Aspirin Alone Is Not Enough to Prevent Deep Venous Thrombosis After Total Joint Arthroplasty

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abstract

Thromboembolic events after total joint arthroplasty are potentially devastating complications. This study evaluated the efficacy of 4 different anticoagulants in preventing deep venous thrombosis and pulmonary embolism after total joint arthroplasty. The demographics and anticoagulant use (warfarin, enoxaparin, and aspirin with and without outpatient mechanical pumps) for patients who underwent primary unilateral total joint arthroplasties performed by a single surgeon from January 2013 to October 2014 were retrospectively reviewed. All patients underwent lower extremity ultrasound at the 3-week postoperative visit. A total of 613 primary unilateral total joint arthroplasties met the study inclusion criteria. There were 288 primary total knee arthroplasties and 325 primary total hip arthroplasties. The patients were 62.2% female, having a mean age of 67.6±10.6 years and a mean body mass index of 30.2±5.9 kg/m^2. There were 119 patients in group 1 (aspirin alone), 40 patients in group 2 (aspirin plus pumps), 246 patients in group 3 (warfarin), and 208 patients in group 4 (enoxaparin). The overall 3-week symptomatic and asymptomatic deep venous thrombosis and symptomatic pulmonary embolism rates in the entire cohort were 5.7% and 0.3%, respectively. The venous thromboembolism rate was significantly affected by the anticoagulant of choice (P<.01). Compared with aspirin alone, warfarin decreased the risk of venous thromboembolism (P<.01). Increasing age led to increased risk of venous thromboembolism (P=.05). This study indicated that aspirin chemoprophylaxis alone was not as efficacious as warfarin and enoxaparin in preventing asymptomatic and symptomatic venous thromboembolism found during routine postoperative surveillance with lower extremity ultrasound. Aspirin alone may be inadequate and should be augmented with an outpatient mechanical pump as part of multimodal prophylaxis. [*Orthopedics*. 2019; 42(1):48-55.]

Deep venous thrombosis (DVT) is a potentially serious complication following elective total joint arthroplasty (TJA). Untreated DVT can be complicated by clot propagation, post-thrombotic syndrome, and pulmonary embolism (PE), with the latter potentially being fatal. The Centers for Medicare & Medicaid Services includes venous thromboembolism (VTE) after total hip arthroplasty (THA) and total knee arthroplasty (TKA) as 1 of 14 hospital-acquired conditions that is high cost, high volume, or both; results in assignment to a diagnosis-related group with a higher payment when present as a secondary diagnosis; and could be prevented with application of evidence-based guidelines.[1] To decrease their incidence, hospital-acquired conditions were subject to a pay-for-performance initiative, resulting in reduced reimbursement to physicians and hospitals.[2,3]

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Without prophylaxis, the occurrence of all VTE has been estimated to be greater than 40%, with the rate of clinically significant VTE estimated to be approximately 4.3% at 35 days following major orthopedic surgery.[4] Chemical and/or mechanical VTE prophylaxis is recommended to prevent potentially serious complications.[5] Many different chemoprophylactic agents are used for this purpose. The ideal chemoprophylactic agent should provide efficacious VTE prevention, have a lower bleeding risk profile, be easily administered and reversed, and have high patient tolerance and compliance.

The American College of Chest Physicians and the American Academy of Orthopaedic Surgeons have published guidelines regarding VTE prophylaxis after TJA.[4,5] Both groups recommend the use of pneumatic compression devices for mechanical prophylaxis. The American Academy of Orthopaedic Surgeons does not name specific agents in its recommendations because of a lack of clear clinical evidence, instead advocating for a risk-stratification approach.[5] The American College of Chest Physicians recommends low-molecular-weight heparin over aspirin and adjusted-dose warfarin at grade 2C level, and prophylaxis for 10 to 14 days with any of those agents over no prophylaxis at grade 1B level.[4] Many anticoagulants are plagued by drawbacks, including poor compliance (subcutaneous injectable agents), injection site morbidity, dose monitoring (warfarin), heparin-induced thrombocytopenia, cost, lack of antidote, and the risk of local and remote bleeding.

