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Non-Inferiority of Aspirin for Venous Thromboembolism Prophylaxis After Hip Arthroplasty in a Statewide Registry

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ABSTRACT

Background: Uncertainty remains surrounding the use of aspirin as a sole chemoprophylactic agent to reduce the risk of venous thromboembolism (deep vein thrombosis or pulmonary embolism) and bleeding after primary total hip arthroplasty.
Methods: We performed a non-inferiority analysis of a retrospective cohort of patients undergoing total hip arthroplasty from April 1, 2013 to December 31, 2018. Cases were retrieved from the Michigan Arthroplasty Registry Collaborative Quality Initiative database and performed by 355 surgeons at 61 hospitals throughout Michigan. Surgical setting ranged from small community hospitals to large academic and non-academic centers. The primary outcomes were post-operative venous thromboembolism event or death and bleeding event.
Results: Of the 59,747 patients included, 32,878 (55.03%) were female, and the mean age was 64.5. A total of 462 (0.77%) composite venous thromboembolism events occurred. There were 221 (0.71%) and 129 (0.80%) venous thromboembolism events in patients receiving aspirin only and anticoagulants only, respectively. Aspirin was non-inferior to anticoagulants for composite venous thromboembolism events (odds ratio 0.99, 95% confidence interval 0.79-1.26, $P < .001$). Bleeding events occurred in 767 (1.28%) patients, with 304 (0.97%) and 281 (1.74%) bleeding events in patients receiving aspirin only and anticoagulants only, respectively. Aspirin was non-inferior to anticoagulants for bleeding events (odds ratio 0.62, 95% confidence interval 0.52-0.74, $P < .001$).
Conclusion: Aspirin is not inferior to other anticoagulants as pharmacologic venous thromboembolism prophylaxis with regards to post-operative risk of venous thromboembolism or bleeding. Sole use of aspirin for venous thromboembolism prophylaxis after total hip arthroplasty should be considered in the appropriate patient.

Total hip arthroplasty (THA) is a highly cost-effective procedure, with estimated societal savings of $32,948 per procedure and an increase of 5.5 quality-adjusted life years (QALYs) [1]. Although the success of this procedure is widely appreciated, post-operative venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a risk associated with significant morbidity and mortality [2]. The use of chemoprophylaxis and multimodal VTE prophylaxis has reduced the incidence of VTE [3]. Historical rates of VTE after THA without routine chemoprophylaxis were as high as 2.27% [4]; however, current rates have been reported to be approximately 0.4%-0.9% [5]. This is likely associated with more rapid mobilization, mechanical prophylaxis, improved pain control, and increased use of regional anesthesia [6].

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When considering chemoprophylaxis, it is also important to recognize the need to control for the risk of bleeding inherent to the agents used for VTE prevention.

There are a wide variety of options for chemoprophylaxis in orthopedic surgery, and these choices have continued to expand with the availability of the novel oral anticoagulants. Studies have attempted to determine if there is a single preferred agent through comparisons of medications such as aspirin, warfarin, low-molecular-weight heparin (LMWH), and factor Xa inhibitors, although strong conclusions have not been reached [7–10].

The most recent update on recommendations for chemoprophylaxis in total joint arthroplasty (TJA) from the American Academy of Orthopedic Surgery and the American College of Chest Physicians has led to a renewed interest in the use and study of aspirin given its ease of administration, low cost, and minimal burden of monitoring [11,12]. Recent literature confirmed its safety and efficacy [13,14]; however, some suggest aspirin should not be a first choice agent [15]. Literature examining aspirin as prophylaxis in TJA often draws on data from prior to or around the time of the most recent recommendations of the American Academy of Orthopedic Surgery and American College of Chest Physicians [8,16–18], which may not adequately reflect current aspirin usage. In fact, many studies have less than 10% of patients on aspirin [8,19]. Additionally, a recent systematic review and meta-analysis of randomized controlled trials (RCTs) of aspirin compared to other anticoagulants in TJA found no significant differences when comparing aspirin to lovenox and rivaroxaban. However, the authors emphasized the need for further studies in lieu of small sample sizes of some studies with significant heterogeneity and non-standard DVT screening practices [20].

The purpose of our study is to utilize a statewide arthroplasty registry to investigate whether aspirin alone is non-inferior to other anticoagulants for reducing the risk of VTE and minimizing bleeding after unilateral, primary THA. Our primary hypothesis is that aspirin is non-inferior to other anticoagulants (LMWH, warfarin, Xa inhibitors), considered as a class, in reducing the risk of VTE and minimizing bleeding events. Our secondary hypothesis is the non-inferiority of aspirin compared to individual anticoagulation agents. Finally, we hypothesize that patients receiving no form of pharmacologic prophylaxis have higher rates of VTE when compared to patients receiving any form of chemoprophylaxis.

Materials and Methods

Study Population

Institutional Review Board approval was obtained prior to initiating this study. Data were obtained through the Michigan Arthroplasty Registry Collaborative Quality Initiative (MARCQI), which began in February 2012. The MARCQI database collects >95% of hip and knee arthroplasties performed throughout the state of Michigan with cases followed for 90 days after the date of surgery. Data abstraction and entry into the database was done by trained clinical data abstractors and supplemented with file-based uploads. In addition, MARCQI supplements the abstracted data with administrative data from the Michigan Inpatient Data Base (MIDB), managed by the Michigan Health and Hospital Association Service Corporation. The MIDB captures all diagnosis codes associated with admissions in the state. Additional information on the organization and operation of MARCQI has been described by Hughes et al [21,22].

