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Does Aspirin Have a Role in Venous Thromboembolism Prophylaxis in Total Knee Arthroplasty Patients?

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Abstract

The objectives of this study were to compare the risk of venous thromboembolism (VTE), bleeding, surgical site infection, and mortality in patients receiving aspirin or guideline-approved VTE prophylactic therapies (warfarin, low-molecular weight heparins, synthetic pentasaccharides) in total knee arthroplasty (TKA). We analyzed clinical and administrative data from 93,840 patients who underwent primary TKA at 307 U.S. hospitals over a 24 month period. 51,923 (55%) patients received warfarin, 37,198 (40%) received injectable agents, and 4,719 (5%) received aspirin. After adjustment for patient and hospital factors, patients who received aspirin VTEP had lower odds for thromboembolism compared to warfarin patients, but similar odds compared to injectable VTEP; there were no differences in risk of bleeding, infection or mortality after adjustment. Our results suggest that aspirin, when used in conjunction with other clinical care protocols, may be effective VTEP for certain TKA patients.

Introduction

Post-operative venous thromboembolic (VTE) complications such as deep-vein thrombosis (DVT) and pulmonary embolism (PE) are well known complications of lower extremity total joint arthroplasty (TJA) procedures. In addition, VTE prophylaxis (VTEP) is an element of widely-disseminated evidence-based clinical practice guidelines which have formed the basis for national initiatives to improve care quality.[1] Lower extremity TJA patients are at particularly high risk because of direct vessel trauma, venous stasis, and

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baseline patient characteristics, including age, immobility, and obesity, [2] making pharmacologic prophylaxis a mainstay of VTEP, beginning in the 1970's with the use of aspirin, unfractionated heparin (UFH) and warfarin.[3, 4] However, aspirin is not currently recommended as a first line VTEP agent by the American College of Chest Physicians (ACCP), because it has been reported to be less efficacious in preventing certain VTE complications (e.g., DVT), than warfarin and injectable VTEP strategies, such as low-molecular weight heparin (LMWH) or synthetic pentasaccharides (e.g., fondaparinux).[5, 6]

Many historical studies of pharmacologic VTEP in TJA, particularly those examining aspirin versus placebo[3, 4, 7], took place in an era when the perioperative care of TJA patients was far different than it is today. Since those original studies, many changes have occurred in the perioperative management of TJA patients, including the introduction of multi-disciplinary clinical care pathways, multi-modal pain management protocols, increased use of regional anesthesia, modifications in surgical technique, aggressive early ambulation and physical therapy, and early discharge to home.[8-17] As a result, the peri-operative risk of VTE is likely to be lower than it was when aspirin was originally studied as a pharmacologic VTEP agent, and the risk-benefit balance of VTEP regimens may have changed. That is, the relative risk reduction in VTE associated with certain pharmacologic agents, such as warfarin, LMWH, and synthetic pentasaccharides, may be offset by complications which increase risk for subsequent adverse events such as post-operative wound hematoma, surgical site infection, and need for reoperation. These complications have been reported to be more common with warfarin and injectable VTEP agents than with aspirin,[18-20] which has prompted some orthopaedic surgeons to advocate the use of aspirin for VTEP following TKA.[21, 22] Furthermore, ACCP guideline-approved VTEP may be less effective in actual clinical practice than in the randomized-trial setting, due to sub-therapeutic dosing or inappropriate dose timing. [23, 24]

This debate has prompted the American Academy of Orthopaedic Surgeons (AAOS) to develop evidenced-based clinical practice guidelines for prevention of symptomatic pulmonary embolism (PE) (rather than DVT) following TJA, which endorse the use of aspirin for patients who are at standard risk of PE and standard or high risk of post-operative bleeding. [25] This recommendation was based in part on concerns about changes in the risk-benefit ratio associated with guideline-approved VTEP, including a higher risk of bleeding complications with guideline approved VTEP agents.[19, 26], as well as data from a number of single-center studies reporting favorable outcomes with aspirin VTEP.[21, 22, 27] However, the level of evidence supporting endorsement of aspirin VTEP is poor relative to guideline-approved therapies, and aspirin is not currently endorsed by national quality reporting initiatives. [1, 28]