Aspirin, a widely used antiplatelet agent, was included as a possible chemoprophylactic agent after TJA in the 2012 American College of Chest Physicians guidelines.[4] Many studies of aspirin prophylaxis have found evidence to support its use.[6-10] Aspirin's familiarity, oral administration, lack of need for monitoring, low bleeding risk profile, low cost, existing widespread use for nonorthopedic reasons, and long history in humanity's pharmacopeia have all led to its rapid rise in popularity. Indeed, the literature supports a significant shift in orthopedist prescribing patterns toward aspirin monotherapy, especially after convergence of both American College of Chest Physicians and American Academy of Orthopaedic Surgeons guidelines in support of aspirin prophylaxis.[11]

Another point of contention is whether aspirin should be administered in combination with intermittent pneumatic compression devices or pumps. Some studies have reported higher DVT rates when aspirin is used alone or when intermittent pneumatic compression device noncompliance is evident.[10,12-14]

The primary objective of this study was to compare the efficacy of aspirin alone, aspirin plus an intermittent pneumatic compression device, warfarin, and enoxaparin as VTE prophylaxis after primary unilateral TJA. The secondary objective was to compare the bleeding risk using these agents following primary unilateral TJA.

Materials and Methods

After institutional review board approval was obtained, the authors performed a retrospective study of patients who underwent primary unilateral cemented resurfaced TKA and mini-posterior approach uncemented THA performed by a single surgeon from January 2013 to October 2014. Patients were assigned to 1 of 4 postoperative VTE prophylaxis treatment arms based on surgeon preference: group 1 (aspirin alone), group 2 (aspirin plus pumps), group 3 (warfarin), or group 4 (enoxaparin). Patients in group 1 (aspirin) were given 325 mg of aspirin twice a day starting the first morning postoperatively. Patients in group 2 (aspirin plus pumps) were treated in a fashion similar to group 1 and used intermittent pneumatic compression pumps. Patients in group 3 (warfarin) were started on 5 mg of warfarin the evening of the day of surgery and titrated to therapeutic levels (international normalized ratio between 1.8 and 2.5) using a warfarin-dosing normogram.[15] Patients in group 4 (enoxaparin) received the first dose of 40 mg of subcutaneous enoxaparin the first morning postoperatively. All patients were treated for 4 weeks postoperatively and mobilized with physical therapy on the day of surgery. All patients underwent uniform lower extremity duplex ultrasound of bilateral lower extremities at the 3-week postoperative visit performed by the same sonographer, who was blinded to the method of chemoprophylaxis. Deep venous thrombosis was classified as suprapopliteal or infrapopliteal.

Inclusion criteria were age older than 18 years and unilateral TJA. Patients undergoing revision arthroplasty or simultaneous bilateral primary TJA procedures (performed under the same anesthetic), with preexisting VTE or a history of coagulopathy or VTE, with bleeding diathesis, and already using anticoagulation for other medical reasons (eg, atrial fibrillation or cardiac stents) were excluded.

A chart review was conducted to gather data including patient age, sex, body mass index, use of intraoperative intravenous tranexamic acid, side of surgery, type of surgery (TKA vs THA), type of anesthesia, and postoperative blood transfusion requirement. Data were collected for symptomatic VTE and included lower extremity duplex scans, computed tomography scans, and ventilation-perfusion studies for PE. Finally, data regarding all routine lower extremity duplex findings were collected.

Statistical comparison of categorical variables was done using chi-square test, or Fisher's exact test for small samples.[16,17] Comparisons of continuous variables in 3 or more groups were made using one-way analysis of variance, with Tukey post hoc analysis for pairwise comparison. Binomial logistic regression models were created to ascertain the effects of chemoprophylactic agent, age, sex, body mass index, use of tranexamic acid, side of surgery (left vs right), type of anesthesia, and type of surgery on the likelihood that patients would

