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Original Research

The Effect of Chronic Anticoagulation on Early Postoperative Outcomes Following Total Knee Arthroplasty: A TriNetX Database Study

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ABSTRACT

Background: Medications used for pharmacologic venous thromboembolism prophylaxis are associated with postoperative complications including bleeding, wound complications, and infection. These same medications are used for chronic anticoagulation, and little research has been done on total knee arthroplasty (TKA) complications associated with these medications, particularly manipulation under anesthesia (MUA) and revision TKA. The purpose of this study is to evaluate the rate of MUA and other early postoperative complications in patients undergoing TKA with a preoperative history of chronic anticoagulation.

Methods: The TriNetX database was retrospectively queried for all patients undergoing TKA with perioperative tranexamic acid. Patients were divided into cohorts by whether or not they had a history of chronic anticoagulant use and had an anticoagulant medication prescribed within 6 months of surgery. The cohorts were propensity score matched on demographic and comorbidity data; 7367 patients remained in each cohort after matching.

Results: Patients with chronic anticoagulant use were 1.72 times more likely to undergo an MUA (odds ratio [OR]: 1.718, 95% confidence intervals [CI]: 1.403-2.104; $P < .001$), 1.32 times more likely to have a revision TKA (OR: 1.324, 95% CI: 1.006-1.742; $P = .044$), and were 1.53 times more likely to have wound disruption (OR: 1.530, 95% CI: 1.214-1.927; $P < .001$) within the 1-year postoperative period.

Conclusions: Patients undergoing TKA while on chronic anticoagulation have worse outcomes within 1 year postoperatively than patients not on chronic anticoagulation. Further studies are needed to validate these findings and to identify sources of the increased risk of complications in this population, as well as identify factors that may mitigate this risk.

Introduction

Total knee arthroplasty (TKA) is one of the most commonly performed orthopedic surgical procedures in the United States and are typically very successful with a manageable complication profile [1-3]. One significant risk following TKA is venous thromboembolism (VTE) which can cause significant morbidity and mortality in this population [4]. As such VTE prophylaxis is an important component of management of TKA patients, and the optimal protocol is a topic of much debate among surgeons due to the known side effects and risks associated commonly with pharmacologic VTE prophylaxis such as bleeding risk, wound complications, and prosthetic joint infection [4-7]. In recent years, low-dose aspirin has emerged as a safe and effective option for VTE prophylaxis for the majority of patients undergoing TKA [5,8]. Patients that are on chronic anticoagulation prior to TKA for other medical conditions such as atrial fibrillation, coagulation disorders, or prior VTE events typically need to continue their preoperative medication regimen and may be at higher risk of postoperative complications related to the anticoagulant medication [9,10].

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Joint stiffness and reduced range of motion (ROM) following TKA is a challenging complication to manage and can lead to persistent pain, reduced functional status, and decreased patient satisfaction [11,12]. The etiology of postoperative joint stiffness leading to arthrofibrosis is not clear; many patient and surgical factors have been identified as possible causes, but little consensus exists [12,13]. One possible factor that has had relatively little research to date is the association of pharmacologic VTE prophylaxis and postoperative stiffness [14,15]. Certain oral anticoagulants used for postoperative VTE prophylaxis, including warfarin, factor Xa inhibitors, and direct thrombin inhibitors, have been associated with increased postoperative stiffness, arthrofibrosis, and the need for manipulation under anesthesia (MUA) [14-16]. On the other hand, aspirin and low-molecular-weight heparin have been identified as possibly protective against postoperative arthrofibrosis [15,17]. Little research has been done examining the effect of chronic anticoagulation on the risk of postoperative stiffness. The purpose of this study is to evaluate the rate of MUA and other early postoperative complications (within 1 year) of patients undergoing TKA with a preoperative history of chronic anticoagulation.