As a result, there is a growing need to understand the safety and effectiveness of aspirin, warfarin and injectable VTEP in the current practice era, particularly when use of these agents is being publicly reported as a quality measure and in some cases even linked to compensation. To examine these questions, we performed a retrospective cohort study of administrative data from a large national sample of patients undergoing primary total knee arthroplasty (TKA). Using these data, we compared the risk of venous thromboembolism,

surgical site bleeding, surgical site infection, and mortality between patients who received aspirin, warfarin, or injectable (LMWH and fondaparinux) VTEP following TKA.

Methods

Sites and subjects

Data were collected from 307 hospitals that participate in Perspective (Premier Inc., Charlotte, North Carolina), a proprietary database developed for measuring quality and health care utilization in hospitalized patients. In addition to the clinical and demographic information available in the standard hospital discharge file, Perspective contains a date-stamped log of all items and services charged to the patient, thereby providing the opportunity to measure the performance of specific care processes, including drug administration. Perspective participants represent all regions of the United States, are predominantly small to mid-size non-teaching facilities, and serve a largely urban patient population.

Patients were included in our analysis if they were admitted between October, 2003 and September, 2005, were 18 years of age or older, and had primary total knee arthroplasty as their principal procedure during their hospitalization as defined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure code 81.54. We excluded patients who had no charges for any VTEP treatments (n=15,930), and those who had charges for VTE treatment in formulations representing therapeutic rather than prophylactic anticoagulation (e.g., Enoxaparin 70mg SC bid vs. Enoxaparin 30mg SC bid, n=3,948). Our institutional review board reviewed and approved our study protocol.

Data

In addition to patient age, gender, race, primary payer, and principal diagnosis on admission, we classified co-morbidities using the method of Elixhauser.[29] To improve our ability to risk adjust venous thromboembolism outcomes, we also generated a VTE risk score based on selecting and weighting clinical criteria used in the risk assessment method of Caprini, et. al.[30] Data regarding in-hospital deaths and readmission to the index hospital within 30 days were obtained from the Perspective discharge file. In addition, Perspective data included the hospital's bed size, teaching status, geographic region, and whether the institution served an urban or rural population.

Definition of VTE prevention groups

We selected venous thromboembolism prevention practices for comparison based on those recommended in the most recently published American College of Chest Physician (ACCP) guidelines.[28] Using itemized charges for each patient's hospitalization, we determined whether or not patients received aspirin, warfarin, low molecular-weight heparins (LMWH's) such as enoxaparin, dalteparin, or tinzaparin (at prophylactic doses; patients who were given therapeutic doses were excluded), or Fondaparinux on the day of or day after surgery. We then grouped patients into three separate categories: 1) patients who received

aspirin and no other VTEP agent; 2) patients who received warfarin VTEP; and, 3) patients who received VTEP with injectable agents (e.g. LMWH's and Fondaparinux).

Definition of outcomes

We defined post-operative complications, including venous thromboembolism (any thromboembolic event, including proximal or distal deep vein thrombosis (DVT) as well as pulmonary embolism (PE)), proximal DVT and PE only, surgical site bleeding, and surgical site infection using principal and secondary ICD-9CM diagnosis codes recorded during the index admission as well as principal diagnosis associated with any readmissions that occurred within thirty days of discharge.[31] [32] Mortality and readmission were determined using flags in administrative data. A detailed list of ICD-9CM codes used to define our key outcomes is provided in Technical Appendix 1.

Analysis

We first characterized patients using univariable methods to define variable distributions, and then compared the three groups (aspirin, warfarin, and injectable VTEP strategies) using bivariable statistics. We then developed a series of multivariable models to assess the independent association between the three VTEP strategies and the risk of complications (venous thromboembolism, surgical site bleeding, and surgical site infection), or death. Alternating logistic regression models (SAS PROC GENMOD) were used to account for the clustering of patients within physicians and physicians within hospitals.[33] Variables were selected for inclusion in models based on an association with the outcome at a significance level of p=0.05 or lower, to maintain face validity, or because of observed confounding with other variables.

