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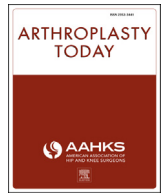
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Original research

What are the incidence and risk factors of in-hospital mortality after venous thromboembolism events in total hip and knee arthroplasty patients?

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ABSTRACT

Background: Pulmonary embolism and deep vein thrombosis, together referred to as venous thromboembolism (VTE), are serious and potentially preventable complications after total hip arthroplasty and total knee arthroplasty. The aim of this study was to investigate the incidence of mortality after VTE events and assess the risk factors that are associated with it.

Methods: The Nationwide Inpatient Sample was used to estimate the total number of total hip arthroplasty, total knee arthroplasty, VTE events, and mortality using the International Classification of Diseases, Ninth Revision procedure codes from 2003 to 2012. Patients' demographics, Elixhauser, and Charlson comorbidity indices were used to identify the risk factors associated with in-hospital VTEs and mortality.

Results: A total of 1,805,621 THAs and TKAs were included. The overall rate of VTE was 0.93%. The in-hospital mortality rate among patients with VTEs was 7.1% vs 0.30% in patients without VTEs (P -value < .0001). The risk factors for mortality after VTE events in descending order were as follows: hypercoagulable state (odds ratio [OR]: 5.3, 95% confidence interval [CI]: 3.6–5.8), metastatic cancer (OR: 5.2, 95% CI: 3.3–5.6), myocardial infarction (OR: 4.2, 95% CI: 2.3–4.7), peripheral vascular disease (OR: 3.6, 95% CI: 3.2–4.0), cardiac arrhythmias (OR: 3.2, 95% CI: 1.6–4.3), advanced age (OR: 3.1, 95% CI: 2.3–3.7), electrolyte disorders (OR: 3.1, 95% CI: 2.2–3.6), pulmonary circulation disorders (OR: 2.9, 95% CI: 2.6–3.3), depression (OR: 2.8, 95% CI: 1.6–3.4), complicated diabetes (OR: 2.7, 95% CI: 2.1–3.2), weight loss (OR: 2.6, 95% CI: 2.2–3.3), renal failure (OR: 2.6, 95% CI: 1.7–3.5), chronic pulmonary disease (OR: 2.5, 95% CI: 1.3–3.1), valvular disease (OR: 2.4, 95% CI: 1.8–2.7), liver disease (OR: 1.7, 95% CI: 1.2–1.9), and obesity (OR: 1.6, 95% CI: 1.5–1.9).

Conclusions: In-hospital VTE has a significant in-hospital mortality rate. Several of the identified risk factors in this study are modifiable preoperatively. We strongly urge the orthopaedic community to be cognizant of these risk factors and emphasize on optimizing patients' comorbidities before an elective arthroplasty.

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Introduction

In the coming decade, the number of total hip and knee arthroplasties is projected to increase significantly in the United States and worldwide. Kurtz et al. [1] predicted that by 2030, number of primary total hip arthroplasties (THAs) increase by 174% and primary total knee arthroplasties (TKAs) by 672%. As with all medical procedures, total joint arthroplasty is often accompanied

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by complications. Pulmonary embolism (PE) and deep vein thrombosis (DVT), together referred to as venous thromboembolism (VTE), are of the most dreaded complications after total hip and knee arthroplasties [2–4]. It has been shown that the median incidence of only in-hospital VTE events during the initial hospitalization is 0.59% (0.55%–0.63%) for primary total hip arthroplasty (THA) and 1.01% (0.94%–1.08%) for primary TKAs in the United States. This rate is significantly higher in revision total joint arthroplasties (up to 2.5%) compared to primaries (1.6%, P -value < .0001) [5]. This not only has a huge economical burden on patients and the health-care system but also can increase the hospital stay and be associated with significant increase in the mortality rate in patients undergoing total hip and knee arthroplasties [4–6].

