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Research Article

Increased Risk of Stiffness following Total Knee Arthroplasty with Direct Oral Anticoagulants and Avoidance of Selective COX-2 Inhibitors

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Conflicts of Interest Statement for Dr. Frederick

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Conflicts of Interest Statement for Mr. Weiner

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Dr. Neuwirth received his medical degree from Rutgers University-Robert Wood Johnson Medical School, where he also completed his undergraduate degree. Following medical school, Dr. Neuwirth trained as a resident in orthopedic surgery at the University of Pennsylvania, where he also spent a year as a postdoctoral research fellowship in the McKay Orthopaedic Research Laboratory. Before joining the faculty at Columbia as an attending physician, Dr. Neuwirth completed a fellowship in adult hip and knee reconstruction at Columbia University Irving Medical Center.

In addition to his clinical practice, Dr. Neuwirth is actively engaged in ongoing clinical outcomes research in the field of joint replacement and reconstruction. His primary research efforts are focused on the eradication of infection following hip and knee replacements.

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d Roshan P. Shah, MD, JD, specializes in hip and knee reconstruction using minimally invasive techniques for less pain and faster recovery times. He believes there are many valuable pain-relieving treatments that do not involve surgery. When an operation is needed, he embraces careful surgical techniques with attention to the biological, anatomical, and mechanical restoration that is critical for a pain-free return of function.

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e Dr. Jeffrey Geller Orthopedic Surgeon, is a specialist in hip and knee arthritic disorders. He has extensive training and experience in procedures such as partial knee replacements, anterior hip replacements, minimally invasive hip replacements and minimally invasive robotic knee replacements. Dr. Geller uses the most advanced minimally invasive surgical techniques. He also evaluates every case to see if a non-operative treatment option is possible.

In any surgery he performs, Dr. Geller's is focused on getting patients back to their normal lives. This includes a quick more comfortable rehabilitation process including preventing post-op surgical pain before it can start. He also specializes in lower extremity trauma, including hip fractures, fractures near joint replacements and osteoporosis-related fractures.

He is the chief of Orthopedic Surgery at New York Presbyterian Westchester hospital and the Vice Chair of the Department of Orthopedic Surgery at Columbia University Irving Medical Center. He is the Division Chief of Hip & Knee Arthroplasty and has been nominated to New York's Best Doctors and Castle Connolly's Top Doctors for 10 years straight.

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Background

Database studies demonstrate a strong association between use of direct oral anticoagulant (DOAC) medications and stiffness following total knee arthroplasty (TKA). The goal of this study was to evaluate whether the risk of stiffness in patients receiving a DOAC was affected by concomitant use or avoidance of a selective COX-2 inhibitor, when compared to a control group of patients receiving aspirin.

Methods

Consecutive primary TKA's performed at a single institution between January 2014 - September 2019 were retrospectively reviewed. During this period, a risk-stratification algorithm for prophylaxis against venous thromboembolism (VTE) was used, with DOACs selected for patients at elevated VTE risk and aspirin for the remainder. Patients who required manipulation under anesthesia (MUA) within six months of index TKA were identified. Arc of motion (AOM) data at 6-weeks, 3-months, and 1-year was collected. Patients were divided into 3 groups based on postoperative medications prescribed: (a) Aspirin, (b) DOAC alone, and (c) DOAC + NSAID. Categorical variables were analyzed using Fisher's Exact Tests and Pearson's Chi-Square, while continuous variables were analyzed using Student's T-test. Multivariate logistic regression was used to assess MUA risk while controlling for demographic differences.

Results

Forty patients underwent MUA from a population of 1,358 TKAs (2.9%). There was a significantly increased risk of MUA in patients where DOACs were used and concomitant NSAIDs were avoided when compared to the control group of patients receiving aspirin (5.4% vs 2.7%, OR 3.17; p = 0.029). This increased risk was not present when DOACs were used concomitantly with NSAIDs (3.1% vs 2.7%, OR 1.30; p = 0.573). In addition, less consistent AOM was achieved at 1-year postoperatively in the DOAC alone group compared to the control group of patients receiving aspirin (p=0.034).

