Effect of Comorbidity Burden on the Risk of Venous Thromboembolic Events After Total Knee Arthroplasty

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Abstract

Background: Venous thromboembolic events (VTEs) are common after total knee arthroplasty (TKA). The rate of VTEs has improved with early mobilization, mechanical prophylaxis, and appropriate chemoprophylaxis. The aim of this study was to analyze the contribution of medical comorbidities to the risk of VTE after TKA **Method:** Medicare claims from 2005 to 2014 were queried. International Classification of Diseases, Ninth revision (ICD-9), and Current Procedural Terminology codes were used to identify the diagnoses, procedures, and complications. 157,200 primary TKAs were age, sex, and Elixhauser Comorbidity Index (ECI) matched with 157,200 osteoarthritis controls. First instances of deep venous thrombosis (DVT) and pulmonary embolism were tracked at 90 days and 2 years. Odds ratios (ORs), confidence intervals, and *P*-values (p) were calculated and used to investigate the contribution of comorbidities. **Results:** 90 days after TKA or OA diagnosis, comorbidities were associated with 45% of the DVT risk, 38% of the PE risk. 1 in 92 patients would be expected to be diagnosed with VTE after TKA and 1 in 136 patients after only the diagnosis of osteoarthritis. After 90 days, medical comorbidities were associated with 70% of the DVT risk, 68% of the PE risk. **Conclusion:** Nearly 50% of DVTs and 40% of PEs within 90 days of TKA may be related to the baseline health of OA patients. Venous thromboembolic events after TKA are a "never" event according to Center of Medicare and services that appropriate VTE prophylaxis likely cannot be neutralized.

Keywords

knee, arthroplasty, venous thromboembolic events, deep vein thrombosis, pulmonary embolism, thromboembolism

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE), together referred to as Venous thromboembolic events (VTEs), remain common complications after major orthopedic surgery. Venous thromboembolic events are associated with significant morbidity and mortality after total knee arthroplasty (TKA).[1,2] The incidence of fatal PE after a TKA has been reported to be .15%.[3] Given the seriousness of this potentially preventable complication, venous thromboembolism has been considered a "never" event by the Center of Medicare and services (CMS) who began financially penalizing institutions in 2009.[4–6] The baseline prevalence of a VTE remains controversial, but overall has declined in association with implementation of early mobilization mechanical prophylaxis, and routine chemoprophylaxis.[7–13]

Although major surgery is an independent risk factor for VTE, we must also consider the other characteristics that

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Table 1. Demographic Characteristics of TKA vs OA (No TKA) Patients.

Variable	TKA	No TKA	OR (95% CI)	P-value
Age (years)				
<65	24,081 (15%)	24,081 (15%)	1.00 (.98–1.02)	1.000
65–69	38,200 (24%)	38,200 (24%)	1.00 (.98–1.02)	1.000
70–74	31,361 (20%)	31,361 (20%)	1.00 (.98–1.02)	1.000
75–79	29,003 (18%)	29,003 (18%)	1.00 (.98–1.02)	1.000
80–84	23,618 (15%)	23,618 (15%)	1.00 (.98–1.02)	1.000
>85	10,937 (7%)	10,937 (7%)	1.00 (.97–1.03)	1.000
Unknown	21 (<.1%)	21 (<.1%)	.95 (.52–1.74)	.879
Gender				
Female	104,187 (66%)	104,187 (66%)	1.00 (.99–1.01)	1.000
Male	53,013 (34%)	53,013 (34%)	1.00 (.99–1.01)	1.000

independently contribute (eg, body mass index, hospitalization, trauma/fracture, active cancer, transvenous pacemaker, varicose veins, urinary tract infection, neurologic disease with leg paresis).[14] Patients diagnosed with osteoarthritis tend to have more comorbid medical conditions than those without osteoarthritis.[15] In end-stage osteoarthritis patients, advanced age as well as pain is associated with an increased risk of a VTE.[16,17] Asymptomatic preoperative DVTs may even be present in 8–17% of patients prior to TKA.[8,9] Little is known about the baseline contribution of a patient's health to the risk of a VTE after a TKA. We hypothesize that medical comorbidities are a potential factor in 50% or more of the VTEs that occur postoperatively in patients diagnosed with OA that undergo TKA.

