**Title: Outcomes of Different Perioperative Management Strategies of Patients on Chronic Anticoagulation in Elective Total Hip and Knee Arthroplasty: A Systematic Review**

**Short/Running Title: Chronic Anticoagulation in Elective Hip and Knee Arthroplasty**

**Systematic Review**

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**KEY MESSAGES**

* Evidence is contradictory for the need of discontinuation of warfarin
* Individual risk stratification and multi-modal prophylaxis had better outcomes
* New evidence for the use of newer oral anticoagulant agents is warranted

**ABSTRACT**

**Introduction:** There are currently different management guidelines for patients undergoing elective total hip arthroplasty (THA) or total knee arthroplasty (TKA) that are on long-term anticoagulation. The timing of discontinuation and restarting the anticoagulation is challenging during the postoperative care, which often involves general practitioners and physiotherapists.

**Methods:**The systematic review followed the PRISMA guidelines and included three databases: PubMed/MEDLINE, EMBASE and Web of Science Core Collection. It was registered in the International Prospective Register for Systematic Reviews and Meta-analysis (PROSPERO) under the registration number: CRD42023408906. The risk of bias assessment was performed using the Methodological index for non-randomized studies (MINORS) criteria.

**Results:** Six retrospective studies involving 727 patients with therapeutic anticoagulation (1540 controls) for elective THA, TKA and revision arthroplasty have been included. The follow-up ranged from 30 days to 1 year postoperatively. All studies evaluated outcomes of warfarin therapeutic anticoagulation versus prophylactic dosages of one or more of the following: warfarin, aspirin, low-molecular weight heparin (LMWH) and unfractionated low dose heparin (UFH). One study did not discontinue therapeutic anticoagulation. Two studies reported no significant differences in complications between groups, whilst three studies had significant higher rates of superficial wound infections, revision surgeries, postoperative haematomas and prosthetic joint infections (PJI).

**Conclusion:** Different anticoagulation-related perioperative management strategies achieve different outcomes following elective arthroplasty in patients with therapeutic chronic anticoagulation. There is contradictory evidence regarding the need of discontinuation of therapeutic warfarin. Retrospective data showed that individual risk stratification with multi-modal prophylaxis resulted in minimal complications.

**Level of Evidence:** Systematic Review of Level III studies.

**Keywords:** total knee arthroplasty; TKA; therapeutic anticoagulation; warfarin; total hip arthroplasty; THA

**INTRODUCTION**

Many patients undergoing elective total hip arthroplasty (THA) or total knee arthroplasty (TKA) are on chronic therapeutic anticoagulation due to other medical conditions, such as atrial fibrillation, coagulation disorders or previous thrombotic events.[1–3] Given the risk of bleeding associated with arthroplasty, as well as the risk of thromboembolic events in the post-operative period in case of insufficient therapeutic anticoagulation, the management of chronic therapeutic anticoagulation agents perioperatively is critical to achieving successful outcomes both in the medical management, as well as for arthroplasty. Over 100,000 TKAs are performed annually for osteoarthritis (OA) in the UK alone.[4] There was a projected growth of primary THAs by 71% and primary TKAs by 85% by the year 2030 when compared to 2014.[5]Moreover, family physicians and allied health professionals are being increasingly responsible for the co-management of anticoagulation peri-operatively.[6]

Balancing the risk of adverse thromboembolic events versus major bleeding is the core consideration of perioperative anticoagulation management in elective arthroplasty.[3] There are independent risk factors that can lead to thrombotic complications, such as: hypercoagulability disorder, presence of metastatic cancer (especially pancreatic, liver and non-small cells lung cancer),[7] sepsis, obesity, chronic obstructive pulmonary disease (COPD), and HIV infection.[8–10]On the other hand, therapeutic anticoagulation following arthroplasty can cause a postoperative bleeding in up to 1.7% - 18% of cases,[11, 12] with variation depending on the definition of bleeding and the potency of antithrombic agents used. There is also no consensus on the best choice of the anticoagulant. [13] There is also a different risk profile for larger procedures such as revision hip and knee arthroplasty, that should be evaluated separately: revision surgery was an independent risk factor for wound drainage (odds ratio, 3.201; 95% confidence interval, 1.594-6.426; P=.001) in a large cohort of 1917 patients by Manista et al.[14] Nevertheless, patients on chronic anticoagulation have significantly higher odds of 90-day and 2-year complications following major surgery, including increased odds of prosthetic joint infection (PJI), surgical site infection, and mechanical prosthetic complications, as highlighted by Heo et al.[15]