Conclusions

Compared to aspirin anticoagulation, patients receiving DOACs without concomitant NSAIDs were more likely to develop postoperative stiffness requiring MUA and achieved less predictable AOM. The addition of selective COX-2 inhibitors may mitigate some risk of stiffness following primary TKA when anticoagulation with DOACs is necessary.

INTRODUCTION

Postoperative stiffness can limit range of motion, cause persistent pain, reduce functional status, and decrease overall patient satisfaction following total knee arthroplasty (TKA) (Bong and Di Cesare 2004; Manrique, Gomez, and Parvizi 2015; Scuderi 2005; Kurosaka et al. 2002; Laubenthal, Smidt, and Kettelkamp 1972). The etiology of stiffness following TKA is multifactorial and incompletely understood, as it has been associated with various demographic, intraoperative, and postoperative factors (Kornuijt

active educator and researcher, he has published over 125 peer-reviewed articles and book chapters. Originally from South Carolina, Dr. Cooper graduated from Duke University with a degree in mechanical engineering and materials science, then completed medical education at Columbia University, residency at Lenox Hill, and fellowship at Rush University Medical Center.

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et al. 2018). Early postoperative stiffness is often attributed to arthrofibrosis, a condition of excessive intraarticular scar tissue formation characterized by proliferation of proinflammatory signal molecules and extracellular matrix components in the joint space (Cheuy et al. 2017). Arthrofibrosis-related stiffness is conservatively estimated to affect approximately 12% of TKAs performed, or over 85,000 patients annually in the United States (Cheuy et al. 2017; Stephenson, Quimbo, and Gu 2010; Thompson et al. 2019).

Manipulation under anesthesia (MUA) is an effective treatment for persistent early stiffness following TKA, one which is typically performed in the first six to twelve weeks following the index surgery (Kornuijt et al. 2018; Cheuy et al. 2017; Gu et al. 2018; Pivec et al. 2013). A 2018 systematic review found that the mean prevalence of MUA following TKA was 5.8% (Gu et al. 2018). MUA rates are often used as a proxy for the number of patients experiencing rates of clinically significant stiffness following TKA.

Chemoprophylaxis is required following TKA to prevent venous thromboembolism (VTE). The American Academy of Orthopedic Surgeons (AAOS) recommends stratification of patients based on VTE risk but acknowledges an inability with current evidence to recommend one anticoagulation regimen as optimal (Nam et al. 2016; Lieberman and Hsu 2005; Mont and Jacobs 2011; Johanson et al. 2009). Our institution uses a risk-stratification protocol in which low-risk patients receive aspirin while high-risk patients receive a direct oral anticoagulant (DOAC) (Parvizi et al. 2016a), typically rivaroxaban. Relevant to this choice of anticoagulant, a large population-level database study recently demonstrated a significant association between use of non-aspirin anticoagulants such as DOACS and increased rates of MUA (Kahlenberg et al. 2018), however the reasons for this association were unclear.

Non-steroidal anti-inflammatory drugs (NSAIDs) with selective COX-2 inhibition are often concurrently prescribed following TKA to reduce inflammation. Routine use of these selective COX-2 inhibitors has been associated with less postoperative pain and increased range of motion in both the immediate post-operative period and at one year postoperatively (Buvanendran et al. 2003; Lin, Zhang, and Yang 2013; Huang et al. 2008; Schroer et al. 2011). While routinely given to patients after TKA, these COX-2 inhibitors are commonly withheld from patients anticoagulated with DOACs due to a perceived increase in bleeding risk (Kreutz et al. 2016; Sherwood et al. 2015; Desai et al. 2013) despite the selective action of the cyclooxygenase-2 inhibition only in the production of prostaglandins. Thus, in the patient population who receives a DOAC for VTE prophylaxis, it is unclear if the increased risk of stiffness in these patients is potentially related to something intrinsic to administration of the DOAC, or if it is simply a reflection of NSAID avoidance during the period of DOAC administration.