Mortality is one of the most worrisome concerns for both the patient and surgeon following any surgical procedure. Despite this concern, to our knowledge, the in-hospital mortality of patients who developed VTE after total knee arthroplasty (TKA) and THA has not been studied. Thus, the aim of this study was to utilize the National Inpatient Sample (NIS) database to (1) identify the risk factors of in-hospital VTEs after TKA and THA, (2) determine the rate of in-hospital mortality in patients who developed VTE, and (3) define the risk factors for mortality in these patients.

Material and methods

Study design

To conduct this study, the NIS data from the Agency for Healthcare Research and Quality were used to establish a 10-year retrospective cohort of patients who underwent primary and revision THA and TKA in the United States between 2003 and 2012 [7]. The NIS is the largest longitudinal, all-payer hospital database in the United States. This database consists of more than 1000 hospitals annually with 7–8 million medical records, which approximately represents 20% of all hospital discharges in the United States. The NIS database contains patients' demographics along with their comorbidities, duration of hospital stay, diagnostic codes based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), patient disposition/discharge destination, and total amount of in-hospital charges. Because of the fact that the available information from the NIS database is deidentified, this study was exempted from institutional review board approval.

Patient selection

The database was queried with ICD-9-CM codes: 81.51 and 81.53, and 00.70–00.73 to identify patient who underwent THA, and 81.54–81.55 and 00.80–00.84 codes for patients who underwent TKA. A total of 1,805,621 THAs and TKAs were identified for analysis including 520,590 primary THAs, 88,162 revision THAs, 1,101,205 primary TKAs, and 95,664 revision TKAs (Table 1).

Outcome variables and statistical analysis

All THA and TKA patients who developed pulmonary embolism ([PE]: ICD-9 codes 415.11 or 415.19) or deep vein thrombosis ([DVT]

ICD-9 codes 455.1, 451.2, 451.8, 451.9, 453.2, 453.4, 453.8, or 453.9) during their admission were identified. Mortality was used as the primary outcome measure; patients who developed VTE and expired during their admission were identified. Patients' demographics including, gender, age, body mass index, and comorbidities using Charlson and Elixhauser indices were taken into account as the predictors for VTE and mortality. A logistic regression model was created using all the predictors.

Standard statistics were used to present the descriptive data. Chi-squared tests were used to compare the incidences. An alpha level of 0.05 was used to determine statistical significance. All the analyses were performed using R 3.1 (R Foundation for Statistical Computing, Vienna, Austria). The "survey" package for R was used to derive estimates of means, medians, standard deviations, standard errors, rates, and confidence intervals (CIs).

Results

The overall rate of in-hospital VTE in the NIS database among the 1,805,621 patients undergoing THA and TKA was 0.93% (10,218 DVT, 6620 PE, and 1072 with both DVT and PE; 16,838 cases of VTE total) (Table 2). The risk factors for developing in-hospital VTEs in descending order were hypercoagulable state (odds ratio [OR]: 4.8, 95% CI: 3.9–5.8), metastatic cancer (OR: 4.2, 95% CI: 3.1–5.0), renal failure (OR: 3.5, 95% CI: 2.4–3.7), pulmonary circulation disorders (OR: 3.4, 95% CI: 2.9–4.1), cerebrovascular disease (OR: 3.3, 95% CI: 2.9–4.1), dementia (OR: 3.2, 95% CI: 2.7–3.6), chronic pulmonary disease (OR: 2.7, 95% CI: 2.1–3.2), cardiac arrhythmias (OR: 2.2, 95% CI: 2.0–2.7), valvular disease (OR: 2.2, 95% CI: 1.7–2.5), fluid and electrolyte disorders (OR: 2.1, 95% CI: 1.9–2.2), weight loss (OR: 2.0, 95% CI: 1.7–2.5), lymphoma (OR: 1.8, 95% CI: 1.1–2.4), myocardial infarction (OR: 1.8, 95% CI: 1.6–1.9), congestive heart failure (OR: 1.7, 95% CI: 1.1–1.9), revision THA (OR: 1.4, 95% CI: 1.1–1.7), peripheral vascular disorders (OR: 1.4, 95% CI: 1.1–1.6), solid tumor without metastasis (OR: 1.3, 95% CI: 1.1–1.6), deficiency anemia (OR: 1.3, 95% CI: 1.1–1.4), advanced age (greater than 70 years old) (OR: 1.3, 95% CI: 1.1–1.4), obesity (OR: 1.2, 95% CI: 1.1–1.5), and female gender (OR: 1.1, 95% CI: 1.0–1.3).