The study population was a retrospective cohort of 68,259 consecutive primary unilateral THA cases performed at MARCQI-participating hospitals from April 2013 to December 2018. Bilateral cases, cases withdrawn from the registry, and patients who had a subsequent contralateral THA were excluded. Cases were also excluded if the patient was taking anticoagulation on a daily basis within 30 days prior to surgery, or had a history of bleeding disorder, contraindication to anticoagulation, or prior history of VTE, and those receiving dialysis. We also excluded cases from ambulatory surgical centers without complete data, and cases without follow-up information or information submitted regarding the provision of prophylaxis or when it was given in relation to the time of surgery.

For a VTE event to be abstracted, it required a documented diagnosis, a positive test, and treatment. This was designed to avoid recording superficial clots which were not felt to be clinically significant. A bleeding event was defined as a drop in hemoglobin of 7 g/dL or more, a hematoma prior to any VTE event and treatment, or a bleeding diagnosis recorded in the MIDB that was not present on admission.

The prophylactic regimen was based on the pharmacologic agent initiated during the 3-day peri-operative period (within 1 day prior until 1 day following surgery). Pharmacologic prophylaxis was categorized as follows: patients taking only aspirin and no other form of chemoprophylaxis were assigned to “Aspirin”; patients taking only one or a combination of the anticoagulants LMWH, warfarin, or factor Xa inhibitor and no other form of chemoprophylaxis were assigned to “Anticoagulant”; patients taking both aspirin and only one agent from the Anticoagulant group were assigned to “Both”; patients taking no form of pharmacologic prophylaxis, or who started chemoprophylaxis after a VTE event, or who started later than the first post-operative day were assigned to “None”; and patients taking a non-recorded chemoprophylactic agent appropriately started within the 3-day peri-operative period, a non-aspirin anti-platelet agent, unfractionated heparin, or any other regimen that does not fit into the previous categories were assigned to “Other”.

VTE and death events were recorded per MARCQI protocol for up to 90 days post-surgery. Since the cause of death was not known in the registry, and in order to avoid underestimating VTE related complications, all deaths were assumed to be due to PE. Death due to other causes is assumed to be distributed randomly between the groups.

Statistical Analyses

The distribution of each variable was checked and continuous variables transformed if necessary. Kruskal-Wallis testing was used to compare continuous variables between patient subgroups. Chi-squared testing was used to test the homogeneity for categorical variables between patient groups. A type I probability of .05 was used as the level of statistical significance. The testing performed was non-inferiority, 1-sided testing. Inverse probabilities of treatment weighting (IPTW) was employed to mitigate confounding variables.

The sample size was determined a priori with a power calculation assuming the clinically important difference for an adverse event was an upper 95% confidence boundary for the odds ratio (OR; aspirin:anticoagulation) of 1.5, with a power of 80%. This margin of non-inferiority was determined based on the clinically important difference used in previous studies [23,24], as well as by discussion among the authors. Power analysis assumptions and minimum sample sizes can be found in the online supplementary material (eMethods). Due to the large sample size available and the clinical importance of detecting a small difference in VTE and bleeding events, the decision was made to use a lower OR than used in other studies [7,25].