The goal of this study was to evaluate whether the risk of stiffness in TKA patients receiving DOAC anticoagulation was affected by concomitant use or avoidance of a selective COX-2 inhibitor, when compared to a control group of patients receiving aspirin.

METHODOLOGY

An institutional registry was used to retrospectively identify all patients who underwent primary TKA between January 2014 and September 2019 performed by one of three fellowship-trained arthroplasty surgeons at a single academic medical center. Approval from an Institutional Review Board was obtained prior to any data collection or data analysis being performed.

Demographic data including sex, body mass index (BMI), age, and American Society of Anesthesiologists (ASA) class scores were collected from patient charts. Medical records were reviewed to determine which postoperative anticoagulant was used, whether a postoperative NSAID was prescribed, and whether the patient required MUA anytime in the first year after surgery. When NSAIDs were prescribed, the patient either received 15 mg of meloxicam or 200 mg of celecoxib to be taken daily. A recent study showed that while meloxicam is less selective than celecoxib as it also partially inhibits COX-1, it is very similar to celecoxib and does not increase rates of gastrointestinal or wound complications (Haffar et al. 2022). In addition, preoperative and postoperative arc of motion (AOM) were documented, with notation of those failing to achieve 118° AOM postoperatively (Ritter et al. 2008).

Over the study period, a minority of patients on preoperative anticoagulation regimens were continued on these same regimens postoperatively. For the majority not on anticoagulation preoperatively, a risk-stratification algorithm was used to determine choice of postoperative anticoagulation. Patients were stratified to receive either aspirin or DOAC anticoagulation based on VTE risk according to published protocols that incorporate demographics and comorbid conditions (Parvizi et al. 2014, 2016b).

Inclusion criteria for this study were based on postoperative medications prescribed. Patients were included if they fit into one of three groups: (a) *Aspirin + NSAID:* aspirin anticoagulation with the addition of a COX-2 inhibitor NSAID, (b) *DOAC Alone:* DOAC anticoagulation without the addition of a COX-2 inhibitor, or (c) *DOAC + NSAID*: DOAC an-

ticoagulation with the addition of a COX-2 inhibitor. Any warnings about concomitant administration of DOACs and NSAIDs were bypassed in the electronic medical record system. Patients on pre-existing anticoagulant medications (such as warfarin or clopidogrel) were continued on that regimen perioperatively and excluded from analysis in this study, as each of these groups were too small for analysis. Patients with unknown anticoagulation regimens as well as those patients with documented compliance difficulties were also excluded. The *DOAC + NSAID* and *DOAC Alone* cohorts were combined for some comparisons to the *Aspirin + NSAID* cohort as noted.

The indication for MUA was made on an individual basis by the attending surgeon and patient between postoperative week 6 and week 12 based on the difference between preoperative AOM and current AOM, patient preference, and physician recommendation. The vast majority of patients undergoing MUA had an AOM less than 90 degrees, but occasional patients were indicated for MUA if they had an AOM of greater than 90 degrees but one that fell well short of expectations.

STATISTICAL ANALYSIS

Categorical variables were analyzed using Fisher's Exact Tests and Pearson's Chi-Square tests where appropriate, while continuous variables were analyzed using Student's T-test. Multinomial logistic regression was then used to obtain odds ratios for MUA risk while controlling for age, BMI, sex, and ASA class. Basic analyses were performed using Excel data analysis tool version 16.0 (Microsoft, Inc.). Multivariate logistic regression, controlling for demographic differences, was performed using SPSS Statistics version 26.0 (IBM, Inc.)