The overall in-hospital mortality rate for THA and TKA without VTEs was 0.30% (5441/1,788,783). The in-hospital mortality rate among patients with VTE was 7.1% (1203/16,838), which was significantly higher than those without VTE (P -value < .0001). The relative risk for mortality in patients with VTE was 23.5 (95% CI: 22.1–24.9) compared to those without VTEs. In-hospital PEs contributed the majority of mortalities in patients with VTE: 13.4% (887/6620) in PEs vs 3.1% (316/10,218) in patients with DVTs (P -value < .0001). Patients who developed in-hospital PEs had a 1.9 higher relative risk for mortality (95% CI: 1.7–2.0) compared to ones who just had DVTs. When THAs and TKAs were complicated with in-hospital PEs, the relative risk for mortality was 44.0 (95% CI: 41.2–47.1) compared to ones with no VTE events (number need to harm: 7.6). Furthermore, when adjusted for potential confounders and stratified by age, patients who developed VTEs had an odds ratio of 23.8 (95% CI: 21.5–26.8) for in-hospital mortality compared to those without VTEs.

Table 2

Overall median incidence between 2003 and 2012 in the United States.

Procedure	Pulmonary embolism (95% CI)	Deep venous thrombosis (95% CI)	Venous thromboembolism (95% CI)
Primary THA	0.41 (0.38–0.44)	0.24 (0.21–0.26)	0.60 (0.55–0.63)
Revision THA	1.12 (0.96–1.22)	0.37 (0.34–0.42)	1.36 (1.24–1.46)
Primary TKA	0.71 (0.57–0.77)	0.45 (0.42–0.48)	1.03 (0.94–1.09)
Revision TKA	0.93 (0.85–1.12)	0.35 (0.31–0.39)	1.17 (1.06–1.30)

Table 1
Demographics.

Procedure	Number of patients	Mean age (95% CI)	Female gender (95% CI)
Primary THA	520,590	67 (65–67)	57 (56–57)
Revision THA	88,162	67 (67–68)	58 (57–58)
Primary TKA	1,101,205	66 (66–67)	64 (63–64)
Revision TKA	95,664	66 (66–67)	58 (58–69)

The risk factors for mortality after VTE events in descending order were as follows: hypercoagulable state (OR: 5.3, 95% CI: 3.6–5.8), metastatic cancer (OR: 5.2, 95% CI: 3.3–5.6), myocardial infarction (OR: 4.2, 95% CI: 2.3–4.7), peripheral vascular disease (OR: 3.6, 95% CI: 3.2–4.0), cardiac arrhythmias (OR: 3.2, 95% CI: 1.6–4.3), advanced age (greater than 70 years old) (OR: 3.1, 95% CI: 2.3–3.7), fluid and electrolyte disorders (OR: 3.1, 95% CI: 2.2–3.6), pulmonary circulation disorders (OR: 2.9, 95% CI: 2.6–3.3), depression (OR: 2.8, 95% CI: 1.6–3.4), complicated diabetes (OR: 2.7, 95% CI: 2.1–3.2), weight loss (OR: 2.6, 95% CI: 2.2–3.3), renal failure (OR: 2.6, 95% CI: 1.7–3.5), chronic pulmonary disease (OR: 2.5, 95% CI: 1.3–3.1), valvular disease (OR: 2.4, 95% CI: 1.8–2.7), liver disease (OR: 1.7, 95% CI: 1.2–1.9), and obesity (OR: 1.6, 95% CI: 1.5–1.9). [Table 3](#) provides the risk factors for VTE events and mortality for a side-to-side comparison.