Material and methods

Study population

This study was deemed institutional review board exempt as a review of de-identified aggregated data by the institutional clinical research committee. The TriNetX Research Network (TriNetX) database was queried as of January 31, 2025. Patient cohorts and outcome measures were defined using International Classification for Disease 10th edition (ICD-10) diagnosis codes and Current Procedural Terminology (CPT) codes. All patients who underwent a primary TKA (CPT: 27,447) with tranexamic acid (RXNORM:10,691) between January 1, 2019 and January 1, 2024 were included to allow for a minimum of 1-year data runout. Patients were then divided into two cohorts: (1) must have had a diagnosis of long-term use of anticoagulants (ICD-10: Z79.01) at the time of TKA and had an anticoagulant medication prescription (VA: BL110) within the 6 months prior to TKA; (2) cannot have had a diagnosis of long-term use of anticoagulants (ICD-10: Z79.01) at the time of TKA and cannot have had an anticoagulant medication prescription (VA: BL110) within 6 months prior to TKA. Cohort 1, chronic anticoagulant use, had 7529 patients, and Cohort 2, no chronic anticoagulant use, had 83,642 patients prior to propensity score matching, and after matching, both cohorts had 7367 patients.

Study outcomes

The primary outcomes examined were any of the following occurring from 1 day to 1 year postoperatively: MUA (CPT: 27,570), revision TKA (CPT: 27,486 and 27,487), and wound disruption (ICD-10: T81.3).

Statistical analysis

Cohorts were propensity score matched on age, sex, race, body mass index (BMI), and the following comorbidities: overweight/obesity (ICD-10: E66), diabetes mellitus (ICD-10: E08-E13), hypertension (ICD-10: I10), peripheral vascular disease (ICD-10: I73), heart failure (ICD-10: I50), ischemic heart disease (ICD-10: I25), chronic obstructive pulmonary disease (ICD-10: J44), anxiety disorder (ICD-10: F41), depressive episode (ICD-10: F32), rheumatic disease (ICD-10: M05-M14), osteoporosis (ICD-10: M81), and personal history of nicotine dependence (ICD-10: Z87.891). Differences in cohort demographics and comorbidities were assessed with two-sided independent sample *t*-tests and chi-squared tests. Differences in outcomes of the matched cohorts were assessed using odds ratios (ORs) and 95% confidence intervals (CIs). A subgroup analysis comparing outcomes between patients on warfarin and other anticoagulants was then performed. Statistical significance was assessed at $P < .05$. All statistical analyses were performed within the TriNetX platform.

TriNetX

TriNetX is a global research network that includes data from more than 170 healthcare organizations across 30 countries and over 400 million patients. Of the participating organizations, 76 share data for aggregated outcomes research and are included in this study. Variables captured include demographics, medications, lab values, diagnoses mapped to ICD-10 coding, and procedures mapped to CPT coding. Health Insurance Portability and Accountability Act–compliant electronic health record data are collected from participating health care organizations who submit structured and unstructured data elements. TriNetX is a federated network and received a waiver from Western Institutional Review Board as the only data received include aggregated counts and statistical summaries of de-identified information. No protected health information is exchanged in retrospective analyses.

Results

Prior to propensity score matching, patients with chronic anticoagulant use, on average, were older (69.9 ± 9.3 vs 67.0 ± 9.1 years; $P < .001$), had a higher BMI (32.9 ± 6.5 vs 31.7 ± 6.1 kg/m^2; $P < .001$), a lower proportion of females (50.0% vs 56.1%; $P < .001$), and a higher proportion of white patients (76.4% vs 71.1%; $P < .001$). In addition, a higher prevalence of the following comorbidities was observed among patients with chronic anticoagulant use: overweight/obesity (50.3% vs 36.3%; $P < .001$), diabetes mellitus (27.7% vs 19.3%; $P < .001$), hypertension (78.8% vs 60.6%; $P < .001$), peripheral vascular disease (6.5% vs 1.9%; $P < .001$), heart failure (18.9% vs 2.6%; $P < .001$), ischemic heart disease (28.2% vs 10.1%; $P < .001$), chronic obstructive pulmonary disease (12.7% vs 4.5%; $P < .001$), anxiety (21.8% vs 14.9%; $P < .001$), depression (20.8% vs 13.1%; $P < .001$), rheumatic disease (20.1% vs 12.9%; $P < .001$), osteoporosis (9.0% vs 5.6%; $P < .001$), and nicotine dependence (35.8% vs 17.4%; $P < .001$) (Table 1).