RESULTS

STUDY GROUPS AND PATIENT CHARACTERISTICS

Over the 69-month study period, 1590 primary TKAs were performed. All 1590 TKAs were completed with a tourniquet. Of these, 1358 (85.4%) met inclusion criteria. 232 (14.6%) patients were excluded secondary to having a pre-existing or unknown anticoagulation regimen. Of those meeting inclusion criteria, 1071 (78.9%) patients were risk-stratified to receive aspirin (*Aspirin + NSAID*) while 287 (21.1%) were risk-stratified to receive a DOAC. A variety of DOACs were prescribed during the study period. Rivaroxaban 10mg daily was the standard regimen prescribed unless the patient was already taking a DOAC or the patient's medical doctor requested a different DOAC medication or dose regimen. Overall, of patients receiving DOACs, 237 (82.6%) received rivaroxaban, 44 (15.3%) apixaban, and 6 (2.1%) dabigatran. Dosing for rivaroxaban consisted of 210 patients at 10mg daily, 9 patients at 15mg daily, and 18 patients at 20mg daily. Dosing for apixaban consisted of 23 patients at 2.5mg daily, 19 patients at 5mg daily, and 2 patients at 10mg daily. Dosing for dabigatran consisted of 5 patients at 150mg daily and 1 patient at 75mg daily. Demographic comparisons between patients receiving aspirin vs. DOAC prophylaxis found that patients receiving DOACs were significantly older with higher ASA scores and were more likely to be female than patients in the *Aspirin + NSAID* cohort (Table 1).

Of the patients receiving a DOAC, 195 (67.9%) received a concomitant NSAID (the *DOAC + NSAID* cohort) while NSAIDs were avoided entirely in 92 (32.1%) patients (the *DOAC Alone* cohort). Demographic comparison of the two patient cohorts who received a DOAC (Table 2) indicates that patients in the *DOAC Alone* cohort were significantly older with higher ASA scores than patients in the *DOAC + NSAID* cohort. Additionally, the proportion of female patients in the *DOAC + NSAID* cohort was significantly greater.

ASPIRIN VS. DOAC ALONE AND ASPIRIN VS. DOAC + NSAID

The multivariate logistic regression demonstrated no significant difference in MUA rates between the overall group of patients receiving DOACs vs those receiving aspirin (OR 1.768, 95% CI: 0.839 – 3.725, p = 0.134) (Table 3). However, comparing the individual *DOAC* cohorts to the *Aspirin + NSAID* cohort using multivariate regression analysis demonstrated a significantly increased risk of MUA in the *DOAC Alone* cohort (OR 3.174, 95% CI: 1.123 – 9.974, p =

Table 1. Aspirin + NSAID and DOAC cohorts demographics comparison

	Aspirin + NSAID	DOAC Cohorts		*p* - value
n =	1071	287		
Age (years)	68.2 ± 9.1	Combined	70.6 ± 9.3	**<0.001***
		DOAC + NSAID	69.8 ± 8.9	**0.022***
		DOAC Alone	72.4 ± 9.9	**<0.001***
BMI	30.4 ± 5.5	Combined	31.0 ± 6.3	0.131
		DOAC + NSAID	30.9 ± 6.5	0.221
		DOAC Alone	31.0 ± 6.1	0.292
Female, n (%)	735 (68.6)	Combined	226 (78.7)	**<0.001***
		DOAC + NSAID	162 (83.1)	**<0.001***
		DOAC Alone	64 (69.6)	0.907
ASA Score		Combined		**<0.001***
		DOAC + NSAID		**0.001***
		DOAC Alone		**<0.001***
I	25 (2.3)	Please refer to Table 2 for DOAC cohorts ASA score summaries		
II	787 (73.5)			
III	259 (24.2)			
IV	0 (0.0)			

NSAID, non-steroidal anti-inflammatory drug; DOAC, direct oral anticoagulant; ASA, American Society of Anesthesiologists; BMI, body mass index.
* Denotes significance at $p < 0.05$

0.029). This increased risk was not present in the *DOAC + NSAID* cohort when compared to the *Aspirin + NSAID* cohort (OR 1.303, 95% CI: 0.518 – 3.277, p = 0.573).

Additionally, significantly more patients in the *Aspirin + NSAID* cohort achieved 118° AOM at 3-month follow-up than in the *DOAC + NSAID* (54.9% vs 42.7%, p = 0.006) or *DOAC Alone* (54.9% vs 38.5%, p = 0.006). Furthermore, at 1-year follow-up, significantly more patients in the *Aspirin + NSAID* cohort achieved 118° AOM than in the *DOAC Alone* cohort (67.5% vs 51.1%, p = 0.034), however, no significant difference was observed between the *Aspirin + NSAID* cohort and the *DOAC + NSAID* cohort (67.5% vs 61.5%, p = 0.252) (Table 4).