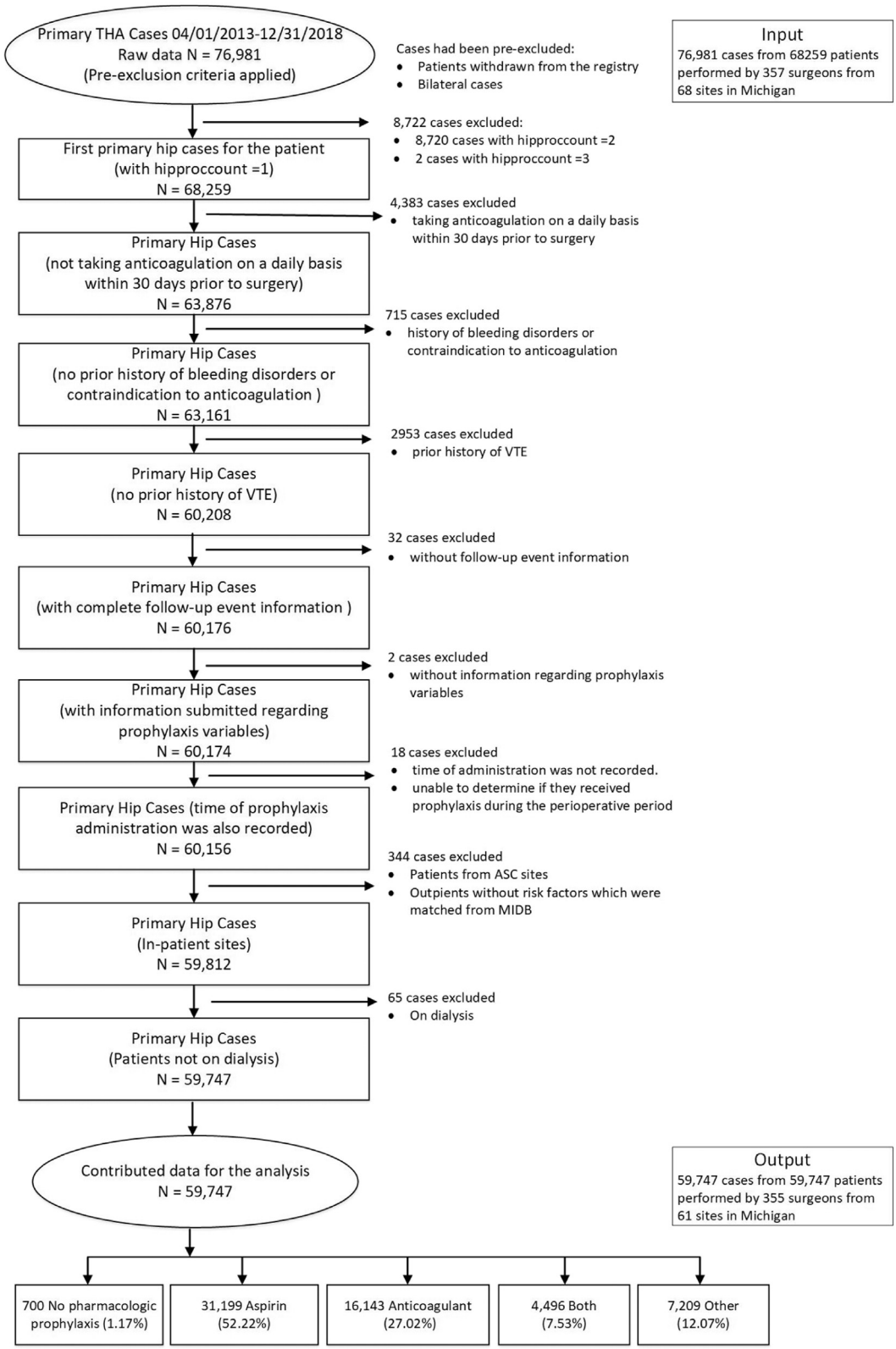

Fig. 1. The flow diagram demonstrates exclusion criteria applied for case selection. THA, total hip arthroplasty; VTE, venous thromboembolism; MIDB, Michigan Inpatient Data Base; ASC, ambulatory surgery center.

Covariates are associated conceptually with both the VTE prophylaxis regimen chosen by the surgeon and the occurrence of the composite outcome of DVT, PE, or death. Because of the potential inter-relationships among candidate confounders (some of which are unidentifiable), a causal directed acyclic graph (DAG; DAGitty Software R) was employed to identify the potential confounders. The description of the DAG methods and minimal set of covariates identified are detailed in the online supplement (eMethods).

Table 1
Demographic Characteristics of Study Population.

Variable	Unit/Level	Population No. (N = 59,747)	None No. (N = 700)	Aspirin Only No. (N = 31,199)	Anticoagulant No. (N = 16,143)	Both No. (N = 4496)	Other/Mixed No. (N = 7209)	Statistical Tests
Age, mean (SD)	y	64.52 (11.08)	64.71 (11.59)	64.36 (10.92)	64.19 (11.31)	66.43 (10.59)	64.79 (11.42)	<0.0001[a]
Body mass index, mean (SD)	kg/m^2	30.37 (6.23)	30.09 (6.28)	30.17 (6)	30.91 (6.65)	30.91 (6.2)	29.69 (6.1)	<0.0001[a]
Pre-op HGB, mean (SD)	g/dL	13.8 (1.39)	13.68 (1.44)	13.89 (1.37)	13.69 (1.41)	13.71 (1.43)	13.75 (1.39)	<0.0001[a]
Race, n (%)	1. White	51,971 (86.99)	602 (86)	27,727 (88.87)	13,970 (86.54)	3738 (83.14)	5934 (82.31)	<0.0001[b]
	2. Black	4880 (8.17)	69 (9.86)	2133 (6.84)	1511 (9.36)	545 (12.12)	622 (8.63)	
	3. Other	2896 (4.85)	29 (4.14)	1339 (4.29)	662 (4.1)	213 (4.74)	653 (9.06)	
Gender, n (%)	Female	32,878 (55.03)	388 (55.43)	16,806 (53.87)	9483 (58.74)	2269 (50.47)	3932 (54.54)	<0.0001[b]
Insurance/primary payer, n (%)	Commercial	18,400 (30.8)	198 (28.29)	9086 (29.12)	5260 (32.58)	1294 (28.78)	2562 (35.54)	<0.0001[b]
	Medicaid	2590 (4.33)	34 (4.86)	1340 (4.3)	806 (4.99)	148 (3.29)	262 (3.63)	
	Medicare	24,636 (41.23)	309 (44.14)	12,058 (38.65)	7088 (43.91)	2229 (49.58)	2952 (40.95)	
	Others	14,121 (23.63)	159 (22.71)	8715 (27.93)	2989 (18.52)	825 (18.35)	1433 (19.88)	
Smoking status, n (%)	Never	28,339 (47.43)	325 (46.43)	15,093 (48.38)	7481 (46.34)	1993 (44.33)	3447 (47.82)	<0.0001[b]
	Previous	22,594 (37.82)	253 (36.14)	11,659 (37.37)	6004 (37.19)	1849 (41.13)	2829 (39.24)	
	Current	8531 (14.28)	112 (16)	4338 (13.9)	2576 (15.96)	605 (13.46)	900 (12.48)	
	Unknown	283 (0.47)	10 (1.43)	109 (0.35)	82 (0.51)	49 (1.09)	33 (0.46)	
ASA score, n (%)	I	1683 (2.82)	16 (2.29)	1015 (3.25)	417 (2.58)	120 (2.67)	115 (1.6)	<0.0001[b]
	II	33,868 (56.69)	362 (51.71)	18,695 (59.92)	8627 (53.44)	2188 (48.67)	3996 (55.43)	
	III	23,565 (39.44)	312 (44.57)	11,251 (36.06)	6921 (42.87)	2107 (46.86)	2974 (41.25)	
	IV	613 (1.03)	10 (1.43)	227 (0.73)	174 (1.08)	79 (1.76)	123 (1.71)	
Anesthesia neuraxial, n (%)	Yes	37,326 (62.47)	388 (55.43)	21,614 (69.28)	9057 (56.1)	2384 (53.02)	3883 (53.86)	<0.0001[b]
Pre-op antiplatelet, n (%)	Yes	21,636 (36.21)	256 (36.57)	11,173 (35.81)	4680 (28.99)	2678 (59.56)	2849 (39.52)	<0.0001[b]
Assistive devices, n (%)	Yes	22,240 (37.22)	319 (45.57)	11,278 (36.15)	6665 (41.29)	1845 (41.04)	2133 (29.59)	<0.0001[b]
Co-morbidities, n (%)[c]	Yes	27,470 (45.98)	324 (46.29)	13,531 (43.37)	7950 (49.25)	2272 (50.53)	3393 (47.07)	<0.0001[b]
Renal function, n (%)	Normal	57,707 (96.59)	670 (95.71)	30,262 (97)	15,516 (96.12)	4303 (95.71)	6956 (96.49)	<0.0001[b]