Of the 7598 patients with chronic anticoagulant use, 20.9% were prescribed warfarin, 39.8% were prescribed apixaban, 24.3% were prescribed rivaroxaban, 22.7% were prescribed enoxaparin, 15.2% were prescribed heparin, and 1.8% were prescribed other anticoagulants (Table 2). Following propensity score matching, patients with chronic anticoagulant use had higher BMIs on average (32.8 ± 6.6 vs 32.2 ± 6.1 kg/m^2; $P < .001$), but no other statistically significant differences in other demographics or comorbidities remained between groups (Table 3). The average follow-up time for patients with chronic anticoagulant use was 341.8 ± 74.3 days, and the average follow-up time for patients with no chronic anticoagulant use was 330.6 ± 92.3 days after propensity score matching ($P < .001$).

Postoperatively, based on the matched cohorts, patients with chronic anticoagulant use were 1.72 times more likely to undergo an MUA (Anticoag: 3.5% vs No Anticoag: 2.1%; OR: 1.718, 95% CI: 1.403-2.104; $P < .001$), 1.32 times more likely to have a revision TKA (Anticoag: 1.6% vs No Anticoag: 1.2%; OR: 1.324, 95% CI: 1.006-1.742; $P = .044$), and were 1.53 times more likely to have wound disruption (Anticoag: 2.5% vs No Anticoag: 1.7%; OR: 1.530, 95% CI: 1.214-1.927; $P < .001$) within the 1-year postoperative period (Table 4). No statistically significant differences in postoperative

Table 1
Patient characteristic prior to propensity score matching.

Characteristic	TKA w/ Anticoagulants (n = 7529)	TKA w/ No anticoagulants (n = 83,462)	*P*-value
Age, years	69.9 ± 9.3	67.0 ± 9.1	**<.001**
Female	3763 (50.0)	46,831 (56.1)	**<.001**
White race	5753 (76.4)	59,348 (71.1)	**<.001**
Body mass index, kg/m^2	32.9 ± 6.5	31.7 ± 6.1	**<.001**
Overweight/Obese	3786 (50.3)	30,260 (36.3)	**<.001**
Diabetes mellitus	2085 (27.7)	16,105 (19.3)	**<.001**
Hypertension	5933 (78.8)	50,586 (60.6)	**<.001**
Peripheral vascular disease	486 (6.5)	1576 (1.9)	**<.001**
Heart failure	1423 (18.9)	2129 (2.6)	**<.001**
Ischemic heart disease	2126 (28.2)	8415 (10.1)	**<.001**
COPD	955 (12.7)	3793 (4.5)	**<.001**
Anxiety	1645 (21.8)	12,467 (14.9)	**<.001**
Depression	1564 (20.8)	10,968 (13.1)	**<.001**
Rheumatic disease	1514 (20.1)	10,779 (12.9)	**<.001**
Osteoporosis	676 (9.0)	4709 (5.6)	**<.001**
Nicotine dependence	2698 (35.8)	14,526 (17.4)	**<.001**

COPD, chronic obstructive pulmonary disease; TKA, total knee arthroplasty.
P-value <.05 are provided in bold format; data are presented as n (%) or mean ± SD.

Table 3
Patient characteristics after propensity score matching.

Characteristic	TKA w/ anticoagulants (n = 7367)	TKA w/ no anticoagulants (n = 7367)	*P*-value
Age, years	69.8 ± 9.3	70.0 ± 8.7	.122
Female	3697 (50.2)	3709 (50.3)	.843
White race	5615 (76.2)	5680 (77.1)	.206
Body mass index, kg/m^2	32.8 ± 6.6	32.2 ± 6.1	**<.001**
Overweight/Obese	3656 (49.6)	3705 (50.3)	.419
Diabetes mellitus	2002 (27.2)	1966 (26.7)	.504
Hypertension	5778 (78.4)	5832 (79.2)	.276
Peripheral vascular disease	433 (5.9)	453 (6.1)	.488
Heart failure	1261 (17.1)	1203 (16.3)	.200
Ischemic heart disease	1988 (27.0)	1992 (27.0)	.941
COPD	878 (11.9)	812 (11.0)	.088
Anxiety	1588 (21.6)	1498 (20.3)	.068
Depression	1495 (20.3)	1466 (19.9)	.551
Rheumatic disease	1452 (19.7)	1434 (19.5)	.709
Osteoporosis	649 (8.8)	602 (8.2)	.165
Nicotine dependence	2564 (34.8)	2575 (35.0)	.849
Follow-up time, days	341.8 ± 74.3	330.6 ± 92.3	**<.001**

COPD, chronic obstructive pulmonary disease; TKA, total knee arthroplasty.
P-value <.05 are in bold format; data are presented as n (%) or mean ± SD.

outcomes were observed when comparing patients on warfarin with those on other anticoagulants (Table 5).