DOAC ALONE VS. DOAC + NSAID

Among the 287 primary TKA patients who received DOAC anticoagulation, 11 (3.83%) required MUA, with no significant difference found between the *DOAC + NSAID* cohort (6 patients, 3.08%) and the *DOAC Alone* cohort (5 patients, 5.43%; p = 0.338) (Table 5). Although statistical trends were noted in favor of the *DOAC + NSAID* group, controlling for demographic factors with multivariate logistic regression again demonstrated no significant difference in MUA rates (OR 0.411, 95% CI: 0.117– 1.437, p = 0.164) (Table 3). No significant difference was found in the change from pre-op AOM at 6 weeks follow-up (-7.7° vs. -10.1°, p = 0.342). The proportion of patients achieving 118° AOM 3 months postoperatively (42.7% vs. 38.5%, p = 0.573) and 1 year postoperatively (61.5% vs. 51.1%, p = 0.285) were also not significantly different (Table 5).

Notably, there were no observed or reported bleeding complications in any of the 195 patients in the *DOAC + NSAID* cohort.

Table 2. DOAC cohort patient demographics

	All DOAC Patients	DOAC + NSAID	DOAC Alone	*p* - value
n =	287	195	92	
Age (years)	70.6 ± 9.3	69.8 ± 8.9	72.4 ± 9.9	**0.026***
BMI	31.0 ± 6.3	30.9 ± 6.5	31.0 ± 6.1	0.904
Female, n (%)	226 (78.7)	162 (83.1)	64 (69.6)	**0.013***
ASA Score				**< 0.001***
I	9 (3.1)	8 (4.1)	1 (1.1)	
II	152 (53.0)	117 (60.0)	35 (38.0)	
III	125 (43.6)	69 (35.4)	56 (60.9)	
IV	1 (0.3)	1 (0.5)	0 (0.0)	

NSAID, non-steroidal anti-inflammatory d NSAID, non-steroidal anti-inflammatory drug; DOAC, direct oral anticoagulant; ASA, American Society of Anesthesiologists; BMI, body mass index.
* Denotes significance at p < 0.05.

Table 3. Multivariate logistic regression for MUA rate

Comparison	Odds Ratio (95% CI)	*p* - value
DOAC + NSAID compared to DOAC Alone	0.411 (0.117 – 1.437)	0.164
Combined DOAC cohorts compared to Aspirin + NSAID	1.768 (0.839 – 3.725)	0.134
DOAC + NSAID compared to Aspirin + NSAID	1.303 (0.518 – 3.277)	0.573
DOAC Alone compared to Aspirin + NSAID	3.174 (1.123 – 9.974)	**0.029***

MUA, Manipulation under anesthesia; NSAID, Nonsteroidal anti-inflammatory drug; DOAC, direct oral anticoagulant
* Denotes significance defined as p < 0.05
Odds Ratios are adjusted to control for Age, BMI, Sex, and ASA Class

DISCUSSION

This single-institution study of 1358 primary elective TKAs presents an interesting contrast to a previous large, population-level database study, which found higher MUA rates in patients anticoagulated with DOACs compared to those receiving aspirin (Kahlenberg et al. 2018). When controlling for baseline differences between the DOAC and aspirin groups, we found no significantly increased risk of MUA in those anticoagulated with DOACs. However, when we stratified the DOAC cohort into those that received a concomitant selective COX-2 inhibitor NSAID versus those in which it was avoided, we found that NSAID avoidance in this group was indeed associated with an increased risk of MUA and poorer AOM outcomes at 3-months and 1-year. Ritter *et al.* reported a substantial decrease in functionality and overall outcome after TKA when patients did not achieve 118° of AOM which is why this cutoff of 118° was used to define poor AOM outcomes (Ritter et al. 2008). Furthermore, concomitant administration of the COX-2 NSAID appeared to mitigate the MUA risk of the DOAC, and since this combination represented the majority of the patients who received DOAC anticoagulation at our institution, this may explain the lack of an observed difference in postoperative stiffness between aspirin and DOACs.