Table 1

Patient Characteristics by Treatment Group

Characteristic	Treatment Group				*P*
	Aspirin Alone (n=119)	Aspirin Plus Pumps (n=40)	Warfarin (n=246)	Enoxaparin (n=208)	
Age, mean±SD, y	67.1±11.4	63.2±8.5	68.3±10.7	67.8±10.3	.03[a,b]
Body mass index, mean±SD, kg/m^2	29.0±5.0	29.1±6.6	30.5±6.1	30.9±5.9	.02[b,c]
Female sex, No.	82 (68.9%)	29 (72.5%)	149 (60.6%)	121 (58.2%)	.12
Patients undergoing total knee arthroplasty, No.[d]	54 (45.4%)	18 (45.0%)	116 (47.2%)	100 (48.1%)	.96
Left side surgery, No.	51 (42.9%)	20 (50.0%)	137 (55.7%)	89 (42.8%)	.03[b]
Use of tranexamic acid, No.	115 (96.6%)	33 (82.5%)	142 (57.7%)	147 (70.7%)	<.01[b]
General anesthesia, No.[e]	107 (89.9%)	35 (87.5%)	213 (86.6%)	188 (90.4%)	.60
Outcome, No.					
Venous thromboembolism	15 (12.6%)	3 (7.5%)	7 (2.8%)	12 (5.8%)	<.01[b]
Transfusion	1 (0.8%)	3 (7.5%)	21 (8.5%)	2 (1.0%)	<.01[b]

[a]*Significant difference in age between warfarin and aspirin with pump (*P=*.022).*
[b]*Significant (*P<*.05).*
[c]*Significant difference in body mass index between enoxaparin and aspirin alone (*P=*.025).*
[d]*Missing patients had total hip arthroplasty.*
[e]*Missing patients had spinal anesthesia.*

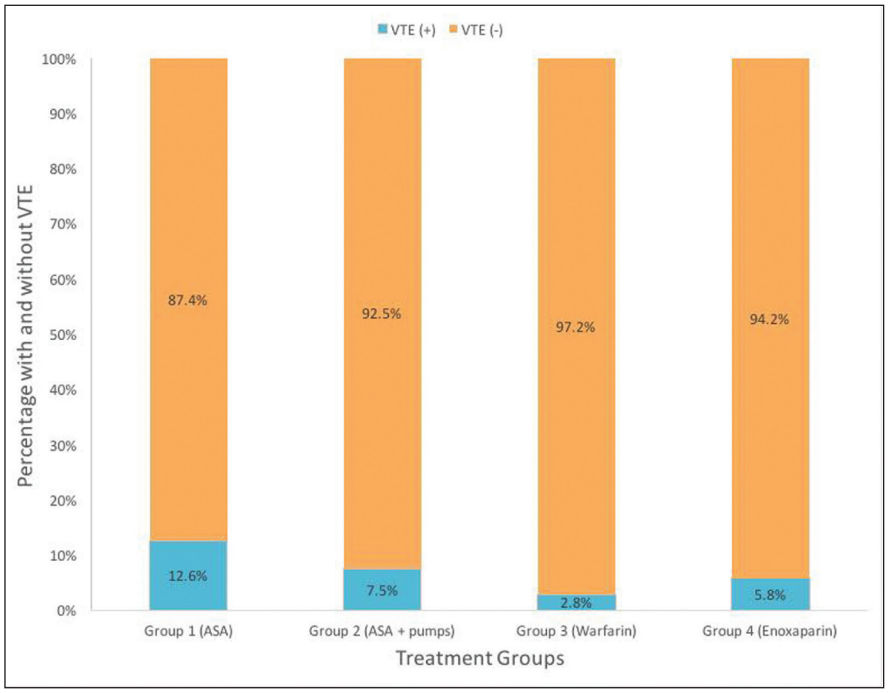

Figure 1: Rates of venous thromboembolism (VTE) in treatment groups. Abbreviation: ASA, aspirin.

have a VTE (DVT or PE) or require a transfusion. A 2-tailed *P*<.05 was considered statistically significant in all analyses.

Results

A total of 613 patients who underwent primary unilateral TJA met the study criteria. Of these, 62.2% were women (**Table 1**). Mean age at surgery was 67.6±10.6 years. Mean body mass index was 30.2±5.9 kg/m^2. There were 288 primary TKAs and 325 primary THAs. Surgery involved the left lower limb in 48.5% of the patients. Spinal anesthesia was used for 11.4% of the patients. Intraoperative tranexamic acid was used for 71.3% of the patients.

