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Systematic Review

Statistical Fragility of Venous Thromboembolism Prophylaxis Following Total Joint Arthroplasty

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ABSTRACT

Background: Statistical fragility is a quantitative measure of the robustness of the statistical conclusions drawn in a study. Although statistical fragility has been comprehensively evaluated in the arthroplasty literature, the statistical fragility of large-scale randomized trials evaluating venous thromboembolism (VTE) prophylaxis has not been evaluated. The purpose of this study was to determine the utility of applying the fragility index (FI) and the fragility quotient (FQ) analysis to randomized controlled trials (RCTs) evaluating VTE prophylaxis following total joint arthroplasty.

Methods: A systematic review was performed by searching multiple databases to identify RCTs that evaluated VTE prophylaxis following total joint arthroplasty from 2000 to 2020. The FI was determined by manipulating each reported dichotomous outcome event until a reversal of significance was appreciated with 2 × 2 contingency tables. The associated FQ was determined by dividing the FI by the sample size.

Results: Thirty-two RCTs were ultimately included for analysis. The overall FI incorporating all 32 RCTs was only 7 (interquartile range 3-9), suggesting that the reversal of only 7 events is required to change study significance. The associated FQ was determined to be 0.01. Of the RCTs that reported lost-to-follow-up data, the majority of studies had lost-to-follow-up numbers greater than 7.

Conclusions: Our findings suggest that RCTs evaluating VTE prophylaxis following total hip arthroplasty and total knee arthroplasty may lack statistical stability as few outcome events are required to reverse the significance of outcomes. Future randomized trials should consider reporting FI and FQ along with the *P* value analysis to provide better context to the integrity of statistical stability.

Introduction

The ideal venous thromboembolism (VTE) prophylaxis following total joint arthroplasty (TJA) remains controversial among orthopedic surgeons. Large randomized controlled trials (RCTs) have sought to define a standard of care, with most studies comparing various dosages of aspirin, enoxaparin, and direct-acting oral anticoagulants (DOACs) [1-3]. Systematic reviews and meta-analyses have also been published on various medications for VTE prophylaxis with conflicting or incomplete conclusions, suggesting that the superior postoperative protocol remains unknown [4,5]. These systematic reviews are largely limited by heterogeneity among studies that can affect the strength of final conclusions.

P values are the main metric that RCTs use to test significance and justify the conclusions they draw. Most often, the alpha value, or the chance that an alternative hypothesis found true is actually due to chance, is utilized, with statistical significance set at a *P* value less than .05. A *P* value that is lower than the alpha suggests that the null hypothesis should be rejected. Although statistical significance correlates to the alpha value, the main metric to test statistical significance against an alpha value to draw a conclusion is the *P* value. Although statistical tests are imperative to help the surgeon draw conclusions from a study, the use of *P* values *in silo* to ascribe significance may not optimize statistical rigor [6]. Because significance is usually assigned an otherwise arbitrary value of less than an alpha of 0.05, outcomes sometimes require a reversal of only 1 to 2 events to change the significance of an outcome itself [7,8]. The fragility index (FI) is a relatively new concept, developed by

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Feinstein in 1990, used to help characterize how stable, or fragile, a given outcome is [9]. The FI is calculated by manipulating outcome events until a reversal of significance is achieved. A low FI signifies that the outcome is statistically fragile as it would require minimal manipulation of outcome event to reverse significance. To mitigate the shortcomings of FI and its independence of sample size, fragility quotient (FQ) was developed not long after [10]. FQ is calculated by dividing the FI by the sample size. Together, FI and FQ can help augment RCTs' statistical reporting and better characterize each outcome's statistical stability.

Although there have been several studies that comment on the fragility of the literature surrounding TJA, the statistical fragility of the conclusions drawn regarding VTE prophylaxis has not been studied separately from other arthroplasty studies. Most studies evaluating statistical fragility in the adult reconstruction literature have evaluated articles in arthroplasty journals although there are several RCTs in medical journals that have not yet been evaluated for their fragility [11-16]. The purpose of this study was to analyze dichotomous outcomes in RCTs evaluating VTE prophylaxis following TJA to determine the FI and FQ. Our hypothesis was that the conclusions drawn regarding VTE prophylaxis following TJA would be statistically fragile and support inclusion of FI and FQ in future RCTs on this topic.