The purpose of this study was to quantify the effect of patient comorbidities on the incidence of DVT and PE after TKA by comparing the VTE rate after TKA to a matched cohort of patients newly diagnosed with knee osteoarthritis that have not undergone arthroplasty.

Methods

PearlDiver Technologies (West Conshohocken, Pennsylvania, United States) was used to retrospectively query the Medicare Standard Analytic Files database containing 100% of inpatient and outpatient facility claims. Only data from 2005 to 2014 was available for analysis. This search identified 314,400 patients who underwent primary TKA patients using International Classification of Diseases, Ninth Revision (ICD-9) procedural code 81.54, and Current Procedural Terminology (CPT) code 27447. We then further stratified patients to include only those who had a single TKA performed during this time frame to ensure appropriate tracking of postoperative VTEs from the date of index surgery. Next, we selected only patients who had their index TKA performed between 2005 and 2012, allowing for a minimum of 2 years of follow-up data

$$\frac{(TKA\ VTE\ incidence\ \% - OA\ VTE\ Incidence\ \%)}{TKA\ VTE\ incidence\ \%} = \%\ Association\ with\ TKA$$

$$\%\ Association\ with\ TKA - 100\% = \%\ Association\ with\ comorbidities$$

Figure 1. Equation used to assign percent incidence associated with total knee arthroplasty (TKA) and patient comorbidities.

for each patient. This narrowed the cohort to 157,200 patients. Demographic information for this group was collected and preexisting comorbidities were identified using prevalence of 29 standardized comorbidities in the Elixhauser Comorbidity Index (ECI, Table 3).[18,19] Using the ICD-9 diagnosis code 715.16 (osteoarthritis, localized, primary, lower leg: primary OA of bilateral knees, left knee, and right knee), we identified 157,200 patients without an arthroplasty that were age-, sex-, and ECI-matched to the TKA cohort and had a new diagnosis of knee osteoarthritis (Table 1). As expected, there was no statistical difference in age, sex, or ECI (TKA: 7.4 ± 4.3, No TKA: 7.4 ± 4.3, P = 1.000).

We identified patients diagnosed with deep venous thrombosis (DVT) and pulmonary embolism (PE) using their corresponding International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes (ie, 453.40, 415.1). Using this method, diagnostic labs and tests to detect/diagnose VTE were not reported and unable to be analyzed. Also, postoperative strategies regarding the type, timing, and duration of VTE prophylaxis used were not reported or analyzed. Only the first instance of deep venous thrombosis (DVT) and pulmonary embolism (PE) were tracked at 90 days and 2 years from the date of TKA or the first-time diagnosis of OA, to prevent any preexisting diagnoses of VTE on the patient's record from confounding the results.

We used the difference in VTE incidence between the 2 cohorts divided by the VTE incidence in the TKA cohort to assign the percent of VTE incidence associated to TKA alone. The remaining value was assumed to be related to patient comorbidities (Figure 1). Outcomes are presented

as proportions with a chi-square test used for comparison. We calculated odds ratios (ORs), 95% confidence intervals (CIs), and *P*-values (p) for each DVT and PE complication with statistical significance was set to an alpha error of 3% after a Bonferroni correction for 2 primary outcomes—DVT and PE—that define VTE.[20]