There were 119 patients in group 1 (aspirin alone), 40 patients in group 2 (aspirin plus pumps), 246 patients in group 3 (warfarin), and 208 patients in group 4 (enoxaparin). The overall 3-week symptomatic and asymptomatic DVT and symptomatic PE rates in the entire cohort were 5.7% (n=35) and 0.3% (n=2), respectively (**Figure 1**).

Thirty-five DVTs were reported, with 80% being infrapopliteal and 20% being suprapopliteal (**Figure 2**). Suprapopliteal DVTs were found in 20% of group 1 (aspirin only), 33% of group 2 (aspirin plus pumps), 0% of group 3 (warfarin), and 27% of group 4 (enoxaparin) patients, with 1 patient having PE in groups 3 and

4, respectively (*P*=.038). Both patients with PE had negative findings on 3-week duplex scans and 1 patient also had a negative finding on in-hospital duplex scan.

The authors found that VTE rate was significantly affected by the anticoagulant of choice (*P*<.01) and that the transfusion rate was significantly affected by the anticoagulant (*P*<.01), sex (*P*=.03), the use of tranexamic acid (*P*<.01), and the type of surgery (THA vs TKA, *P*<.01) (**Table 2**). Using a binomial logistic regression model for predicting VTE (**Table 3**), the authors found that, compared with aspirin alone, warfarin decreased the risk of VTE (odds ratio, 0.20; 95% confidence interval, 0.08-0.50; *P*<.01), whereas increasing age increased the risk of VTE (odds ratio, 1.04; 95% confidence interval, 1.00-1.07; *P*=.05). Type of anesthesia and body mass index were not significant predictors of VTE. Using a binomial logistic regression model for predicting postoperative blood transfusion (**Table 4**), the authors found that, compared with aspirin alone, warfarin increased the risk of transfusion (odds ratio, 8.51; 95% confidence interval, 1.08-67.27; *P*=.04), whereas intraoperative intravenous tranexamic acid decreased the risk of transfusion (odds ratio, 0.42; 95% confidence interval, 0.18-0.97; *P*=.04). Compared with THA, TKA was also less likely to require transfusion (odds ratio, 0.17; 95% confidence interval, 0.06-0.52; *P*<.01).

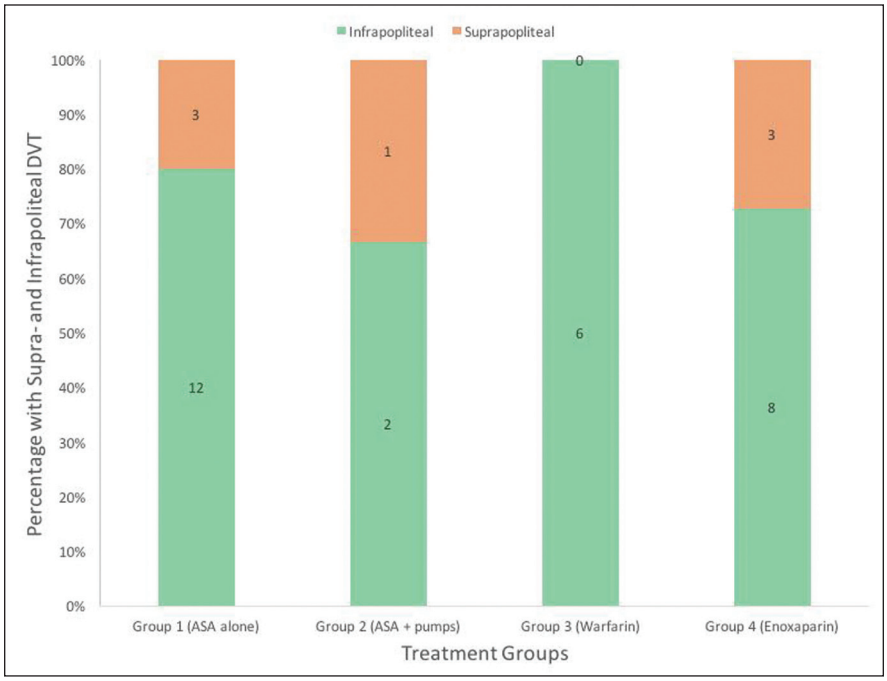

Figure 2: Rates of suprapopliteal and infrapopliteal deep venous thrombosis (DVT) in treatment groups. Abbreviation: ASA, aspirin.