Our population included 287 patients who were prescribed DOACs because of a perceived elevated risk of postoperative VTE. A direct comparison of the two subgroups receiving DOACs (*DOAC Alone vs DOAC + NSAID*) found no significant differences in MUA rates or postoperative AOM, but was likely underpowered to adequately evaluate for any differences. Notable is the trend toward a potential benefit of concomitant NSAID use with DOAC anticoagulation (p = 0.164). Including comparison to the 1071 standard-risk patients in the *Aspirin + NSAID* cohort allows us to further characterize the impact the addition of an NSAID had on the patients receiving DOACs. After controlling for BMI, sex, age, and ASA class, the odds ratio found no significant difference for having an MUA when the *DOAC + NSAID* cohort was compared to the *Aspirin + NSAID* cohort (OR = 1.303, p = 0.573). In contrast, the odds ratio for patients taking the DOAC without an NSAID demonstrated significantly greater odds of having an MUA than the aspirin group (OR = 3.174, p = 0.029).

Kahlenberg *et al*. proposed in their database study that their finding of lower rates of MUA when aspirin is used postoperatively might be explained by aspirin's inhibitory effect on the cyclooxygenase enzymes (Kahlenberg et al. 2018). Cyclooxygenase-2 (COX-2) has been implicated as a key mediator for the molecular pathway by which fibrotic periarticular tissue forms and persists in arthrofibrosis (Parvizi et al. 2006). Arthrofibrosis is noted as the most significant cause of intrinsic postoperative knee stiffness once technical factors in component sizing, positioning, and design are excluded (Jaiswal et al. 2012). Blockade of the COX-2 enzyme may potentially explain why the addition

Table 4. Aspirin + NSAID arc of motion and MUA rate comparison

	Aspirin + NSAID	DOAC Cohorts		*p* - value
Pre-op AOM (degrees)	109.0 ± 17.5	Combined	106.8 ± 16.8	0.076
		DOAC + NSAID	107.7 ± 15.8	0.361
		DOAC Alone	105.0 ± 18.7	**0.048***
Change in AOM at 6 weeks post-op (degrees)	-7.0 ± 19.1	Combined	-8.5 ± 18.7	0.267
		DOAC + NSAID	-7.7 ± 17.6	0.655
		DOAC Alone	-10.1 ± 20.7	0.160
Proportion of patients achieving 118° AOM 3 months post-op	54.9%	Combined	41.2%	**<0.001***
		DOAC + NSAID	42.7%	**0.006***
		DOAC Alone	38.5%	**0.006***
Proportion of patients achieving 118° AOM 1 year post-op	67.5%	Combined	58.3%	**0.048***
		DOAC + NSAID	61.5%	0.252
		DOAC Alone	51.1%	**0.034***
MUAs Performed	29	Combined	11	0.326
		DOAC + NSAID	6	0.811
		DOAC Alone	5	0.183
% Patients Requiring MUA	2.71%	Combined	3.83%	
		DOAC + NSAID	3.08%	
		DOAC Alone	5.43%	

MUA, manipulation under anesthesia; NSAID, Nonsteroidal anti-inflammatory drug; DOAC, direct oral anticoagulant; AOM, arc of motion
* Denotes significance at $p < 0.05$.