Material and methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using a PRISMA checklist. Two independent reviewers, along with an academic librarian, searched the PubMed, Scopus, Embase, ClinicalTrial, and Cochrane Library databases up to December 31, 2021. These databases were searched using a string of keywords that pertained to VTE prophylaxis following primary TJA. Key terms included were total hip arthroplasty (OR THA OR total hip replacement) or total knee arthroplasty (or TKA or total knee replacement) or venous thromboembolism (or VTE) or deep vein thrombosis (or DVT) or pulmonary embolism (or PE). The selected articles were further evaluated for a randomized control design. To meet inclusion criteria, RCTs had to be comparative RCTs that evaluated at least 1 dichotomous outcome and reported *P* values. Exclusion criteria included studies that did not evaluate VTE prophylaxis following TJA, did not report any dichotomous outcome variables, that were not written in English, or did not implement a randomized, controlled design. Data extraction from each study was performed independently and reconciled by a second author. Additional searching was performed by reviewing reference lists of included studies. There was no need for funding or a third party to obtain any collected data.

The FI and FQ were calculated for all dichotomous outcome variables in the selected RCTs.

In order to calculate the FI and FQ, outcome events were recorded in a 2×2 contingency table. Both significant and nonsignificant dichotomous outcomes were evaluated. Iterative manipulation of each outcome event was subsequently performed until a reversal of significance ($P < .05$) was achieved; at this point, the number of events required for a reversal of significance was recorded as the FI. The FI of all dichotomous outcomes within included RCTs was calculated in an identical manner. The FQ was determined by taking each FI as a proportion of the total sample size. The original *P* value was recorded for each outcome, and Fischer exact test was used to verify the accuracy of the original, reported *P* value. Mean and interquartile ranges (IQRs) were computed for the FI and FQ of each outcome to better comment on the variability in the statistical fragility between the 25th and 75th percentiles.

Lost-to-follow-up data were also evaluated for all studies by determining the sample size of patients that were initially included and then subsequently analyzed for each outcome. For example, if 450 patients were included in the study, but only 437 returned to undergo evaluation for VTE, the lost-to-follow-up value was documented as 13. However, if 445 returned for evaluation of VTE, the lost-to-follow-up value for VTE was documented as 5.

Results

A total of 2749 studies were initially identified on the subject of VTE prophylaxis following TJA from the aforementioned search (Fig. 1). Thirty-two RCTs met all inclusion criteria and were included in the statistical fragility analysis [2,11-35]. Of those RCTs that met the inclusion criteria, 30 (93.8%) were classified as level I evidence and 2 (6.2%) as level II evidence. Twenty-nine (90.6%) studies performed an *a priori* power analysis, 2 (6.25%) studies did not comment on a power analysis, and 1 study performed a *post hoc* power analysis. The average sample size for the included RCTs was 3002 ± 1376.7 patients. A total of 293 dichotomous outcomes from the included articles were evaluated for this study, with 70 initially reported as statistically significant and 233 as insignificant. Forty-two (14.3%) of the dichotomous outcomes evaluated were primary outcomes. The rate of all VTE cases was the most common dichotomous outcome across the 32 RCTs included within this study (Table 1). Other commonly evaluated dichotomous outcomes included clinically relevance, major bleeding, minor bleeding, transfusion, and mortality.

The average FI of 293 dichotomous outcome events was 7 (IQR 3-6) (Fig. 2). The average FQ, taken as a ratio of the FI to sample size, of 293 dichotomous outcomes was 0.01354 (0.008-0.018). The average FI of the 73 significant dichotomous outcome events was 6 (IQR 1-3), and the FQ of significant outcome events was 0.00327 (0.025-0.050) (Fig. 3). The average FI of the 220 insignificant, dichotomous outcome events was 7 (IQR 5-11), and the FQ of insignificant outcome events was 0.012 (Fig. 4).

Of the 293 outcome events across 32 RCTs, 39 outcome events across 7 studies did not have lost-to-follow-up data. One hundred and twenty-four of the 293 outcome events with lost-to-follow-up data (42.3%) had a lost to follow-up value over 7, indicating that over 40% of the outcome events may have demonstrated a reversal of significance had appropriate follow-up been maintained for all enrolled patients.