Because we recognized the potential threat of allocation bias in determining which patients received aspirin, warfarin, or injectable VTEP, we used a propensity score in all models. Our a priori hypothesis was that the major bias influencing our results would be that driving differences between choosing aspirin VTEP over guideline-approved therapies (e.g. warfarin and injectable agents). As a result, our propensity score was constructed by dichotomizing our VTEP groups into aspirin vs. guideline-accepted therapies, and then selecting covariates for inclusion in the propensity score model if they had a statistical association with receipt of aspirin of p = 0.20 or lower. This propensity score model had excellent discriminative power, with c-statistic of 0.725. This continuous likelihood score was then included in all core multivariable models as a covariate intended to adjust for allocation bias.

We recognized that there were additional biases which may have driven selection of patients for each of our three VTEP strategies, and that traditional dichotomous propensity score models created in logistic models would not adequately adjust for these biases in a three-cohort study. As a result, in secondary analyses, we also constructed 3 separate propensity scores including assignment to injectable VTEP vs. other VTEP, assignment to warfarin vs. other VTEP, and assignment to aspirin vs. other VTEP; these scores, in linear combination, account for the three separate directions of treatment bias. However, these individual models had lower discriminative power, and inclusion of them in our core multivariable models did not substantially or directionally alter our results. As a result, our primary analyses

employed the aspirin vs. other propensity score adjustment described above. All analyses were carried out using the Statistical Analysis System (version 9.1, SAS Institute, Inc. Cary, NC).

Results

Patient and procedure characteristics (Tables 1-4)

93,840 patients aged 18 or older who underwent primary TKA during our study time period were included in the analysis. Aspirin was the sole VTEP agent used in 4719 patients (5.0%), injectable agents in 37,190 (39.6%), and warfarin in 51,923 (55.3%).

Aspirin was used at 147 of the 307 hospitals (48%) in our dataset; a total 63,387 patients in our cohort (67%) received care at these sites. In hospitals where aspirin was used, the mean proportion of patients receiving aspirin as a sole VTEP agent was less than 5% overall in 103 (70% of centers where aspirin was used), 5 to 20% of patients in 22 (15% of hospitals where aspirin was used), and 20% or greater in the remaining 15% of hospitals where aspirin was used; 3 hospitals administered aspirin VTEP to 75% or more of patients. There was significant geographic variation in the use of aspirin VTEP.

Due to the large size of the dataset, small absolute differences between groups produced strong statistical significance, even if these differences may not be clinically significant. The mean age of the aspirin patients was similar to that of the LMWH/fondaparinux group (66.4 years vs. 66.5 years, $p = 0.5$), but aspirin patients were younger than warfarin patients by 0.9 years ($p<0.001$). Aspirin patients had a lower baseline venous thromboembolism risk score than warfarin or LMWH/fondaparinux patients ($p<0.001$), and aspirin patients also had slightly lower APR DRG severity of illness scores (indicating fewer medical co-morbidities) than LMWH/fondaparinux ($p = 0.001$), but similar to warfarin patients ($p=0.69$). Patients who received aspirin were less likely to have hypertension, chronic iron-deficiency anemia, and diabetes without chronic complications, but more likely to be obese than patients who received other VTEP agents. Aspirin patients were much less likely to have a charge for sequential compression devices in the perioperative time period (38% aspirin group vs. 48% LMWH, vs. 55% warfarin, all $p<0.001$). Patients who received aspirin had a shorter length of stay, and were more likely to be discharged home (versus to an extended care facility) compared to LMWH/fondaparinux or warfarin patients (30% vs. 23% vs. 21%, $p<0.0001$ for all comparisons).