Table 5. Arc of motion and observed MUAs in DOAC patients

	All DOAC Patients	DOAC + NSAID	DOAC Alone	*p* - value
Pre-op AOM (degrees)	106.8 ± 16.8	107.7 ± 15.8	105.0 ± 18.7	0.231
Change in AOM at 6 weeks post-op (degrees)	-8.5 ± 18.7	-7.7 ± 17.6	-10.1 ± 20.7	0.342
Proportion of patients achieving 118° AOM 3 months post-op	41.2%	42.7%	38.5%	0.573
Proportion of patients achieving 118° AOM 1 year post-op	58.3%	61.5%	51.1%	0.285
MUAs Performed	11	6	5	0.338
% Patients Requiring MUA	3.83%	3.08%	5.43%	

MUA, manipulation under anesthesia; NSAID, Nonsteroidal anti-inflammatory drug; DOAC, direct oral anticoagulant; AOM, arc of motion

of a selective COX-2 inhibitor NSAID in patients receiving DOACs may provide some clinical benefit in decreasing risk of stiffness, as occurs in those receiving aspirin anticoagulation along with selective COX-2 inhibitor NSAIDs. However, it is unclear whether patients with decreased stiffness are seeing these benefits due to better pain management and increased physical therapy sessions or due to reduced scar tissue formation.

Hemarthrosis has also been proposed as another possible explanation for the increased stiffness associated with non-aspirin anticoagulation and is thus often used as rationale limiting the use NSAIDs in those patients given the presumed increased risk of bleeding. However, the stage 3 randomized RECORD and ADVANCE trials which led to FDA approval for rivaroxaban and apixaban, respectively, for use as VTE prophylaxis following TKA observed rates of hemarthrosis as low as 0.1% when using these medications (Turpie et al. 2009; Lassen et al. 2010). A recent randomized trial comparing 81mg ASA to 10mg rivaroxaban following TKA and THA also found lower rates of any bleeding event in the rivaroxaban group (0.99% vs. 1.29%) (Anderson et al. 2018). With the low rates of overall bleeding events and the scarcity of reported hemarthrosis, this explanation does not appear to adequately explain the previously reported

increased rates of stiffness in patients receiving DOAC anticoagulation. Further investigation is necessary both clinically and in molecular lab studies to provide clarity to the underlying cause of an increased MUA risk in patients who take DOACs following primary TKA.

This study is most notably limited by its sample size and statistical power. An *a priori* format power analysis demonstrates that based on the MUA rate of 4.17% in patients receiving DOACs (Kahlenberg et al. 2018), to achieve 80% power towards detecting a 30% reduction in incidence of MUA in a comparison of patients receiving DOACs vs DOACs + NSAIDS would require 3,555 patients in each cohort for a total number of 7,110 patients in each of those groups. Given that only patients deemed high-risk for VTE typically receive this treatment, this study size is likely unrealistic for a single-center series without spanning many years. The large sample size required stems from the relative rarity of MUAs observed in a given patient population. The authors feel that despite the low power achieved and given that the required sample size is likely unattainable for a single-institution, the current study makes valuable observations indicating possible beneficence of NSAID administration in DOAC patients and notes a lack of bleeding complications with that treatment in this sample. Ideal future follow-up to this study would consist of multicenter aggregation of data to achieve the statistical power necessary to make more definitive conclusions.

Other limitations exist, primarily those inherent to retrospective design. Patient adherence to prescribed anticoagulant and NSAID protocols is not certain, though patients with recorded compliance difficulties were excluded. All dosages of the anticoagulants and NSAIDs were treated equally within this study, though a potential dose effect could exist within the primary outcome measure; this was necessary to prevent further erosion to statistical power and the dosages encountered are described in the results section. Furthermore only 195 patients received concomitant NSAID and DOAC administration after surgery. While intravenous tranexamic acid (TXA) was administered perioperatively to all patients as standard of care and postoperative bleeding was not a concern in this retrospective study, this deserves further attention in future work. Despite these challenges, we believe this study adds to the growing body of literature that demonstrates the complexity of persistent postoperative stiffness following TKA and provides valuable insight on the use of DOAC drugs in this scenario.

In conclusion, patients receiving DOACs without concomitant NSAIDs were more likely to develop postoperative stiffness requiring MUA and achieved less predictable AOM when compared to aspirin anticoagulation. The addition of a selective COX-2 inhibitor to a postoperative DOAC regiment appeared to mitigate this risk of stiffness, though further study is required for definite conclusion and assessment of safety.

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