Discussion

In this study, we found that the conclusions regarding VTE prophylaxis following TJA had, on average, a FI of 7 (IQR 3-9) and a FQ of 0.01. Furthermore, for 42.3% of outcomes, the lost-to-follow-up numbers were greater than 7. Our findings on the statistical fragility of conclusions regarding VTE prophylaxis following TJA suggest that future statistical reporting on this subject should include FI and FQ in addition to *P* values to provide clinicians with a more complete picture of the robustness of the data and aid in clinical decision-making.

VTE prophylaxis following TJA has been extensively studied in the literature although the results are conflicting and often incomplete. For example, a recent systematic review that evaluated new oral anticoagulants (DOACs) found that they were more effective than non-DOACs without an increased bleeding risk [36]. However, other systematic reviews have championed aspirin or low-molecular-weight heparin as the prophylactic agent most effective at minimizing the incidence of postoperative VTE [4,37,38]. Moreover, these systematic reviews rarely include a comparison of all available VTE prophylactic medications, thereby

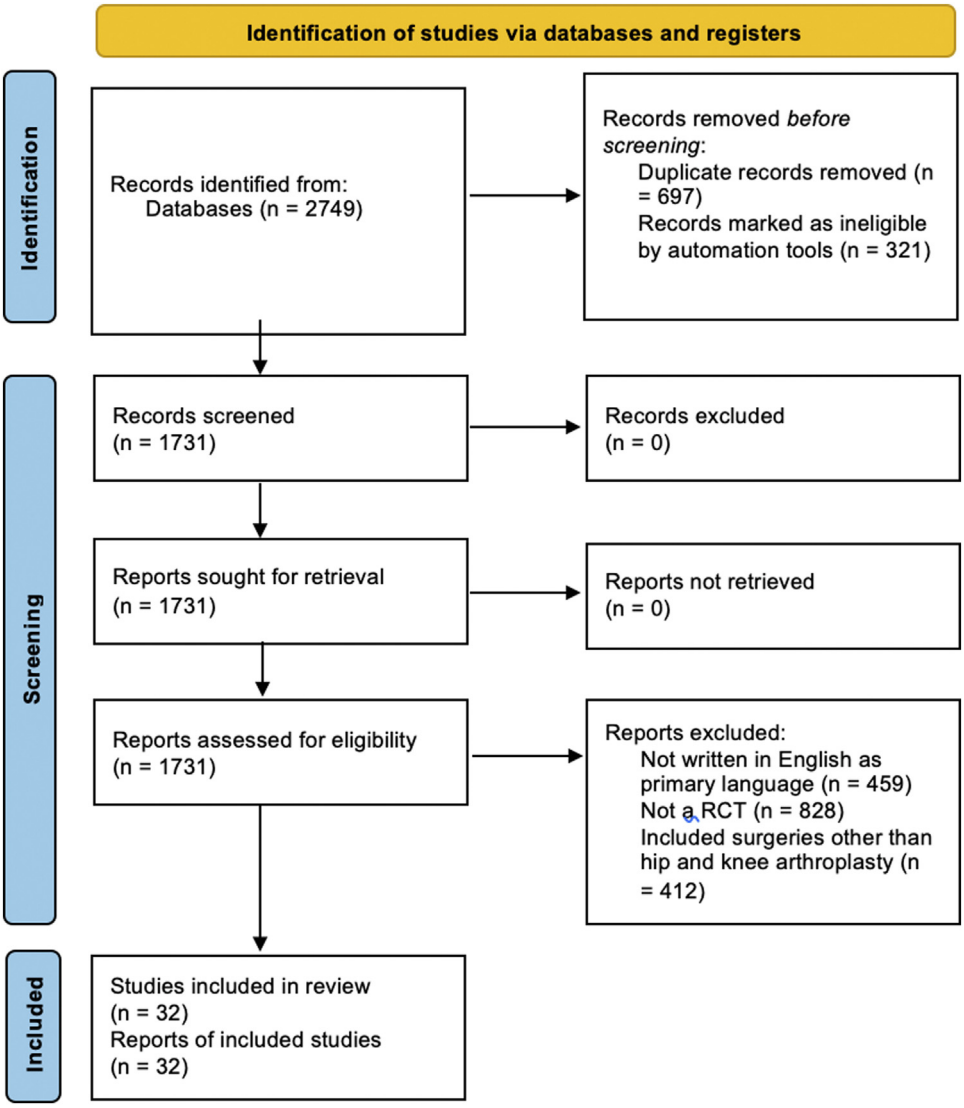

Figure 1. PRISMA flowchart of search strategy and results.

making their conclusions often incomplete [5]. Furthermore, these reviews and meta-analyses are limited by the heterogeneity of the included studies. We recommend the regular inclusion of FI and FQ in future RCTs to enhance the robustness of statistical reporting for each individual study, in addition to improving the quality of meta-analyses.