Results

Within 90 days

55% of the DVT rate was associated with the TKA and 45% with baseline medical comorbidities (Figure 2). There was a doubling of the odds of a DVT (OR 2.2, CI 2.1-2.3, $P < .001$) associated with a TKA. The elevation in absolute risk of a DVT associated with a TKA was 1.7%; therefore, 1 in 59 patients would be expected to be diagnosed a DVT related to their TKA alone and 1 in 71 related to their medical comorbidities (Table 2). 61% of the PE rate was associated with the TKA and 39% with baseline medical comorbidities (Figure 2). There was a doubling of the odds of a PE (OR 2.6, CI 2.4-2.8, $P < .001$) associated with a TKA. The elevation in absolute risk of a PE associated with a TKA was .8%; therefore, 1 in 125 patients would be expected to be diagnosed with PE related to their TKA alone and 1 in 200 related to their medical comorbidities (Table 2). For VTE (DVT and PE), 1 in 92 patients would be expected to be diagnosed with VTE after TKA and 1 in 136 patients after only the diagnosis of osteoarthritis.
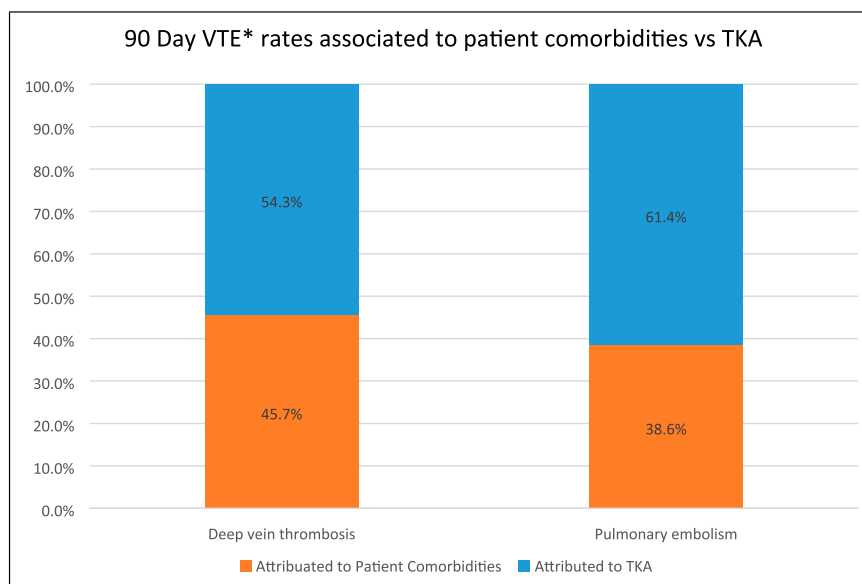

Figure 2. At 90 days, percentage of venous thromboembolism, complications statistically associated with patient comorbidities vs those who underwent a TKA. Total knee Arthroplasty, Venous Thromboembolism (deep vein thrombosis or pulmonary embolism).* TKA: total knee arthroplasty.

Table 2. Incidence and Percent Association.

90 Days	TKA patients	OA patients	OR	CI	P-value	% Associated with Comorbidities	% Associated with TKA
Deep venous thrombosis	4,823 (3.1%)	2,204 (1.4%)	2.2	2.1–2.3	<.001	45.7%	54.3%
Pulmonary embolism	1,977 (1.3%)	764 (.5%)	2.6	2.4–2.8	<.001	38.6%	61.4%

2 Years	TKA patients	OA patients	OR	CI	P-value	% Associated with Comorbidities	% Associated with TKA
Deep venous thrombosis	3,136 (2.0%)	3,411 (2.2%)	0.9	.9–1.0	<.001	70.6%	29.5%
Pulmonary embolism	1,487 (1.0%)	1,586 (1.0%)	0.9	.9–1.01	.070	67.8%	32.2%