Unadjusted patient outcomes (Table 5)

Among patients treated with aspirin, 110 (2.3%) had any DVT or PE, compared to 1152 (3.1%) of LMWH/fondaparinux patients, and 2009 (4.0%) of warfarin patients ($p=0.0037$ for aspirin vs. LMWH/fondaparinux, $p<0.001$ for aspirin vs. warfarin). Unadjusted rates of proximal DVT or PE were also lower for aspirin, as were rates of bleeding at the surgical site, although the number of events was very low. 30-day mortality rates were extremely low (<0.25%), and did not differ significantly between patient groups. There were no unadjusted differences in surgical site infection between VTEP groups.

Adjusted patient outcomes (Tables 6a and 6b)

Compared to aspirin patients, unadjusted odds ratios for and DVT or PE were significantly higher in the warfarin group (1.69 times higher odds, 95% CI 1.39-2.05), and the LMWH/ Fondaparinux group (1.34 times higher odds, 95% CI 1.10-1.63). After adjusting for patient factors, site characteristics, our propensity score, and including accounting for the hierarchical nature of our data, the magnitude of the differences in risk of VTE between the aspirin and warfarin groups decreased, and for the LMWH group was no longer significant. Similar trends were seen with proximal DVT/PE outcomes. Although there was a markedly higher unadjusted odds ratio for surgical site bleeding with VTEP agents other than aspirin, this difference was not significant after adjustment. There were no differences in unadjusted or adjusted odds ratios for surgical site infection or mortality between patients who received aspirin or other VTEP agents.

Secondary analyses

Because use of aspirin VTEP was not uniform across sites in our study, we performed subset analyses within only the group of hospitals where aspirin VTEP was employed. At these sites, warfarin continued to have higher odds for all VTE, similar to that observed in the overall cohort (1.59 higher, 95% CI 1.20, 2.12), and there were no statistical differences in adjusted odds ratios among injectable VTEP-treated patients. Analyses of VTEP for other key outcomes in the aspirin-site subset were also not different than our overall analyses. We also performed analyses where we matched patients based on their propensity for aspirin vs. guideline-approved treatments (n = 8696 patients, 50% of which received aspirin VTEP, and 50% received guideline-approved treatment); results from these analyses were generally similar to our core analyses, although with wider confidence intervals. Analyses within the middle 50% of propensity score were also similar, as were analyses employing instrumental variables as an approach to accounting for hospital-level treatment biases.

Discussion

In this large observational cohort study, use of aspirin VTEP was associated with a lower adjusted risk for all venous thromboembolic events compared to warfarin, and similar adjusted VTE risk compared to injectable VTEP agents. Aspirin was also associated with similar adjusted complication rates (e.g., surgical site bleeding and infection) and mortality to other VTEP groups. Aspirin VTEP was used in patients who on average had slightly fewer baseline medical co-morbidities and a lower baseline risk for VTE, and who received care in hospitals that had a shorter average length of stay and more often discharged patients directly home after their surgery, suggesting differences in peri-operative care likely contributed to the variations in patient outcomes that we observed.

Previous investigators have studied the use of aspirin for the prevention of deep vein thrombosis and pulmonary embolism following hip and knee arthroplasty procedures.[3, 5, 7, 28, 34] In 1977, Harris and Salzman[3]reported a significant reduction in thromboembolism in men (but not women) receiving aspirin vs. placebo following total hip arthroplasty. In 1980, McKenna and Galante[34] reported that high doses of aspirin and an intermittent low-pressure pneumatic compression device were effective, even in women, in

preventing thromboembolic disease following total knee arthroplasty. In 2000, an RCT was reported in *The* Lancet[7]comparing low dose aspirin to placebo for VTE prophylaxis in hip fracture and elective arthroplasty patients. The investigators reported a 36% reduction in DVT and a 58% reduction in PE among patients who received aspirin vs. placebo. A higher rate of postoperative transfusion was also reported among patients who received aspirin. However, in a subsequent meta-analysis of RCT's comparing VTEP agents in elective TKA with mandatory screening for DVT using venography, Brookenthal and Freedman[5]reported that aspirin was no better than placebo in preventing DVT in TKA patients. Similarly, the ACCP has specifically recommended against the use of aspirin for VTE prophylaxis following elective hip and knee replacement procedures, citing lower efficacy than other VTEP agents, including warfarin, LMWH, and synthetic pentasaccharides.[28]