Discussion

Patients undergoing TKA with a history of chronic anticoagulation usage were at increased risk of complications when compared with a matched population of patients who did not have a history of chronic anticoagulation. These patients had a 1.7 times increased risk of MUA, 1.3 times the risk of revision TKA, and 1.5 times increased risk of wound disruption in the first year after primary TKA when compared to the patients without a history of chronic anticoagulation.

The majority of patients undergoing TKA receive some sort of pharmacologic anticoagulation postoperatively for VTE prophylaxis, although the medication choice and dosage is often different than what is prescribed for patients who require long-term anticoagulation [10]. Therapeutic anticoagulation can increase the risk of postoperative bleeding and the associated complications related to bleeding following TKA [18,19]. In a study by Piple et al [6], patients prescribed rivaroxaban for prophylaxis after TKA experienced an increased risk of bleeding events, including hemarthrosis, compared to patients prescribed aspirin, and when compared to patients prescribed enoxaparin, the risk of total bleeding events was greater, although the risk of hemarthrosis was not significant between groups. In a meta-analysis by He et al [4] examining the risk of multiple medications used for VTE prophylaxis after TJA apixaban, aspirin and warfarin had a bleeding risk over 60%, low-molecular-weight heparin had a bleeding risk of over 50%, and rivaroxaban had a bleeding risk under 25%. Hemarthrosis is a known cause of ongoing pain after TKA and may lead to other complications [11]. The bleeding risk associated with anticoagulant usage after TKA has been somewhat mitigated in recent years with the increasing usage of tranexamic acid in the perioperative period [20]. Tranexamic acid has been shown to be safe for use even in patients that are at high risk of VTE and can be used in conjunction with anticoagulant medications [21]. In this study, all patients received perioperative tranexamic acid; despite this, patients on chronic anticoagulation prior to surgery had an increased risk of postoperative complications. While we did not directly assess bleeding complications, excess bleeding could have contributed to each outcome.

There have been limited studies examining the link between postoperative anticoagulation type and the need for MUA. Walton et al [16] found that patients on therapeutic levels of warfarin required MUA at greater rates than those who were managed with low-molecular-weight heparin; Desai et al [22] found that patients who were on chronic warfarin therapy had increased stiffness and reduced ROM even after MUA. One possible cause for the increased rates of MUA for these patients is hematoma and hemarthrosis limiting ROM in the early postoperative period due to the anticoagulation, although a study by Kahlenberg et al found that the rate of postoperative hematoma was lower with oral anticoagulants than with low-molecular-weight heparin, but patients taking oral anticoagulants (other than aspirin) had a higher rate of MUA [15]. Another possible reason for increased postoperative stiffness in patients using anticoagulant medications is a more limited use of nonsteroidal anti-inflammatory drugs (NSAIDs) in this population. The development of arthrofibrosis has been linked to cyclooxygenase-2, so limiting NSAIDs may increase the need for postoperative MUA [15,23]. Lower rates of NSAID use may lead to increased or poorly managed postoperative pain and limitations in physical therapy participation, both of which can contribute to increased postoperative stiffness [12,14,15]. In addition, conditions of increased fibroblast proliferation, such as Dupuytren's, Ledderhose, and Peyronie's diseases, have been shown to increase the risk of arthrofibrosis and MUA after TKA [24]. Based on these risk factors

Table 2
Preoperative anticoagulant distribution.

Medication	TKA w/ anticoagulants (n = 7598)
Warfarin	1589 (20.9%)
Direct oral anticoagulants	
Apixaban	3022 (39.8%)
Rivaroxaban	1848 (24.3%)
Enoxaparin	1723 (22.7%)
Heparin	1158 (15.2%)
Other	137 (1.8%)

Percentages sum to >100% due to patients on multiple medications or switching medications.

Table 4
One-year outcomes.