TKA: total knee arthroplasty; OR: odds ratio; CI: confidence interval.
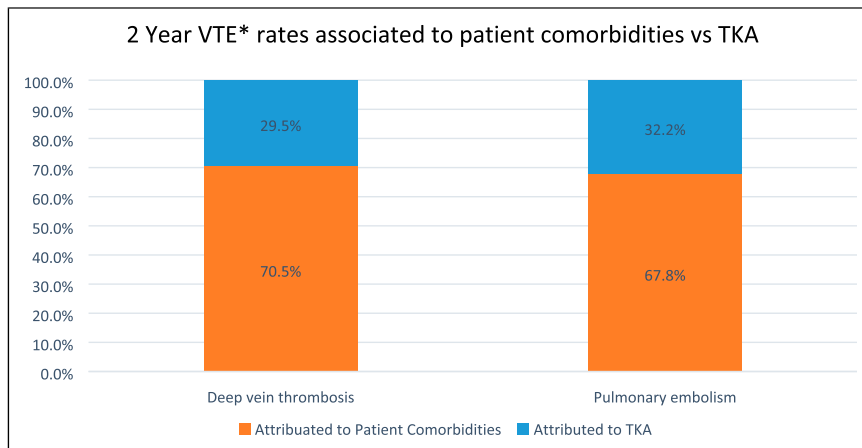Statistical significance = $P < .05$.

Figure 3. At 2 years, percentage of venous thromboembolism, complications statistically associated with patient comorbidities vs those who underwent a TKA. Rates were calculated by dividing incidence of VTE in osteoarthritis group (OA) by rate in total knee arthroplasty group (TKA), then subtracting from 100. Venous thromboembolism (deep vein thrombosis or pulmonary embolism).* TKA: total knee arthroplasty; VTE: venous thromboembolic events.

After 90-days

30% of the DVT rate was associated with the TKA and 70% to the patients' baseline medical comorbidities (Figure 3). There was a slight decrease of the odds of a DVT (OR .9, CI .9–1.0, $P < .001$) associated with a TKA (Table 2). 32% of the PE rate was associated with the TKA and 68% to the patients' baseline medical comorbidities (Figure 3). There was no statistically significant difference in the odds of a PE (OR .9, CI .9–1.0, $P = .070$) associated with a TKA (Table 2).

Discussion

To our knowledge, this represents the largest database study on the contribution of baseline health status to the risk of VTE after TKA on standard chemoprophylaxis. A total number of 157,200 patients who underwent TKA were compared to a matched cohort of 157,200 who received the diagnosis of osteoarthritis. Within 90 days of a TKA, almost half of the VTE rate appear to be related to the patients baseline medical comorbidities. However, 90 days after a TKA, the likelihood of a VTE returns to the baseline established by comorbid medical conditions.

It is well established that patients with more comorbid conditions are at higher risk of VTE. In an extensive review of the literature, Goldhaber et al concluded that hospitalized patients with a history of major surgery, cancer, congestive heart failure, chronic obstructive pulmonary disease, and chronic kidney disease were especially susceptible to VTE. In the community, incidence of VTE increased significantly with age, venous insufficiency, pregnancy, trauma, frailty, and immobility.[21] Specifically looking at knee OA patients in a retrospective single-center study, Jiang et al reported

that Preoperative D-dimer >.5 mg/mL and age >75 were independent risk factors for preoperative DVT. They also cited literature reporting significantly higher risk of thromboembolism in women undergoing TKA. Their study confirmed this finding.[7]

Patients with a diagnosis of osteoarthritis also tend to have more comorbid medical conditions. In a meta-analysis of 42 observational studies from 16 countries by Swain et al, they found that 67% of individuals with osteoarthritis had at least 1 other chronic condition, 20% higher than those without osteoarthritis. The body systems most likely to be affected by comorbidities in individuals with osteoarthritis were upper gastrointestinal, psychological, cardiovascular, and endocrine. Stroke, peptic ulcer, and metabolic syndrome were the most common comorbidities in osteoarthritis.[15] These comorbid conditions likely drive an increased baseline VTE risk that cannot be neutralized with standard VTE prophylaxis used in the TKA perioperative period.

We found the rate of VTE after TKA in our population to be around 4% at 90 days; this aligns with those previously cited in the literature;[10,22,23] however, in patients with only the diagnosis of osteoarthritis, our population demonstrated a lower VTE rate of 2% at 90 days. In a retrospective study spanning 10 years with over 9,000 patients undergoing primary TKA who received either low (81 mg twice daily) or high (325 mg twice daily) dose aspirin for VTE prophylaxis, the median time to VTE was 8 days (interquartile range [IQR] 2-15.5).[24] Given that our study examined TKA patients at 90 days, it is reasonable that this may be an overestimate of VTE incidence in this group that is required/tolerated because of bundled payment models.