Although our data do not support the idea that aspirin is pharmacologically superior or more efficacious than guideline-approved VTEP, our results do suggest that aspirin may have a role in multi-modal VTE prophylaxis for TKA patients. There are several possible explanations for the difference between our observations and those of previous investigators who have reported higher rates of thromboembolic complications with aspirin VTEP when compared with other, guideline-approved strategies in randomized, controlled trials.[5, 6, 28] First, since VTE prophylaxis following TKA is rarely administered under the idealized conditions of an RCT, an observational cohort study provides a better means of evaluating the true clinical *effectiveness* of a treatment strategy, which is the improvement achieved by an intervention in ‘real world’ clinical practice, as opposed to it's *efficacy*, which is the degree to which an intervention improves health under idealized conditions. Therefore, it is possible, and even probable, that guideline-approved VTEP is less effective outside of the RCT setting, due to sub-therapeutic dosing and variable dose timing. Previous investigators have shown that variation in warfarin dose-timing and dose-response produce variable degrees of anticoagulation despite similar dosing.[23] Also, due to concerns about bleeding risk, orthopaedic surgeons rarely give warfarin in sufficient doses to maintain a goal INR of 2.0-3.0, which is the dose used in RCT's comparing warfarin to aspirin. Furthermore, LMWH and Fondaparinux may have been given outside the recommended dosing schedule and/or dosed inappropriately for a patient's weight in certain cases, which may influence it's effectiveness in preventing VTE complications in actual clinical practice when compared to its efficacy in an RCT.

It is also possible that each VTEP agent is an indicator of a specific care pattern present at a site or in a surgeon's practice. For example, it may take longer for warfarin to become therapeutic, thereby increasing length of stay or making discharge home more challenging. Use of aspirin VTEP may be a marker of a multi-modal care pathway which, as our data suggest, also involves a shorter hospital stay and more frequent discharge directly to home. Our findings are consistent with the description of care patterns in a number of limited observational studies which suggest a multi-modal pathway that includes aspirin, pre-emptive analgesia, regional anesthesia, early aggressive post-operative mobilization, and rapid return to function may be associated with a lower risk of VTE. Berend and Lombardi[21] have reported a very low incidence of VTE complications with the use of a

multi-modal VTEP protocol which includes aspirin. Similarly, Lotke and Lonner have reported a comparable risk of VTE between aspirin and warfarin using a multi-modal VTEP program in TJA patients.[35]

However, unlike reports from Burnett et al[19] and Ozdemir et al[26] describing a higher risk of bleeding associated with guideline-approved VTEP, our results do not support the widely held belief that aspirin use is associated with lower risk for bleeding or surgical site infections after adjusting for relevant patient, hospital, and treatment factors. This may be due to sub-therapeutic dosing and/or inappropriate dose timing of warfarin and injectable agents, as described above. In addition, our observation that the risk for VTE was similar after adjustment for confounders and accounting for the hierarchical nature of our data suggest reporting bias in previous reports, as well as the idea that patient selection, surgical technique, and modern multi-modal peri-operative care pathways may be as important as aspirin itself in reducing risk for VTE and bleeding. While we cannot discern which factors are most important from our data, patient risk stratification is a key element of the AAOS evidence based clinical practice guidelines for prevention of symptomatic PE.[25]