SD, standard deviation; ASA, American Society of Anesthesiologists; HGB, hemoglobin.

[a] *P* value for Kruskal-Wallis test.

[b] *P* value for Pearson chi-squared tests of homogeneity/independence.

[c] Co-morbidities include any of chronic obstructive pulmonary disease, diabetes, renal failure, drug abuse, alcohol use, heart failure, hypothyroidism, lymphoma/metastatic cancer/cancer, neurological, vascular disease, valvular heart disease.

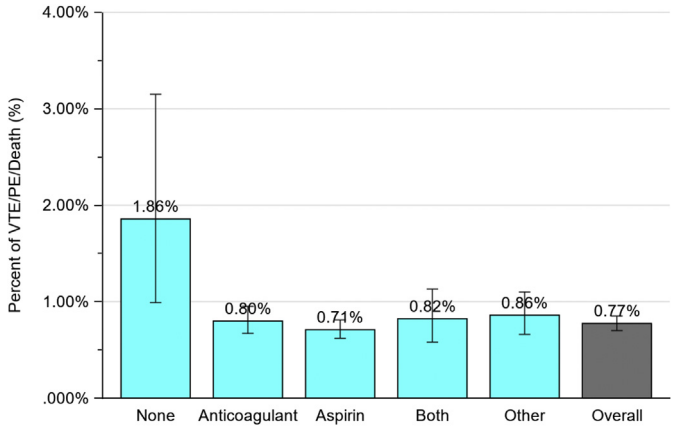

Fig. 2. The bar graphs depict VTE/death rates by chemoprophylactic regimen, with 95% CI. VTE, venous thromboembolism; PE, pulmonary embolism; CI, confidence interval.

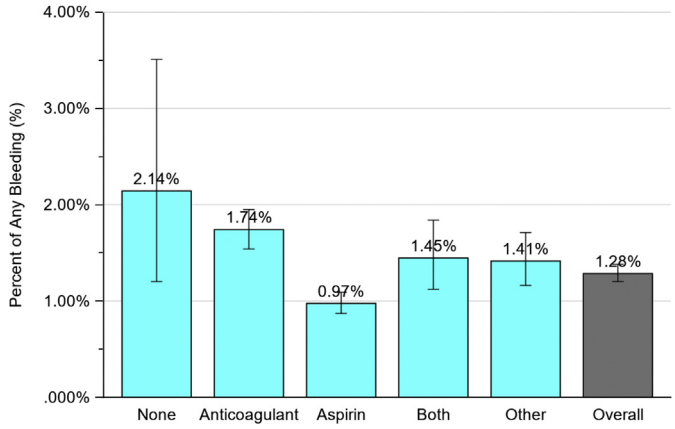

Fig. 3. The bar graphs depict bleeding rates by chemoprophylactic regimen, with 95% CI. CI, confidence interval.