Discussion

Aspirin has had rapid growth in popularity as a VTE prophylaxis agent. Evidence-based guidelines proposed by various associations inform the practice of anticoagulation. Because these guidelines are created independent of one another with differing methodology, their recommendations may differ.[3] For example, the American Academy of Orthopaedic Surgeons guidelines concluded that available data were inadequate to favor any commonly used prophylactic agent over others. The American Academy of Orthopaedic Surgeons recommended a risk-stratification approach with aggressive prophylaxis for high-risk patients with a history of previous VTE and less aggressive measures for patients with bleeding diathesis.[5,8,18] In contrast, according to the American College of Chest Physicians guidelines, aspirin was recognized as an effective agent for low- to standard-risk patients as a grade 1B recommendation.[4,8] Similarly, Surgical Care Improvement Project guidelines allow for aspirin monotherapy or intermittent pneumatic compression device monotherapy after arthroplasty.[19,20] In the United Kingdom, the National Institute for Health and Care Excellence guidelines recommend the use of both mechanical and pharmacological methods and do not regard aspirin or other antiplatelet agents as adequate for VTE prophylaxis.[8,21]

In the literature, various authors have successfully employed aspirin alone or in combination with other anticoagulants for symptomatic VTE prophylaxis following primary unicompartmental knee arthroplasty, TKA, THA, and revision arthroplasty.[6,7,9,22] In a review of 11,459 patients in the National Joint Registry for England and Wales, Ogonda et al[8] found that aspirin monotherapy was not associated with an increase in symptomatic DVT, PE, or death. In a review of 28,923 patients, Raphael et al[6] found that, compared with patients receiving warfarin, patients receiving aspirin had lower rates of symptomatic PE and symptomatic DVT, fewer wound problems, and shorter hospital stay. Hamilton et al[7] found that the combination of inpatient enoxaparin and outpatient aspirin was comparable to 2 weeks of enoxaparin followed by 2 weeks of aspirin.

This study showed that aspirin chemoprophylaxis alone was not as efficacious as warfarin and enoxaparin in preventing asymptomatic and symptomatic VTE found during routine postoperative surveillance with lower extremity ultrasound. These findings add to the growing body of literature suggesting that aspirin monotherapy may be inadequate and should be either augmented with outpatient mechanoprophylaxis via an intermittent pneumatic