Because we used administrative data, our outcomes likely represent clinically apparent, documented events which occurred during the first 30 days post-operatively. This is especially important for our VTE outcomes because this implies that thrombosis or pulmonary embolism had to have been documented as being diagnosed during hospitalization or at readmission, rather than only being detected during routine screening ultrasonography. However, it should be noted that the rate of documented DVT in our study was 2-4%, which is similar to the rate of DVT reported in other large, prospective RCT's and clinical cohort studies[6, 28] where venography, ultrasound, and other diagnostic modalities were used to detect asymptomatic DVT. These findings, along with the fact that the rate of duplex ultrasonography in our data was low and similar across VTEP groups, suggest that detection bias likely played an insignificant role in our study. Our bleeding complication rates are based on codes which would have been recorded only if clinically apparent, which have been shown by previous investigators to be valid using administrative data.[36] Similarly, previous work suggests that administrative data are an insensitive but specific method to detect surgical site infections.[37] As a result, while the overall rate of adverse events in our study may have been slightly lower because of our reliance on administrative data, the adverse events detected were likely clinically important and relevant to patient care. Furthermore, any detection bias would be expected to be similar among treatment groups. Our data also confirm that mortality following TKA is an extremely rare event, making it difficult to determine differences in mortality ascribable to VTEP strategies with any precision, even in our large dataset. This observation reinforces the idea that more sensitive measures of outcome (e.g. complication rates, functional outcomes) are more relevant than mortality in comparing the effectiveness of VTEP strategies in TKA patients.

Our study has several other limitations. As with any study that uses large administrative claim databases, the accuracy of the data is dependent on proper documentation. Furthermore, we were unable to measure certain clinical factors that are known to influence VTE complications, including the use of regional anaesthesia, operative time, and smoking history. However, the large number of patient records reviewed, and the inclusion of a broad

range of primary and secondary diagnosis and procedure codes from a large number of institutions serve to mitigate these limitations. Secondly, our study is limited to inpatient hospital admissions and readmissions to the index hospital within 30 days of the index procedure, and therefore does not include VTE events that are diagnosed and treated in the outpatient setting. However, this bias is likely to be similar across treatment groups, and we did not observe a difference in use of ultrasonography after surgery in any treatment group. Furthermore, as noted above, our observed rates of VTE complications (2-4%) are consistent with previous reports of VTE in TKA patients receiving chemoprophylaxis[28], which suggests detection bias did not play a significant role in our study. Finally, our study is an observational study, not an interventional trial, and thus although we adjusted for a large number of patient, hospital and physician factors, the decision to use aspirin as a VTEP agent may be associated with other unmeasured factors that were not accounted for in our models.

VTE prophylaxis remains an important clinical practice in TKA, and controversies about the appropriate use of pharmacologic agents and how they fit into multi-modal VTEP protocols will have important clinical and policy implications. Hospital and payer-driven quality reporting initiatives currently include public reporting of compliance with guideline-approved VTEP strategies following TKA, which is evidence that clinicians and policy makers agree that VTE prophylaxis is both appropriate and necessary to reduce the risk of preventable VTE complications following TKA. However, clinicians continue to have concerns about the untoward effects associated with guideline-approved VTEP therapies, including the risk of surgical site bleeding and infection. [19, 26]

Our findings suggest that aspirin, when used in conjunction with other modern clinical care protocols, may be effective VTEP for certain TKA patients. However, given the observational, retrospective design of our study, our conclusions should be considered hypothesis generating, rather than conclusive evidence of the comparative safety and efficacy of aspirin for use in VTE prophylaxis following TKA. Our results, along with results from other observational studies, provide justification for future trials of multi-modal VTEP strategies involving aspirin and other chemoprophylactic agents in TKA, and evaluation of the relative risks and benefits of these strategies.

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Appendix

Technical Appendix 1

ICD-9-CM diagnosis codes used to define outcomes

Outcome	ICD-9CM Diagnosis Codes
Any DVT	453.40, 453.41, 453.42, 453.8, 453.9, 671.9, V12.51, 415.1, 415.11, 415.19

Outcome	ICD-9CM Diagnosis Codes
PE or proximal DVT	V12.51, 415.1, 415.11, 415.19 453.41
Surgical site bleeding	998.1, 998.11, 998.12, 719.10, 719.16, 719.17
Wound infection	891.0, 891.1, 891.2, 894.0, 894.1, 894.2, 998.6, 998.83, 998.3, 998.31, 998.32, 998.13, 998.5, 998.59, 998.89, 998.51, 686.9, 682.0-682.6, 996.66, V43.60-V43.69