Table 3. Elixhauser Comorbidities for Total Knee Arthroplasty Patients (TKAs) and Osteoarthritis Patients (OAs).

Comorbidity	TKA	OA (no TKA)	OR (95% CI)	X^2	P
Congestive heart failure	16,683 (10.6%)	22,747 (14.5%)	.70 (.69–.72)	1066.32	<.001
Valvular disease	17,281 (11.0%)	19,599 (12.5%)	.87 (.85–.89)	165.05	<.001
Pulmonary circulation disorders	6,121 (3.9%)	7,022 (4.5%)	.87 (.84–.90)	64.46	<.001
Peripheral vascular disease	20,403 (13.0%)	24,819 (15.8%)	.80 (.78–.81)	503.67	<.001
Hypertension (uncomplicated)	104,210 (66.3%)	108,697 (69.2%)	.88 (.86–.89)	292.93	<.001
Hypertension (complicated)	16,519 (10.5%)	22,005 (14.0%)	.72 (.71–.74)	890.32	<.001
Hypertension (uncomplicated and complicated)	105,458 (67.1%)	110,275 (70.2%)	.87 (.85–.88)	342.73	<.001
Paralysis	2,159 (1.4%)	3,942 (2.5%)	.54 (.51–.57)	531.39	<.001
Other neurological disorders	13,172 (8.4%)	18,601 (11.8%)	.68 (.67–.70)	1031.93	<.001
Chronic pulmonary disease	35,497 (22.6%)	42,740 (27.2%)	.78 (.77–.79)	892.68	<.001
Diabetes without chronic complications	42,082 (26.8%)	48,476 (30.8%)	.82 (.81–.83)	634.10	<.001
Diabetes with chronic complications	9,303 (5.9%)	14,177 (9.0%)	.63 (.62–.65)	1093.40	<.001
Hypothyroidism	32,023 (20.4%)	32,828 (20.9%)	.97 (.95–.99)	12.59	<.001
Renal failure	11,828 (7.5%)	15,211 (9.7%)	.76 (.74–.78)	463.09	<.001
Liver disease	4,805 (3.1%)	5,906 (3.8%)	.81 (.78–.84)	117.16	<.001
Chronic peptic ulcer disease	432 (.3%)	427 (.3%)	1.01 (.88–1.16)	.03	.864
HIV/AIDS	165 (.1%)	412 (.3%)	.40 (.33–.48)	105.93	<.001
Lymphoma	1,568 (1.0%)	1,989 (1.3%)	.79 (.74–.84)	50.40	<.001
Metastatic cancer	1,814 (1.2%)	3,031 (1.9%)	.59 (.56–.63)	310.48	<.001
Solid tumor without metastasis	16,303 (10.4%)	18,748 (11.9%)	.85 (.84–.87)	191.95	<.001
Rheumatoid arthritis/Collagen vascular diseases	13,453 (8.6%)	13,394 (8.5%)	1.00 (.98–1.03)	.14	.707
Coagulation deficiency	6,367 (4.0%)	7,421 (4.7%)	.85 (.82–.88)	84.27	<.001
Obesity	22,535 (14.3%)	22,884 (14.6%)	.98 (.96–1.00)	3.13	.077
Weight loss	6,589 (4.2%)	9,681 (6.2%)	.67 (.65–.69)	619.68	<.001
Fluid and electrolyte disorders	30,591 (19.5%)	35,601 (22.7%)	.83 (.81–.84)	480.33	<.001
Blood loss anemia	3,415 (2.2%)	3,952 (2.5%)	.86 (.82–.90)	40.08	<.001
Deficiency anemias	33,141 (21.1%)	38,869 (24.7%)	.81 (.80–.83)	590.99	<.001
Alcohol abuse	2,588 (1.7%)	3,575 (2.3%)	.72 (.68–.76)	161.23	<.001
Drug abuse	2,571 (1.6%)	3,246 (2.1%)	.79 (.75–.83)	79.80	<.001
Psychoses	8,415 (5.4%)	13,598 (8.7%)	.60 (.58–.61)	1312.22	<.001
Depression	20,773 (13.2%)	24,722 (15.7%)	.82 (.80–.83)	400.77	<.001
Elixhauser Comorbidity Index (ECI)	7.37	7.37			
Total cohort	157,200	157,200			

TKA: total knee arthroplasty.