Table 2

Rates of Venous Thromboembolism and Transfusion by Patient Characteristics

	Venous Thromboembolism			Transfusion		
	No.			No.		
Characteristic	Yes	No	*P*	Yes	No	*P*
Agent			<.01[a]			<.01[a]
Aspirin alone (n=119)	15 (12.6%)	104 (87.4%)		1 (0.8%)	118 (99.2%)	
Aspirin plus pumps (n=40)	3 (7.5%)	37 (92.5%)		3 (7.5%)	37 (92.5%)	
Warfarin (n=246)	7 (2.9%)	239 (97.1%)		21 (8.5%)	225 (91.5%)	
Enoxaparin (n=208)	12 (5.8%)	196 (94.2%)		2 (1.0%)	206 (99.0%)	
Sex			.49			.03[a]
Female (n=381)	21 (5.5%)	360 (94.5%)		22 (5.8%)	359 (94.2%)	
Male (n=232)	16 (6.9%)	216 (93.1%)		5 (2.2%)	227 (97.8%)	
Tranexamic acid			.54			<.01[a]
Yes (n=437)	28 (6.4%)	409 (93.6%)		13 (3.0%)	424 (97.0%)	
No (n=176)	9 (5.1%)	167 (94.9%)		14 (8.0%)	162 (92.0%)	
Side			.32			.72
Left (n=297)	15 (5.1%)	282 (94.9%)		14 (4.7%)	283 (95.3%)	
Right (n=316)	22 (7.0%)	294 (93.0%)		13 (4.1%)	303 (95.9%)	
Type of arthroplasty			.58			<.01[a]
Total hip (n=325)	18 (5.5%)	307 (94.5%)		23 (7.1%)	302 (92.9%)	
Total knee (n=288)	19 (6.6%)	269 (93.4%)		4 (1.4%)	284 (98.6%)	
Type of anesthesia			.14			.24
General (n=543)	30 (5.5%)	513 (94.5%)		22 (4.1%)	521 (95.9%)	
Spinal (n=70)	7 (10.0%)	63 (90.0%)		5 (7.1%)	65 (92.9%)	
Body mass index			.29			.49
>30.2 kg/m^2 (n=267)	13 (4.9%)	254 (95.1%)		10 (3.7%)	257 (96.3%)	
≤30.2 kg/m^2 (n=346)	24 (6.9%)	322 (93.1%)		17 (4.9%)	329 (95.1%)	
Age			.36			.72
<67.6 y (n=293)	15 (5.1%)	278 (94.9%)		12 (4.1%)	281 (95.9%)	
≥67.6 y (n=320)	22 (6.9%)	298 (93.1%)		15 (4.7%)	305 (95.3%)	

[a]*Significant* (P<*.05*).

compression device as part of multimodal prophylaxis or only implemented after targeted risk stratification.[3,10] Many authors have documented the effectiveness of combination therapy.[12-14,23,24] Gelfer et al[12] found that aspirin plus an intermittent pneumatic compression device led to significantly lower DVT rates than enoxaparin after unilateral THA or TKA. Vulcano et al[10] found that aspirin plus pneumatic compression after elective unicompartmental knee arthroplasty, TKA, or THA did not increase VTE rates compared with warfarin plus pneumatic compression. Other measures used in both arms in their study included autologous blood transfusion, regional anesthesia, and early mobilization. Westrich et al[14] found that aspirin plus an intermittent pneumatic compression device was not inferior to enoxaparin plus an intermittent pneumatic compression device following TKA. In a prospective, randomized study comparing aspirin monotherapy with aspirin plus an intermittent pneumatic compression device after TKA, Westrich and Sculco[13] found that DVT rates were higher in the group treated with aspirin monotherapy. They also noted inhomogeneity within the combination therapy group, with higher DVT rates among patients who used the compression device for shorter periods. They concluded that device compliance

and duration of use did contribute to its efficacy. Comerota et al[25] evaluated the use of an intermittent pneumatic compression device. They found that device failure was partially attributed to improper use, with patients removing the device because of discomfort and inconvenience. These difficulties were reflected in the 2012 American College of Chest Physicians guidelines, which recommended compliance for 18 hours per day for a minimum of 10 days using a device with a monitoring chip.[4,20] These guidelines also suggested dual prophylaxis with an antithrombotic agent and an intermittent pneumatic compression device during the inpatient stay. However, an even longer period of use of an intermittent pneumatic compression device may be beneficial. Snyder et al[26] found that, after TKA, aspirin plus extended-use compression devices for 6 weeks led to lower DVT rates and better patient satisfaction than compression devices used during the in-hospital stay only.[26]

Whereas warfarin seemed to provide greater protection against VTE compared with aspirin alone, the authors also found a greater transfusion requirement in patients receiving warfarin. Clinicians must keep this in mind when selecting warfarin, as hematoma formation and wound drainage are both significant risk factors for wound infection.[27,28] In contrast, Patel et al[28] found that patients receiving low-molecular-weight heparin had a longer period of wound drainage than those receiving warfarin or aspirin with an intermittent pneumatic compression device. They concluded that, for each day of prolonged wound drainage, the risk of wound infection after THA and TKA was increased by 42% and 29%, respectively.[28]

One of the strengths of this study was uniform duplex scan surveillance, with 100% compliance and follow-up, at the 3-week office visit performed by a blinded, clinic-based sonographer with extensive experience. From a research standpoint, this objective test permits detection and quantification of asymptomatic subclinical DVT and symptomatic DVT.