In the context of growing numbers of patients on chronic therapeutic anticoagulation undergoing elective hip and knee arthroplasty, orthopaedic surgeons, as well as general practitioners[16] and allied health professionals[17] involved in the postoperative care and rehabilitation process, need competence in the management of perioperative treatment interruption of antithrombotic regimens, as mostly they are the primary healthcare workers to see the patient before surgery.[18–20] The purpose of this systematic review was to appraise the available literature and identify successful strategies for anticoagulation management in elective primary hip and knee arthroplasty for patients on chronic therapeutic anticoagulation therapy.

**METHODS**

*Strategy of the Systematic Search*

The systematic review followed The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[21]. It was registered in the International Prospective Register for Systematic Reviews and Meta-analysis (PROSPERO) under the registration number: CRD42023408906. A systematic computer-based database search was conducted using PubMed/MEDLINE, EMBASE and Web of Science Core Collection. Combinations of the following key-words were used: ["therapeutic"] AND [“anticoagulation”] AND [“TKR” OR “THR” OR "THA" OR "TKA”]. All published original research articles describing clinical outcomes depending on management strategies of therapeutically anticoagulated patients receiving elective knee or hip arthroplasty without any demographic limitations from inception until May 1st, 2023 were included in the systematic search.

*Selection Process*

Two authors (DA and PE) performed blind and independent study selection by applying the eligibility criteria. In cases where consensus could not be reached, a third author (OA) was consulted.

The inclusion criteria were: (1) published peer-reviewed original reports of human studies in English, with publication date between January 1st, 1973, and May 1st, 2023; (2) a minimum reported level of evidence of IV using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence;[22, 23] (3) patients received a primary total hip or total knee arthroplasty, including bilateral cases; 4) subjects had an indication for therapeutic anticoagulation which was reported; 5) the management of the therapeutic anticoagulation was reported; 6) minimum follow-up of 1 month.

The exclusion criteria were: (1) review/hypothesis/technique articles or oral presentations; (2) non-English articles; (3) prophylactic thromboprophylaxis alone; (4) lack of clinical follow-up; (5) cadaveric or animal studies. Review articles, surgical techniques, oral presentations, experimental or animal studies, as well as studies mixing and overlapping patient populations were excluded.

*Risk of Bias Assessment*

The risk of bias assessment was performed by two authors (EA and PE) using the Methodological index for non-randomized studies (MINORS) criteria[24] for each type of study design. Rating discrepancies were resolved through consensus and consultation of the senior author (RC). MINORS criteria assess eight critical aspects of study design for non-comparative clinical studies and an additional four aspects of study design for comparative clinical studies. Each item is scored zero if information is not reported, one if information is reported but inadequate, and two if information is reported and adequate. Therefore, the maximum possible score is 16 for comparative studies and 24 for non-comparative studies. A scoring system was then used per study such as studies that answered yes to a question from the checklist scored 2, not clear scored 1 and no scored 0. Each score was then converted into a percentage.

*Data synthesis and statistical analysis*

The statistical analysis was initially planned to be performed using SPSS (IBM SPSS Statistics, Version 24.0; Chicago, Illinois) and R Software. Although a random-effects-model of meta-analysis was intended as per PROSPERO protocol, along with a heterogeneity analysis using a I² test, the included studies and collected data was too inconsistent in terms of reported outcomes and did not allow the performance of a meta-analysis.

**RESULTS**

*Study Identification*

The systematic search included EMBASE, Medline/PubMed and Web of Science databases. A total of 425 records was initially identified (**Fig. 1**). After duplicate removal and title/abstract screening stages, a total of 21 studies were eligible for full-text assessment. Only 6 studies evaluated outcomes for patients with pre-existing therapeutic anticoagulation and were included for final analysis.