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Table 1

Demographic characteristics of patients and sites according to treatment group (N=93,840)

Characteristic	Aspirin (n=4719)	Injectable VTEP (n=37198)	Warfarin (n=51923)
Patient age (Mean, SD)	66.4 (10.7)	66.5 (10.5)	67.3 (10.4)
Male (n, %)	1679 (36%)	12505 (34%)	18085 (35%)
Race (n, %)			
Black	416 (9%)	3259 (9%)	3471 (7%)
Hispanic	56 (1%)	1076 (3%)	921 (2%)
White	3543 (75%)	28502 (77%)	36476 (70%)
Other	704 (15%)	4361 (12%)	11055 (21%)
Primary payer (n, %)			
Uninsured	7 (0.2%)	29 (0.4%)	133 (0.3%)
Indemnity	368 (8%)	3247 (9%)	5035 (10%)
Capitated	25 (0.5%)	493 (1%)	397 (0.8%)
Managed care	1442 (31%)	9979 (27%)	13441 (26%)
Medicaid	92 (2%)	939 (3%)	915 (2%)
Medicare	2750 (58%)	22113 (59%)	31436 (61%)
Other	35 (0.7%)	298 (0.8%)	566 (1%)
Area			
Midwest	1416 (30%)	8100 (22%)	12556 (24%)
Northeast	158 (3%)	3263 (9%)	10171 (20%)
South	2345 (50%)	19798 (53%)	22815 (44%)
West	800 (17%)	6037 (16%)	6381 (12%)
Number of beds			
Mean (SD)	399 (192)	455 (261)	426 (217)

Table 2

Clinical characteristics of patients according to treatment group (N=93,840)

Characteristic	Aspirin (n=4719)	Injectable VTEP (n=37198)	Warfarin (n=51923)
APR DRG severity (n, %)			
1	2520 (53%)	18866 (51%)	28120 (54%)
2	1986 (42%)	16298 (44%)	21408 (41%)
3	197 (4%)	1878 (5%)	2232 (4%)
4	16 (0.3%)	156 (0.4%)	163 (0.3%)
APR DRG risk of mortality (n, %)			
1	4035 (86%)	31291 (84%)	43655 (84%)
2	589 (12%)	5130 (14%)	7283 (14%)
3	73 (2%)	632 (2%)	790 (2%)
4	22 (0.5%)	145 (0.4%)	195 (0.4%)
VTE risk score			
4	33 (0.7%)	274 (0.7%)	263 (0.5%)
5	927 (20%)	7504 (20%)	9880 (19%)
6	1541 (33%)	11650 (31%)	15767 (30%)
7	1821 (39%)	14501 (39%)	21059 (41%)
8	338 (7%)	2523 (7%)	3661 (7%)
≥9	59 (1%)	746 (2%)	1293 (3%)

Table 3

Prevalence of co-morbid conditions of patients according to treatment group (N= 93,840)

Characteristic	Aspirin (n=4719)	Injectable VTEP (n=37198)	Warfarin (n=51923)
Individual comorbidities (n, %)			
Congestive heart failure	125 (3%)	981 (3%)	1407 (3%)
Valvular disease	143 (3%)	1221 (3%)	2188 (4%)
Peripheral vascular disease	85 (2%)	616 (2%)	947 (2%)
Hypertension	2965 (63%)	24213 (65%)	33727 (65%)
Paralysis	14 (0.3%)	114 (0.3%)	151 (0.3%)
Chronic pulmonary disease	574 (12%)	5018 (13%)	6442 (12%)
Diabetes	754 (16%)	6561 (18%)	8839 (17%)
Hypothyroidism	681 (14%)	5207 (14%)	7435 (14%)
Liver Disease	15 (0.3%)	208 (0.6%)	244 (0.5%)
Metastatic Cancer	3 (0.1%)	23 (0.06%)	29 (0.06%)
Solid tumor w/o metastatis	12 (0.3%)	157 (0.4%)	263 (0.5%)
Collagen vascular disorders	128 (3%)	1271 (3%)	1648 (3%)
Coagulopthy	38 (0.8%)	435 (1%)	489 (0.9%)
Obesity	833 (18%)	5105 (14%)	6454 (12%)
Chronic blood loss anemia	64 (1%)	608 (2%)	574 (1%)
Deficiency anemia	456 (10%)	5056 (14%)	5824 (11%)
Depression	386 (8%)	3399 (9%)	4489 (9%)
Smoking	303 (6%)	2342 (6%)	2524 (5%)
Atrial fibrillation	138 (3%)	1152 (3%)	3122 (3%)

