further research. Firstly, different kinds of KA surgeries, which imply different operation time and different tourniquet duration, may exert an influence on the incidence of VTE. Thus, further studies based on specific KA surgery like ligament reconstruction should be conducted to gain more detailed insights into this field. Secondly, types of anticoagulants, doses, and durations of treatment were not consistent in studies included in our meta-analysis, so further studies can explore this field to build evidence-based standard in the future.

Authors' Note

Y.Y. and S.L. were responsible for the design, databases search, studies selection, and data extraction. W.Z. and Y.Y. were responsible for the quality assessment and data analysis. H.L. and J.S. took charge of manuscript draft and revision. All the authors contributed to the interpretation of the data and precisely reviewed the manuscript for publication. All data generated or analyzed during this study are included in this article. This article does not contain any studies with human participants or animals performed by any of the authors.

Acknowledgments

Thanks to professor Guang-heng Li for his help in revising the manuscript and financing the study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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