A logistic regression model was used to obtain the propensity of the patient receiving the anticoagulation regimen used based on the measureable covariates identified through the DAG process. Both unadjusted and multivariable-adjusted ORs (with 95% confidence intervals [CIs] and *P*-values) of the association of VTE and bleeding events with the prophylaxis method were determined. For the adjusted analyses, hierarchical multivariable logistic regression models with IPTW were fitted. Surgeons were treated as the random effect to account for the hierarchical data structure and heterogeneity of surgeons. Separate models were developed for the outcomes VTE event and bleeding event.

One-sided, non-inferiority tests were performed using an OR of 1.5 as the clinically determined threshold as previously described. The *P*-value for non-inferiority and one-sided 95% upper CI were reported and a *P*-value <.05 indicates that the non-inferiority is unlikely to be due to chance or insufficient sample size. All *P* values and ORs reported are risk adjusted.

We planned a post hoc analysis to look at the potential changes in the frequency of recorded bleeding events in administrative data that might reflect changes from International Classification of Diseases, 9th Revision (ICD-9) to International Classification of Diseases, 10th Revision (ICD-10) coding that began October 1, 2015. A 2-level indicator variable (before and after October 1, 2015) was created. The post hoc analyses were conducted by adding this variable to the model to reflect this change. The results were compared in terms of relative percent changes of ORs.

SAS version 9.4 and SAS macro language (SAS Institute, Cary, NC) were used for the statistical analyses. The DAGitty (R package) was used for the causal model. SAS and Rx64 3.5.3 were used for the power and sample size analysis.

Results

A total of 68,259 primary THA cases were identified with 59,747 included for analysis after exclusions, and were performed by 355 surgeons operating at 61 hospitals (Fig. 1). There were 31,199 (52.22%) patients in the "Aspirin" group and 16,143 (27.02%) patients in the "Anticoagulant" group (LMWH, Xa inhibitor, or warfarin). LMWH was received by 5424 (33.60%) patients, 5838 (36.16%) patients received only Xa inhibitors, 3891 (24.10%) patients received only warfarin, and 990 (6.13%) received more than one agent. A total of 4496 (7.53%) patients received "Both," 700 (1.17%) patients received "None," and 7209 (12.07%) patients received "Other." Patient demographics and baseline characteristics are listed in Table 1, and co-morbidities are listed in the online supplement(Table e1).

A total of 462 (0.77%) composite VTE events occurred (95% CI 0.70- 0.85), with 78 (16.9%) deaths, 175 (37.9%) PEs, and 209 (45.2%) DVTs. There were 221 (0.71%) and 129 (0.80%) VTE events in patients receiving "Aspirin" and "Anticoagulant," respectively. Within "Anticoagulant" group, there were 45 (0.83%) VTE events in patients receiving LMWH, 27 (0.46%) VTE events in patients receiving factor Xa inhibitors, 54 (1.39%) VTE events in patients receiving warfarin, and 3 (0.30%) VTE events in patients using more than one agent. There were VTE events in 1.86% of patients receiving "None," 0.82% of patients receiving "Both," and 0.86% of patients receiving "Other" (Fig. 2).

"Aspirin" was non-inferior to "Anticoagulant" as a group for risk of VTE or death (OR 1.00, 95% CI 0.80-1.26, $P < .001$) (Table 2). For the comparison to individual anticoagulants for VTE, "Aspirin" was non-inferior to both warfarin (OR 0.60, 95% CI 0.44, 0.84, $P < .001$) and LMWH (OR 1.00, 95% CI 0.80-1.26, $P < .001$). However, non-

Table 2
Odds Ratio for the Outcomes Venous Thromboembolism/Death and Bleeding Event.

Comparison	VTE/Death Outcome			Bleeding Event Outcome		
	Unadjusted	Adjusted[a]		Unadjusted	Adjusted[a]	
	OR (95% CI)	OR (95% CI)	Non-Inferiority Test *P* Value	OR (95% CI)	OR (95% CI)	Non-Inferiority Test *P* Value
Aspirin vs anticoagulant	0.90 (0.71-1.13)	1.00 (0.80-1.26)	.0003	0.57 (0.48-0.68)	0.62 (0.52-0.74)	<.0001
Aspirin vs LMWH	0.88 (0.63-1.24)	1.09 (0.79-1.52)	.0308	0.53 (0.41-0.68)	0.71 (0.56-0.90)	<.0001
Aspirin vs warfarin	0.53 (0.38-0.73)	0.66 (0.48-0.90)	<.0001	0.57 (0.43-0.76)	0.69 (0.53-0.90)	<.0001
Aspirin vs Xa inhibitors	1.50 (0.99-2.28)	1.69 (1.14-2.51)	.2715	0.57 (0.44-0.74)	0.65 (0.50-0.83)	<.0001

VTE, venous thromboembolism; OR, odds ratio; CI, confidence interval; LMWH, low-molecular-weight heparin; DAG, directed acyclic graph.
[a] Risk-adjusted model. Confounders determined by DAG modeling.