Discussion

Complications after major surgery, including VTE, have been a well-established concern for clinicians. [8]. VTE is one of the most serious and potentially preventable complications after THA and TKA. Studies have shown that the venographic rates (asymptomatic and symptomatic) of VTE after TKA and THA can be as high as 60% without proper prophylaxis [9]. Zahir et al. [10] investigated the incidence of inpatient PE after elective primary THA and TKA in the United States. The authors showed that elective TKAs are associated with a higher incidence and odds of in-hospital PEs than primary THAs. While many studies evaluated the perioperative mortality following THA and TKA [11,12], only a few studies have touched on the impact of VTE as a sole cause of postoperative mortality in THAs and TKAs [13,14]. This study investigated the incidence and risk factors of perioperative in-hospital mortality for TKA and THA patients who were complicated with VTE events.

Numerous studies have assessed the risk factors associated with the development of VTEs after total joint arthroplasty [15–18]. Parvizi et al. [19] created an individualized model to assess the risks of VTE development after total joint arthroplasty. The authors concluded that several comorbidities, namely, hypercoagulability,

metastatic cancer, stroke, sepsis, and chronic obstructive pulmonary disease were highly associated with postoperative VTEs [19]. Our findings were in line with the previous studies; however, we found that some modifiable risk factors such as iron deficiency anemia and obesity can contribute significantly to the incidence of postoperative VTEs. Our study emphasizes on the importance of perioperative health modifications before an elective THA and TKA [20–22].

The results of this study demonstrated that when THAs and TKAs are complicated by VTE events, the relative risk for in-hospital mortality was 23.5 (95% CI: 22.1–24.9). This risk was even higher when only PEs were taken into account 44.0 (95% CI: 41.2–47.1). Together, the previously discussed studies along with this study indicate that VTE is a strong independent risk factor for mortality after THA and TKA, even when adjusting for different patient factors, including comorbidities and stratifying by age. The reason for the higher incidence of mortality in this population may be multifactorial. The VTE events themselves or the complications of treatment protocols can be the cause of mortality [23]. Many of the patients who receive anticoagulants for treatment of VTEs develop upper gastrointestinal bleeding and acute anemia due to blood loss that requires transfusion [24]. Neviasser et al. [25] investigated the complications of enoxaparin treatment after arthroplasty. The authors reported that 10% of patients being treated with therapeutic doses of enoxaparin had major bleeding in their cohort and up to 27% of their patients had minor complications. PEs are frequently diagnosed within the first few postoperative days; therefore, anticoagulation agents are instituted at therapeutic doses when the risk of bleeding is the highest. It is reasonable to recommend the medical team to weight the risks and benefits of treatment in such patients, especially the ones with small subsegmental PE with minimal symptoms [26,27]. Moreover, the identified risk factors for mortality in this study should be taken into account when encountering a postoperative VTE. Engleke et al. [28] assessed the 1-year morbidity and mortality of patients with a computed tomography pulmonary angiogram (CTPA)–confirmed PE that were treated with anticoagulation, and a group of patients who had a false-negative CTPA read in their initial assessment and therefore

Table 3
Risk factors for VTE and mortality after VTE in total knee and hip arthroplasty patients.