Table 4

Procedural characteristics according to treatment group (N= 93,840)

Characteristic	Aspirin (n=4719)	Injectable VTEP (n=37198)	Warfarin (n=51923)
Ultrasound or venogram anytime after operative day	1 (0.02%)	73 (0.20%)	28 (0.05%)
Use of pneumatic compression devices on operative or first postoperative days	1795 (38%)	17756 (48%)	28757 (55%)
Any ICU charges (n, %)	84 (2%)	635 (2%)	809 (2%)
Median Length of stay (IQR)	3 (3,4)	4 (3, 4)	3 (3, 4)
Discharge status (n, %)			
To home	1397 (30%)	8374 (23%)	10796 (21%)
Transfer	43 (0.9%)	680 (2%)	494 (1%)
SNF	913 (19%)	10147 (27%)	13376 (26%)
Home Health Care	1686 (36%)	10949 (29%)	17119 (33%)
Dead	7 (0.2%)	35 (0.1%)	45 (0.1%)
Hospice	2 (0.04%)	13 (0.03%)	3 (0.01%)
Rehab	667 (14%)	6902 (19%)	9873 (19%)
Other	4 (0.1%)	98 (0.3%)	217 (0.4%)

Table 5

Unadjusted rates of postoperative adverse events

Outcome	Aspirin (n=4719)	Injectable VTEP (n=37198)	Warfarin (n=51923)
Any thromboembolism	110* (2.3%)	1152 (3.1%)	2009 (4%)
Proximal deep vein thrombosis or pulmonary embolism	77* (1.6%)	901 (2.4%)	1632 (3%)
Wound Infection	559 (12%)	4366 (12%)	6349 (12%)
Bleeding related to surgical site	30* (0.6%)	459 (1%)	548 (1%)
Mortality	9 (0.2%)	46 (0.1%)	54 (0.1%)

** <=0.02 for comparison with aspirin

* $p < 0.01$ for all comparisons

Table 6

Unadjusted and adjusted odds for outcome according to VTE preventive strategy

	Any DVT or PE (n=3271)		Proximal DVT or PE (n=2610)		Surgical Site Bleeding (n=1037)	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Aspirin	Referent	Referent	Referent	Referent	Referent	Referent
Injectable VTEP	1.34* (1.10, 1.63)	1.03 (0.76, 1.39)	1.50* (1.18, 1.89)	0.99 (0.76, 1.28)	1.95* (1.35, 2.83)	1.11 (0.77, 1.60)
Warfarin	1.69* (1.39,2.05)	1.36* (1.02, 1.82)	1.96* (1.55, 2.46)	1.34* (1.05, 1.70)	1.67* (1.15, 2.41)	0.97 (0.65, 1.47)

Table 6b

Unadjusted and adjusted odds for outcome according to VTE preventive strategy

	Surgical Site Infection (n=1037)		Mortality (n=109)	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Aspirin	Referent	Referent	Referent	Referent
Injectable VTEP	0.99 (0.90, 1.09)	1.08 (0.95. 1.24)	0.65 (0.32, 1.32)	0.63 (0.30, 1.34)
Warfarin	1.04 (0.95, 1.14)	1.10 (0.96, 1.26)	0.54 (0.27, 1.10)	0.54 (0.25, 1.15)