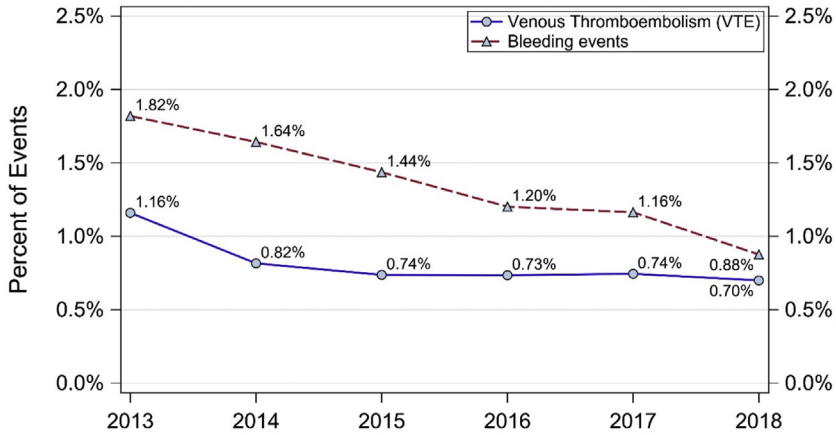

Fig. 4. The line plots represent the trend of VTE and bleeding events over time. VTE, venous thromboembolism.

inferiority of "Aspirin" was not established for factor Xa inhibitors with regards to risk of VTE (OR 1.74, 95% CI 1.15-2.64, $P = 0.24$) (Table 2).

Patients receiving "None" had a significantly higher risk of VTE when compared with "Anticoagulant" (OR 2.44, 95% CI 1.35-4.39, $P = .003$), "Aspirin" (OR 2.44, 95% CI 1.37-4.34, $P = .003$), and "Both" (OR 1.99, 95% CI 1.05-3.78, $P = .036$). The risk of VTE with "None" compared to "Other" approached significance (OR 1.8, 95% CI 0.97-3.42, $P = .064$).

Bleeding events occurred in 767 (1.28%) patients. There were 304 (0.97%) and 281 (1.74%) bleeding events in patients receiving "Aspirin" and "Anticoagulant," respectively. Within the "Anticoagulant" group, there were 105 (1.94%) bleeding events in patients treated with LMWH, 94 (1.61%) with factor Xa inhibitors, 69 (1.77%) with warfarin, and 13 (1.31%) in patients receiving more than one agent. There were bleeding events in 2.14% of patients receiving "None," 1.45% of patients receiving "Both," and 1.41% of patients receiving "Other" (Fig. 3).

"Aspirin" was non-inferior to "Anticoagulant" for risk of bleeding (OR 0.62, 95% CI 0.5-0.74, $P < .001$) (Table 2). Individually, non-inferiority of "Aspirin" for bleeding was also detected when comparing aspirin to LMWH (OR 0.60, 95% CI 0.47-0.77, $P < .0001$), Xa inhibitors (OR 0.58, 95% CI 0.45-0.75, $P < .0001$), and warfarin (OR 0.62, 95% CI 0.47-0.82, $P < .0001$).

Throughout the study period from 2013 to 2018, the rates of VTE decreased from 1.16% to 0.70% and the rates of bleeding events decreased from 1.82% to 0.88%, as seen in Figure 4. The use of "Aspirin" increased from 10.27% to 78.23%, the use of "Anticoagulant" decreased from 65.51% to 10.87%, and the use of "Both" decreased from 14.36% to 4.71%. The trends in use of "None" and "Other" decreased as well (Fig. 5).

The post hoc analyses that controlled for the impact of the conversion to ICD-10 coding did not overturn the findings regarding aspirin vs anticoagulants for bleeding or VTE events.

Discussion

We found that aspirin as a sole chemoprophylactic agent is non-inferior to commonly used anticoagulation agents considered as a class for rates of VTE events or death and bleeding events after primary THA. We also found aspirin to be non-inferior for VTE or death compared to warfarin and LMWH as individual agents, although not for factor Xa inhibitors. Aspirin was non-inferior to all 3 anticoagulants studied with regard to bleeding events. Despite a large increase in aspirin use as a sole agent within this registry over recent years, VTE rates remained stable and bleeding demonstrated a decreasing trend.

Orthopedic co-management teams are increasingly utilized in arthroplasty due to evidence of improved care and reduced costs and therefore, knowledge of the safety and efficacy of chemoprophylaxis after THA is necessary for all teams involved [26]. Aspirin is widely used for VTE prophylaxis following arthroplasty due to its

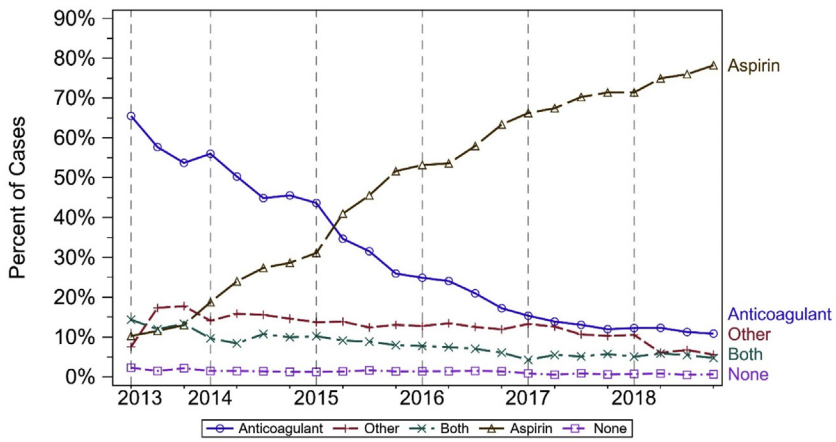

Fig. 5. The line plots represent the use of the prophylactic agents over time.

safety profile, ease of administration, low cost, and efficacy [10,14,24]. However, studies have been limited by small patient populations [20], low rates of aspirin use [19], and non-recommended DVT screening methods [16]. To our knowledge, this is the first study to utilize a large registry database for a non-inferiority comparison of aspirin with warfarin, LMWH, and factor Xa inhibitors for rates of VTE and bleeding events after primary THA.