Jiang et al examined 521 patients with knee degenerative osteoarthritis scheduled to undergo knee arthroplasty with ultrasonography and found an incidence of preoperative DVT just under 7%.[7] Wakabayashi et al performed a retrospective single center study in which 17% of 322 TKAs had a DVT prior to surgery.[8] Of note, over one-third of revision TKAs as well as patients with comorbid rheumatoid arthritis had a preoperative DVT.[8] In a prospective study, Watanabe et al examined 71 TKAs with 16 row multidetector computed tomography for asymptomatic preoperative VTE and found 8% of the patients had a DVT with no history of a disease known to cause thrombosis.[9] We believe the variability in sample sizes, and method of VTE diagnoses, as well as different levels of evidence account for the discrepancy in detectable VTE rates when compared to our rate. The median time to VTE after diagnosis of OA is not clearly defined in the literature; therefore, evaluating this group at 90 days may also be an overestimation. In our study, uniform methodology and matching of both groups help to negate the potential overestimation in the absolute value of the VTE incidence and substantiate the overall result that almost 50% of the VTE rate may be related to medical comorbidities alone.

Limitations

This is a retrospective database study that has limitations when compared to retrospective and prospective chart review in that it relies on the accuracy, precision, and inclusiveness of coding. Full patient histories and physical exams cannot be collected; therefore, it is unclear if the VTEs were symptomatic. Perioperative data such as the

type of anesthesia, duration of surgery, tourniquet use, pain control, and speed of mobilization were not reported or analyzed. Diagnostic labs and tests to detect/diagnose VTE such as ultrasound, CT, and d-dimer were not reported or analyzed. The type, timing, and duration of VTE prophylaxis used were not reported or analyzed. Taken together, these findings can only highlight possible associations and cannot establish causation between TKA, OA, or medical comorbidities and the diagnosis of VTE. We analyzed patients from 2005–2014; any advancements related to VTE prevention and management since this time were not captured in this study. All of the matched comorbidities in the ECI are not necessarily independent risk factors for VTE events. Even with the ECI and demographic data matched for the cohorts, a multivariate analysis would be difficult to perform as no individualized data is available to allow further stratification to determine the specific impact of TKA. This type of study, nevertheless, has been shown to be useful in the TKA literature: even though the data may be incomplete, it has been reported to be accurate.[25] There continues to be a growing use of large databases to answer clinical questions and trends related to TKA that would have otherwise been very difficult to answer without large numbers. The study does not take account of potential ascertainment bias. After surgery, the physicians will be actively looking for VTE as a known complication of TKA, whereas after diagnosis of OA the diagnosis is only likely to be made if the patient presents (rather than the physician looks).

Conclusion

While VTEs are considered a "never" event according to CMS, this study suggests that not all VTEs in the postoperative period are the result of TKA alone as it demonstrates that nearly 50% of DVTs and 40% of PEs within 90 days of TKA may be related to the baseline health of OA patients. Appropriate VTE prophylaxis likely does not neutralize all baseline medical risk, and patients may have had a VTE event regardless of their TKA. Given the limitations of this type of study, we can only highlight possible associations and cannot establish causation. Therefore, future studies via retrospective, randomized, or observational scrutiny should explore the details surrounding the VTE events in both cohorts and how modern anticoagulation protocols impact this baseline VTE risk.

Author's Note

Investigation performed at [Stanford Health Care, Palo Alto, California, USA].

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