*Risk of Bias Assessment*

All six studies were retrospective cohort/case-controlled studies providing a maximum level III of evidence according to Oxford Centre for Evidence-Based Medicine.[25] Every study was assessed individually using the MINORS tool (Methodological index for non-randomized studies).[24] The extended version for comparative studies was used all studies included comparators (**Table 1**). Five studies [26–30]have equally scored 71% and all lacked prospective data collection, as well as a-priori or prospective calculation of the sample size. One article[31] had only scored 58% (**Table 1**) mostly based on the unclear baseline demographics of the control group and outcome endpoint assessment.

*Demographics and Indications*

A total of 732 patients and 1535 controls were included in the systematic review. The follow-up following elective TKR, THR or revision arthroplasty ranged from 1 month to 1 year. The ratio of study sample size and controls was inconsistent among studies, ranging from 1:1[28] to 1:10[31] (**Table 2**). Looking at the distribution of age, gender and comorbidities, only McDougall et al. have matched the study population with the controls for those 3 variables.[27] Simpson and colleagues[26] have matched the groups based on the presence of diabetes, but did not report the age and gender distribution separately. The indication for pre-existing therapeutic anticoagulation was heterogenous and included a variety of indications without a clear breakdown of complexity (**Table 2**): atrial fibrillation (AF); history of pulmonary embolism (PE), deep venous thrombosis (DVT) or venous thromboembolism (VTE); cardiac valves or stents and coagulation disorders. Two studies included revision arthroplasty in their study population along with primary joint arthroplasty.[28, 30]

*Perioperative Anticoagulation Management*

All six studies have used warfarin for therapeutic anticoagulation in the study population.[26–31]Aggarwal et al. had included patients receiving Dabigatran in about 10% of their cohort, whilst the control group consisted of patients receiving prophylactic dosage of Warfarin (**Table 3**). Three studies[26, 27, 29] compared the therapeutic anticoagulation with warfarin versus prophylactic oral aspirin administration with prophylactic doses ranging from 300 to 650mg a day. Walton et al[31] included a control group receiving low-molecular weight heparin (LMWH) and had only evaluated outcomes related to the incidence of postoperative stiffness and rates of mobilization under anaesthesia (MUA) (**Table 4**). Rhodes[30] compared results of elective arthroplasty between patients that did not discontinue their therapeutic dosage of warfarin to a similar cohort that discontinued it 1 week prior to surgery and used prophylactic doses of LMWH for bridging (**Table 3**).

Heparin bridging was used for all patients in a study[28], whilst it was used for high-risk patients only in 3 other studies.[26, 27, 29] Postoperatively, warfarin was restarted and aimed to achieve a therapeutic level of international normalized ratio (INR)[26–30] or activated partial thromboplastin time (aPTT)[27] in all studies, however, the time-point of escalation to a therapeutic dosage was unclear with two studies emphasizing the surgeon’s preference as the leading factor[26, 29]. There was no clear data about when and how the therapeutic dosage was restarted and achieved based on patient risk factor stratification.

*Outcomes and Complications*

A detailed description of the differences in the rates of incidence of complications is given in **Table 4**. Apart from Walton et al, who only reported a significantly higher incidence of stiffness and need for MUA postoperatively in the chronic anticoagulation group[31], studies have consistently reported complications related to superficial wound infection and wound dehiscence. Three studies[26–28] have experienced significantly higher rates of superficial wound infections in the chronic anticoagulated group using their management strategies, as opposed to two reports that did not find significant differences.[29, 30] The same trend of differences in complications was observed for incidence of PJIs and postoperative bleeding incidents (**Table 4**). Only Simpson et al[26] experienced a higher rate of revision surgery in their chronic anticoagulated cohort. Data about incidence of venous thromboembolism (VTE), mean length of inpatient stay and readmission rates were inconsistent. Moreover, no study reported anything regarding intraoperative blood loss.