We found a significantly higher risk of VTE event if no pharmacologic prophylaxis is utilized, reinforcing the consensus among orthopedic surgeons of the need for some form of chemoprophylaxis even with the widespread adoption of multimodal VTE prophylaxis such as neuraxial anesthesia, pneumatic compression devices, and early mobilization [3,27].

Several studies have investigated factor Xa inhibitors as VTE prophylaxis after TJA [19,28–30] and have suggested no differences between factor Xa inhibitors and aspirin for VTE rates [7,31–33], although we were not able to establish the non-inferiority of aspirin in our study. A recent RCT found that rates of symptomatic VTE after THA and TKA (total knee arthroplasty) were not statistically different between aspirin and rivaroxaban [7]. However, their protocol included the use of rivaroxaban for 5 days post-operatively in all participants before stratification into aspirin or rivaroxaban, limiting conclusions regarding the sole use of aspirin. Bala et al retrospectively matched patients receiving aspirin to factor Xa inhibitors, warfarin, or LMWH in primary TKA and THA, and concluded that aspirin and factor Xa inhibitors had similar rates of symptomatic VTE [31,32]. Limitations included small sample sizes for aspirin, and the inability to collect data at all time points. Finally, a recent systematic review and meta-analysis comparing aspirin to rivaroxaban in patients after TKA and THA, which included 4 RCTs, did not find any difference in VTE or bleeding rates [33]. There was significant heterogeneity in the prophylactic regimens among the studies, however. Further study is needed to determine whether the possible difference in risk for VTE with factor Xa inhibitors is clinically significant enough to justify the difference in risk profile and cost.

Our study is a large-scale, registry, multicenter, observational cohort study designed to focus on detection and minimization of early harmful outcomes, including post-operative 90-day VTE events and any type of bleeding events. A major strength of this registry is the statewide nature and inclusion of a wide range of clinical practice settings. However, retrospective observational studies of prophylaxis after TJA were recently criticized for their inability to control for selection bias and other potential confounders [34]. We did attempt to limit the effect of confounders and bias by excluding patients with a history of VTE, bleeding disorder, and current anticoagulation use; however, unmeasured variables such as intraoperative events and post-operative rehabilitation protocols may have affected the results. MARCQI surgeons were advised to follow published guidelines, but the actual criteria for each decision are unknown. Likely, toward the end of the study period, only the highest risk patients were receiving something other than aspirin. The statistical techniques used here to account for this, such as IPTW, cannot completely eliminate these biases. Fortunately, the continued drop in VTE events supports the surgeons' clinical judgment.

Other limitations include that the dose of medications is not available in the database so no recommendations on dosing can be made. The cause of death is not known in the registry so some deaths assumed to be due to PE could be from other causes. Events occurring at the same or other hospitals could have been missed but the data is captured by imbedded, trained data abstractors who are regularly audited and supplemented with billing and diagnosis codes from the statewide administrative database, MIDB. Also, this is a Michigan-based database, and it is possible that the VTE prophylaxis regimens in our state do not represent the current practice in other settings. Moreover, these data reflect an active quality improvement initiative with motivated, collaborative participants.

Despite these limitations, this study adds important information to the body of literature on prophylaxis after THA. The non-inferiority of aspirin is especially important given that the monthly cost for aspirin therapy is much less compared with other agents. A cost analysis study found that the cost of LMWH compared to aspirin in patients undergoing THA is greater than $1 million per QALY gained [35]. Similarly, cost analyses have shown warfarin to have a higher cost per QALY gained after THA when compared to aspirin, even when excluding the known increased costs due to warfarin monitoring [36,37]. Factor Xa inhibitors are also known to be expensive, with higher costs per QALY gained compared to aspirin use in stroke patients [38]. Consideration must also be given to the complexities of warfarin monitoring and LMWH prophylaxis [39]. Given the low cost, ease of administration, lack of monitoring, and non-inferiority, aspirin is a preferred prophylaxis for elective THA patients.

Conclusion

For primary THA, our registry experience indicates that aspirin is non-inferior to LMWH or warfarin in reducing VTE or minimizing bleeding. Aspirin appeared to be non-inferior to factor Xa inhibitors with regards to minimizing bleeding, but non-inferiority was not established for the risk of VTE, and further research is needed. Lack of any chemoprophylaxis resulted in higher rates of VTE compared to pharmacologic VTE prophylaxis.