Variables	VTE			Mortality		
	OR	Lower 95% CI	Upper 95% CI	OR	Lower 95% CI	Upper 95% CI
Advanced age	1.3	1.1	1.4	3.1	2.3	3.7
Cardiac arrhythmias	2.2	2	2.7	3.2	1.6	4.3
Cerebrovascular disease	3.3	2.9	3.6	NS		
Chronic pulmonary disease	2.7	2.1	3.2	2.5	1.3	3.1
Congestive heart failure	1.7	1.1	1.9	NS		
Deficiency anemia	1.3	1.1	1.4	NS		
Dementia	3.2	2.7	4.1	NS		
Depression	NS			2.8	1.6	3.4
Diabetes, complicated	NS			2.7	2.1	3.2
Female gender	1.1	1	1.3	NS		
Fluid and electrolyte disorders	2.1	1.9	2.2	3.1	2.2	3.6
Hypercoagulable state	4.8	3.9	5.8	5.3	3.6	5.8
Liver disease	NS			1.7	1.2	1.9
Lymphoma	1.8	1.1	2.4	NS		
Metastatic cancer	4.2	3.1	5	5.2	3.3	5.6
Myocardial infarction	1.8	1.6	1.9	4.2	2.3	4.7
Obesity	1.2	1.1	1.5	1.6	1.5	1.9
Peripheral vascular disorder	1.4	1.1	1.6	3.6	3.2	4.0
Pulmonary circulation disorders	3.4	2.9	3.7	2.9	2.6	3.3
Renal failure	3.5	2.4	4.1	2.6	1.7	3.5
Revision THA	1.4	1.1	1.7	NS		
Solid tumor without metastasis	1.3	1.1	1.6	NS		
Valvular disease	2.2	1.7	2.5	2.4	1.8	2.7
Weight loss	2	1.7	2.5	2.6	2.2	3.3

NS, not statistically significant.

received no treatment. The authors concluded that patients who were clinically unsuspected to have PEs may remain undiagnosed at routine CTPA, and these patients had favorable short-term outcome even without therapeutic anticoagulation.

We identified several risk factors that should be recognized preoperatively to minimize the risk of mortality in patients who develop VTEs. Perhaps one of the most interesting risk factor was depression. This could be due to the disease itself or antidepressant agents that are commonly used by these patients. Parklin et al. [29] reviewed more than a million women through the National Health Service Breast Screening Program in England and Scotland. They reported that the risk of VTE is not increased in women who were diagnosed with depression; however, the use of antidepressants significantly increased the rates of VTE. There are also case reports of massive PE with the use of olanzapine [30]. In another study by Browne et al. [31], the authors found that depression was associated with a greater risk of postoperative psychosis (OR = 1.74), anemia (OR = 1.14), infection (OR = 1.33), and PE (OR = 1.20) after total joint arthroplasty.

Our study had several shortcomings, and our findings should be interpreted in light of these limitations. First, the inherent limitations with the NIS database; this database only includes inpatient information and it considers each hospitalization as a separate record. Therefore, we could only investigate in-hospital mortalities and VTE events during initial hospitalization, which represents a proportion of the total VTEs and mortalities that may occur after THA and TKA over a longer postoperative period when patients are being discharged [32–34]. Second, the NIS data does not differentiate between clinically significant and insignificant VTEs; pursuantly asymptomatic events may not have been captured. Third, the NIS database uses claimed based coding, which may contain coding variability and inaccuracies [35]. Fourth, we were also unable to evaluate the type of prophylactic modalities and the anticoagulant protocols that were applied for the management of VTE events. Fifth, because of the nature of the NIS database, patients who developed VTEs after their discharge and mortalities after discharge could not be investigated. Finally, the NIS database does not contain information about the cause of mortality in deceased patients.

Conclusions

Notwithstanding of all these limitations, this study is the first of its kind, to our knowledge, that reflects population-based estimates of in-hospital mortality after VTE events in THA and TKA patients. Based on the findings of this study, VTEs are beyond doubt one of the major causes of mortality after THA and TKA. Furthermore, using a regression modeling strategy, this study identified several risk factors that are associated with increased mortality in these patients. Owing to the fatal consequences of the in-hospital VTE events, we strongly urge the medical community to recognize these risk factors and optimize the modifiable comorbidities before an elective arthroplasty.

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