Overall, successful strategies with minimal complications were achieved in the study of Della Valle et al,[29] who used a multimodal prophylaxis and a risk stratification management with individual patient assessment and therapeutic anticoagulation postoperatively at the discretion of surgeon. The same successful outcomes were achieved by Rhodes et al,[30] who did not discontinue the therapeutic dosage of warfarin at all.

**DISCUSSION**

The most important finding of our study is the highlighted contradictory evidence regarding the most optimal management of chronic therapeutically anticoagulated patients receiving elective hip and knee arthroplasty. Successful and less successful outcomes with higher rates of complications were achieved both when using a strategy of discontinuation and bridging therapy,[28] as well as when simply continuing the therapeutic dosage perioperatively.[30] However, there are many potential factors (type of surgery primary/revision arthroplasty; choice of control group and other) that could have influenced these results and as such, these have to be interpreted with caution. There is also no evidence on how and when to restart therapeutic anticoagulation following elective arthroplasty.

Numerous professional colleges and societies have built and published guidelines on the management of chronic antithrombotic agents in the perioperative setting. The most common guidelines include: American Academy of Orthopaedic Surgeons (AAOS),[32, 33] American College of Cardiology (ACC),[34] American Society of Haematology (ASH),[35] American College of Surgeons (ACS),[36] British Committee of Standards for Haematology,[37] and French working group on perioperative haemostasis (GIHP). [38] Although these guidelines share similar factors that are considered to decrease the risk of VTE and medical-associated complications depending on the urgency of surgery, surgical bleeding risk, individual thromboembolism risk (based upon the patients’ CHADS2 or CHA2DS2-VASc score, presence and type of heart valves or stents and other medical risk factors),[3] the guidelines are validated to decrease the risk of VTE perioperatively but have less value in the prediction of the periprocedural bleeding risk.

For the purpose of predicting postoperative bleeding hazards, al bleeding risk score (HAS-BLED) has been previously described and is being recommended by ACC.[39] A HAS-BLED score of ≥ 3 was described to be predictive of bleeding events. The following factors each scoring 1 point were included in the scoring: arterial hypertension (HTN), abnormal renal function, abnormal liver function, prior stroke, history of anaemia, labile INR (<60% of time therapeutic), >65 years of age, on antiplatelet therapy or non-steroidal anti-inflammatory (NSAIDs), history of drug or alcohol use. Although it gives indicators for the risk of periprocedural bleeding for patients with therapeutic anticoagulation for atrial fibrillation, the validation results have been contradictory and further improvements are necessary.[40, 41] However, these studies all agreed that a concomitant antiplatelet therapy was significantly associated with the risk of major bleeding event,[40, 41] further highlighted in other reports with similar findings,[42] even if appropriate discontinuation is performed. Also, the score does not relate specifically to the surgical site bleeding, but instead for extraarticular bleeding as well. These findings may explain why the results by Aggarwal et al[28] highlighted significantly higher rates of surgical site complications, as their cohort included more complex surgeries and patients on concomitant antiplatelet therapy.

Even when consensus is achieved among the most common published guidelines (AAOS, ACC, and ACS) that warfarin can be resumed at the normal dose the evening of or the morning after surgery if adequate hemostasis has been achieved (12 to 24 h later),[3]the results of this systematic review highlight the need of consideration of surgeon’s judgement on the timing to restart therapeutic anticoagulation. The multi-modal prophylaxis by Della Valle[29]included the surgeon’s perspective along with the assessment of the risk of recurrent VTE and the risk of postoperative bleeding. Additionally, a series of additional measures for minimizing the risk of VTE and bleeding were performed: unfractionated heparin, 10 units/kg, was given intravenously after implantation of the acetabular component before the femur was prepared, to minimize the strong activation of the clotting cascade which occurs as the intramedullary contents are forced into the venous circulation;[43] Preheating of the cement and stem to 40°C reduced the fixation time by approximately five minutes. We also minimized the duration of proximal femoral vein occlusion which occurs during femoral preparation while the lower limb is held in extreme flexion, adduction, and internal rotation when using the posterolateral approach.[29, 44]