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Appendix. eMethods

Power Analysis

Based on previous studies and author discussion [3,4], assumptions for power analysis were as follows: venous thromboembolism (VTE) percentage in anticoagulant of 0.6% and in aspirin of 0.5%, and sample size ratio 5:4 for anticoagulant vs aspirin; bleeding percent in anticoagulant of 1.1% and in aspirin of 1%, and sample size ratio 5:4 for anticoagulant vs aspirin. For the primary analysis, the *a priori* power analysis showed that the required sample sizes for comparing aspirin vs anticoagulant were 5,970 and 7,462 for VTE events, respectively, and 4,281 and 5,351 for bleeding events, respectively. To compare the individual agents for VTE event, aspirin vs low-molecular-weight heparin (LMWH) needed 7,762 and 5,544, aspirin vs Xa inhibitors needed 10,549 and 4,521, aspirin vs warfarin needed 20,761 and 11,863. To compare the individual agents for bleeding events, aspirin vs LMWH needed 17,804 and 12,717 and aspirin vs warfarin needed 61,051 vs 34,886. There were not enough cases to compare aspirin only vs Xa inhibitors for bleeding events during the analysis time window.

Description of Directed Acyclic Graphs Method

Two outcomes, VTE and bleeding events within 90 days postoperatively were analyzed in this report. Covariates to be used in the statistical analyses were selected using modern causal inference methods in epidemiology [1,2], which is called causal directed acyclic graph (DAG, DAGitty Software R, http://dagitty.net/dags.html). This method allows users to identify which covariates are needed to control for confounding for the multivariable models and closes all identifiable backdoor pathways between the exposure (choice of prophylaxis) and outcome (VTE, bleeding). The software reduces the chance of collider stratification bias that could occur if collider variables by themselves were included in the multivariable regression models.

In the analysis, the key part of the mechanics of causal inference analysis on DAGs is selecting variables that "block" all "back-door" paths from exposure to outcome. Specifically, a back-door path is an undirected path from exposure to outcome whose first edge (going from exposure to outcome) is directed into the exposure. A back-door path is blocked if it contains a variable in the set of variables to adjust for in the statistical modeling. The set of all the variables required to block all back-door paths is the "minimum set of variables sufficient to remove confounding" [2]. The set is also analyzed to make sure that variables are not added to the set in a way that creates collider stratification bias [5]. The software DAGitty (*DAGitty v2.3*) was used to choose the minimal set of variables for sufficient exposure and the outcomes. DAGitty indicated that the set of variables necessary for adjustment was age, BMI, sex, ASA score, insurance, anesthesia types, smoking status, preop antiplatelet, using of assistive devices, renal function, pre-op HGB, and Elixhauser variables from Michigan Inpatient Database (MIDB), including COPD, diabetes, drug abuse, EtOh alcohol, heart failure, hypothyroidism, lymphoma/METS/cancer, neurological, vascular disease, valvular heart disease.

Table e1
Comorbidities of Study Population From Michigan Inpatient Database.

Variable	Population No. (N = 59,747)	None No. (N = 700)	Aspirin Only No. (N = 31,199)	Anticoagulant No. (N = 16,143)	Both No. (N = 4,496)	Other/Mixed No. (N = 7,209)	Statistical Tests
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
COPD (CHRNLUNG)	8,787 (14.71)	106 (15.14)	4,248 (13.62)	2,694 (16.69)	674 (14.99)	1,065 (14.77)	< 0.0001 [a]
Diabetes (DM, DMCX)	8,855 (14.82)	103 (14.71)	4,223 (13.54)	2,539 (15.73)	887 (19.73)	1,103 (15.30)	< 0.0001 [a]
Drug abuse (DRUG)	884 (1.48)	N < 10[b]	445 (1.43)	285 (1.77)	65 (1.45)	80 (1.11)	< 0.0001 [a]
EtOh alcohol (ALCOHOL)	1,015 (1.70)	15 (2.14)	526 (1.69)	308 (1.91)	87 (1.94)	79 (1.10)	< 0.0001 [a]
Heart failure (CHF)	1,222 (2.05)	19 (2.71)	525 (1.68)	333 (2.06)	162 (3.60)	183 (2.54)	< 0.0001 [a]
Hypothyroidism (HYPOTHY)	9,250 (15.48)	113 (16.14)	4,551 (14.59)	2,691 (16.67)	701 (15.59)	1,194 (16.56)	< 0.0001 [a]
Lymphoma/METS/cancer (LYMPH/METS/TUMOR)	420 (0.70)	N < 10[b]	175 (0.56)	145 (0.90)	36 (0.80)	56 (0.78)	< 0.0001 [a]
Neurological (NEURO)	2,290 (3.83)	46 (6.57)	1,150 (3.69)	649 (4.02)	181 (4.03)	264 (3.66)	< 0.0001 [a]
Vascular disease (PERIVASC)	1,293 (2.16)	22 (3.14)	548 (1.76)	308 (1.91)	147 (3.27)	268 (3.72)	< 0.0001 [a]
Renal fail (RENLFAIL)	3,181 (5.32)	44 (6.29)	1,505 (4.82)	944 (5.85)	304 (6.76)	384 (5.33)	< 0.0001 [a]
Valvular heart disease (VALVE)	1,725 (2.89)	23 (3.29)	861 (2.76)	419 (2.60)	184 (4.09)	238 (3.30)	< 0.0001 [a]

[a] *P* value for Pearson χ^2 tests of homogeneity/independence with prophylaxis groups.
[b] Actual numbers for cell size less than 10 are not shown

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