Outcome	TKA w/ anticoagulants (n = 7367)	TKA w/ No anticoagulants (n = 7367)	Odds ratio (chronic anticoagulant vs no chronic anticoagulant)	95% CI	*P*-value
MUA	259 (3.5)	153 (2.1)	1.718	1.403-2.104	**<.001**
Revision TKA	120 (1.6)	91 (1.2)	1.324	1.006-1.742	**.044**
Wound disruption	185 (2.5)	122 (1.7)	1.530	1.214-1.927	**<.001**

CI, confidence interval; MUA, manipulation under anesthesia; TKA, total knee arthroplasty.
P-value <.05 are in bold format; data are presented as n (%).

and the findings of the current study, patients with both genetic predispositions for arthrofibrosis and those on chronic anticoagulation may benefit from increased early postoperative monitoring and aggressive physical therapy in an attempt to prevent postoperative stiffness leading to MUA.

Persistent wound drainage is a known concern with certain anticoagulant medications used for VTE prophylaxis in patients following TKA, particularly warfarin and enoxaparin, and is associated with an increased risk of complication including periprosthetic joint infection [7,25-27]. The cause of the persistent wound drainage related to anticoagulant usage is not clear, and few studies have looked at this complication in detail. Initial treatment recommendations for patients experiencing persistent wound drainage after TKA include immobilization and temporary discontinuation of physical therapy which could lead to longer term reduced mobility and less-optimal recovery [28]. If the wound drainage does not resolve in a timely fashion, surgical intervention and TKA revision may be required, further compounding morbidity in this population [7,28]. While not specifically defined as persistent wound drainage, patients in this study who were receiving chronic anticoagulation prior to TKA had nearly twice the rate of wound disruption as patients who were not on chronic anticoagulation.

This study does have a number of limitations. The use of a conglomerate research database that relies solely on coded data limits our ability to obtain additional information that may provide clarity to this subject such as the type, dosage, and postoperative duration of the anticoagulant medication used and concomitant use of NSAIDs, both of which may have significant impacts on the results of this study. While we were able to identify the percentage of patients receiving each type of anticoagulant medication preoperatively, we were unable to determine which patients had multiple medications and for what reason and whether patients received bridging therapy prior to surgery. We were also unable to assess additional postoperative details such as physical therapy intensity and duration, postoperative ROM, and pain, all of which would add additional nuance to this topic. In addition, as with all administrative database studies, our results are dependent on the accuracy of electronic medical record documentation and coding, which have been shown to be variable across databases [29-31]. ICD-10 codes for complications may not have been reported completely accurately, which may bias the results. Due to the de-identified nature of the database and inclusion of multiple sites, we were unable to audit the accuracy of documentation and coding and to assess the extent to which discrepancies may have impacted our results. The TriNetX database is an opt-in database and may bias the sample to larger, research-oriented facilities. There are also the inherent biases of a retrospective observational study that may limit the generalizability to a wider population. A strength of this study is the ability to analyze a large, matched cohort that takes into account important demographic factors and comorbidities, and as such, we feel that this study is a valuable contribution to the literature in an understudied topic.

Conclusions

Patients undergoing TKA while on chronic anticoagulation have worse outcomes within 1 year postoperatively than patients not on chronic anticoagulation after controlling for a number of comorbidities and perioperative tranexamic acid use. These include a 72% increased risk of MUA, a 32% increased risk of early revision surgery, and 53% increased risk of postoperative wound disruption, although the overall rate of complications was low. Further studies are needed to validate these findings and to identify sources of the increased risk of complications in this population, as well as identify factors that may mitigate this risk.

Conflicts of interest

Paul King received research support from Depuy and Firstkind LTD; is in the editorial or governing board of the *Journal of Arthroplasty*; and is a paid consultant for Smith & Nephew. All other authors declare no potential conflicts of interest.

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CRediT authorship contribution statement

Andrea H. Johnson: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Jane C. Brennan:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Shawn S. Simpson:** Writing – review & editing, Methodology, Conceptualization. **Justin J. Turcotte:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **Paul J. King:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Table 5
Subgroup analysis of warfarin vs other anticoagulants.

Outcome	Warfarin (n = 1589)	Other anticoagulants (n = 6009)	Odds ratio (warfarin vs other anticoagulants)	95% CI	*P*-value
MUA	56 (3.5)	212 (3.5)	0.999	0.740-1.348	.994
Revision TKA	28 (1.8)	95 (1.6)	1.117	0.730-1.708	.611
Wound disruption	33 (2.1)	158 (2.6)	0.785	0.537-1.148	.211

CI, confidence interval; MUA, manipulation under anesthesia; TKA, total knee arthroplasty.
P-value <.05 are in bold format; data are presented as n (%).

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