Another topic with contradictory findings in this systematic review is the need of warfarin discontinuation and the difference in surgical-related complications when compared to patients with bridging therapy. There is a large consensus among the published guidelines regarding the need of perioperative bridging for patients with high-risk of VTE (CHA2DS2-VASc score 7–9). Interestingly, Rhodes et al[30] chose to continue therapeutic warfarin perioperatively. Their results compared to the bridging control group showed no significant differences in the surgical-related complications, whilst concomitantly minimizing the medical VTE risk. These results are in accordance with previous reports that questioned the need of bridging therapy and discontinuation of chronic warfarin therapy for both elective knee and hip arthroplasty.[45, 46] However, the evidence is retrospective with limited sample size and further research is warranted. Due to the lack of inclusion of the whole possible variety of key-words for the systematic search, the studies from Mussa[45] and Philipps[46] were not included in the analysis. The results and quality of evidence are however identical to those of Rhodes[30] and would not have changed the overall scientific message in the context of appropriate acknowledgement.[47]

Even though no study included in the systematic review gives any insights in the risk profile and outcomes expected of newer oral anticoagulant agents, it is important to highlight the increasing of such anticoagulants (Dabigatran, Rivaroxaban, Apixaban). These have fixed daily dosing as a result of predictable pharmacokinetics, with no requirement for coagulation monitoring, convenient oral administration, and fewer drug–drug and drug–food interactions.[48] In the scenario of thromboprophylaxis, a pooled analysis of the 4 large trial studies (sample size 12383) showed that rivaroxaban significantly reduced the composite of symptomatic VTE and all-cause mortality when compared with enoxaparin (0.6% versus 1.3%; hazard ratio, 0.42; 95% confidence interval, 0.29–0.63), with similar safety profiles, although there was a trend toward a higher risk of major bleeding and significantly higher risk of clinically relevant bleeding.[48, 49] However, these findings are contradicted by the data from the XAMOS study (sample size 17701), where no significant increased risk of major bleeding was found.[50] A meta-analysis on trials with dabigatran did not highlight any benefit or superiority over enoxaparin: dabigatran was as effective as enoxaparin in reducing the risk of major VTE and VTE-related mortality, with a similar bleeding profile.[51]

However, the utility and risk profile of oral anticoagulants for chronic anticoagulated patients undergoing elective knee and hip arthroplasty is poorly described. It is also important to assess when re-initiating oral anticoagulants is safe and necessary, a timing that is usually depending on the approval from the surgeon to achieve adequate wound haemostasis and lessen bleeding risk. This is the point where the subjective decision-making may impact outcomes and where more research is warranted.

Optimal peri-operative management should reduce the incidence not only of surgical, but also of medical complications that may cause a significant morbidity on the long-term, such as the post-thrombotic syndrome (PTS). The PTS is a long-term complication of deep-vein thrombosis (DVT), manifesting as swelling, pain, oedema, venous ectasia, and skin induration of the affected limb. PTS has been estimated to affect 23-60% of individuals with DVT, frequently occurring within 2 years of the DVT episode.[52] Optimizing the anticoagulation should also reduce hospital inpatient stay and cost-effectiveness of the procedure., especially in an emerging trend of outpatient arthroplasty.[53, 54]

There are major limitations in the evidence available. There is a variety of management guidelines that are geographically-based. Reporting standards are inconsistent in outcome studies such as those included in this systematic review. There is a lack of high-quality prospective evidence to support the validity of a specific management strategy. The multitude of therapeutic anticoagulation agents, including newer oral anticoagulants,[55–57] is not addressed in the same amount and detail when compared to warfarin therapy. The need for individual assessment of both the VTE and bleeding risk according to the type of elective surgery complicates the development of a generalized tool.

**CONCLUSION**

Different anticoagulation-related perioperative management strategies achieve different outcomes following elective arthroplasty in patients with therapeutic chronic anticoagulation. There is contradictory evidence regarding the need of discontinuation of therapeutic warfarin. Retrospective data showed that individual risk stratification with multi-modal prophylaxis resulted in minimal complications.

**FIGURE LEGENDS**

**Figure 1**. Flowchart of the systematic search

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