Table 3

Results of Regression Model for Venous Thromboembolism

Characteristic	Odds Ratio	95% Confidence Interval	*P*
Anticoagulant			
Aspirin only	Reference		
Aspirin plus pumps	0.66	0.18-2.46	.53
Warfarin	0.20	0.08-0.50	<.01[a]
Enoxaparin	0.45	0.20-1.01	.05
Covariate			
Age at surgery	1.04	1.00-1.07	.04[a]
Type of anesthesia	2.13	0.87-5.21	.10
Body mass index	0.96	0.90-1.03	.25

[a]*Significant (*P<*.05).*

Table 4

Results of Regression Model for Transfusion

Characteristic	Odds Ratio	95% Confidence Interval	*P*
Anticoagulant			
Aspirin only	Reference		
Aspirin plus pumps	8.36	0.80-87.75	.08
Warfarin	8.51	1.08-67.27	.04[a]
Enoxaparin	0.98	0.09-11.24	.99
Covariate			
Age at surgery	1.02	0.97-1.06	.50
Type of anesthesia	1.48	0.51-4.30	.47
Body mass index	0.95	0.88-1.03	.24
Use of tranexamic acid	0.42	0.18-0.97	.04[a]
Side of surgery	0.90	0.39-2.04	.79
Type of surgery	0.17	0.06-0.52	<.01[a]

[a]*Significant (*P<*.05).*

The authors realize that the American Academy of Orthopaedic Surgeons guidelines strongly recommend against routine duplex ultrasonography screening following elective joint arthroplasty because of the lack of a significant difference in PE rates when routine sonography was controlled against sham ultrasonography in one study[29] and prolonged prophylaxis in another.[5,30,31] Similarly, the American College of Chest Physicians guidelines caution against ultrasonography prior to discharge.[4] The authors add a caveat to these recommendations. The authors acknowledge that, in a clinical practice, avoiding routine ultrasonography will confine aggressive therapeutic anticoagulation, which is not without risk, to the management of symptomatic and persistent DVT while not overwhelming avail-

able resources. This is because, based on studies of the natural history of DVT, it is known that most thrombi are conceived intraoperatively on valve cusps in the calf, and half resolve within 72 hours of surgery.[32] Routine inpatient postoperative sonography will lead to needless treatment of thrombi that would otherwise have dissolved with routine mobilization and cessation of stasis. However, in a research setting, duplex sonography only when clinically indicated, relying on red flags such as pain, swelling, and warmth, for quantification of absolute DVT rates, including subclinical DVT, is apt to lead to under-detection because of significant symptom overlap in patients after arthroplasty.[10]

This study had a few limitations. First, group assignment depended on the anticoagulation protocol at the time. Second, an extended-use intermittent pneumatic compression device was not covered by most insurance plans. Many patients opted out of using an extended-use intermittent pneumatic compression device with aspirin, leading to the small number of patients in group 2. As a result, statistical analysis of this group was more challenging. Third, this study measured the incidence of asymptomatic and symptomatic VTE after unilateral TJA. One should not attempt to draw conclusions regarding the natural history of asymptomatic DVT based on these data. The optimal treatment of asymptomatic, isolated distal DVT remains a subject of debate.[20,33] Fourth, only 2 patients had symptomatic PE, and 2 treatment groups lacked this complication altogether. This low overall incidence limited the ability to draw meaningful conclusions from the data regarding PE.

Conclusion

This study reported a statistically significant increase in asymptomatic and symptomatic DVT after unilateral TJA when using aspirin alone compared with warfarin or low-molecular-weight heparin. The authors recommend using a risk-stratification approach to guide clinical decision-making and adopting multimodal measures.[10,18] Further study is needed comparing the results of newer anticoagulants, including direct factor Xa and direct thrombin inhibitors. The authors think that if aspirin is the VTE prophylactic drug of choice, clinicians should consider adding intermittent pneumatic compression device mechanoprophylaxis to further diminish the risk of VTE.

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