Our findings on the conclusions regarding VTE prophylaxis following TJA are consistent with reviews that have evaluated statistical fragility of other orthopaedic literature. Khan et al. evaluated the statistical fragility of conclusions drawn in the orthopaedic sports medicine literature and found that, over a 10-year period, the average FI of study outcomes was 2 [39]. A more recent study of the statistical fragility of the orthopaedic sports literature determined that the FI was 5 [39,40]. Recently, Parisien et al. found that the statistical fragility of the conclusions regarding the efficacy of platelet-rich plasma was demonstrated with an FI of 4 and FQ of 0.092 [41]. In this analysis, they also found that for about one-third of outcomes, the study had a lost-to-follow-up number greater than the FI, suggesting that had better follow-up been maintained, statistical significance and conclusions may have been reversed. Even studies outside of orthopaedic surgery, including those in gynecologic surgery and cardiovascular research, have found similarly low FI and FQ, suggesting that the poor rigor of statistical reporting is not unique to orthopaedic surgery [42,43]. A study of journals with the highest impact factors, including the *New England Journal of Medicine* and *The Lancet*, found that study conclusions were comparatively less fragile than what is found in other journals [44]. By focusing our literature review on higher-impact journals and more recent literature, our study found that the literature comparing VTE prophylaxis regimens following TJA is comparatively less fragile. Interestingly, the American Academy of Orthopaedic Surgeons (AAOS) released guidelines that suggested that an FI of greater than 2 was statistically robust. Therefore, according to those guidelines, the statistical fragility of VTE RCTs is

Table 1
Commonly reported outcomes in the 32 included RCTs.

Outcomes	Rate
All VTE	61 (20.8%)
Clinically significant bleeding	32 (10.9%)
Symptomatic VTE	45 (15.4%)
Asymptomatic VTE	29 (9.9%)
Transfusion	23 (7.8%)
Mortality	32 (10.9%)

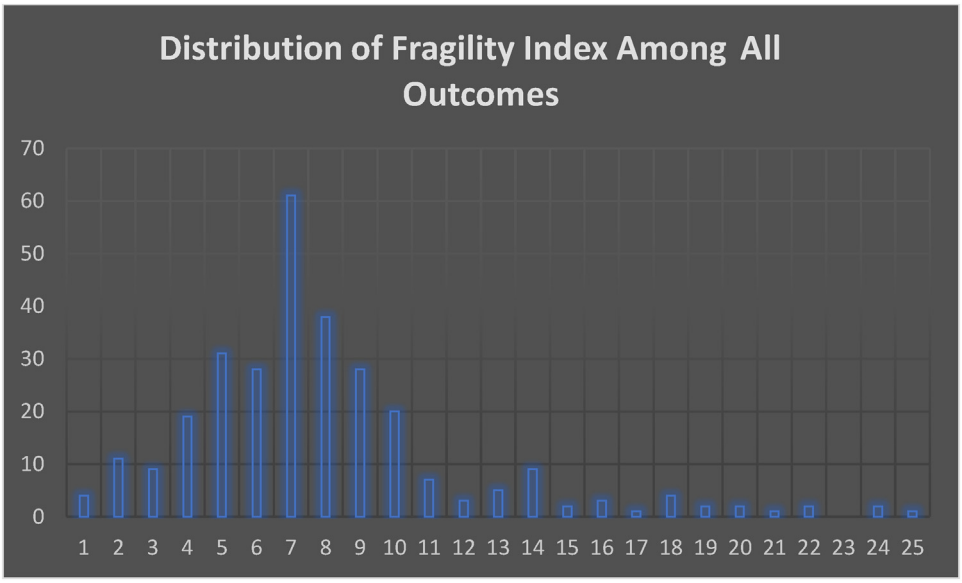

Figure 2. Distribution of fragility index among all 293 significant and insignificant dichotomous outcomes.

statistically robust. However, regardless of the AAOS guidelines, these and other reviews of statistical reporting and fragility of current orthopaedic literature suggest that FI and FQ should be regularly reported in orthopaedic RCTs to provide another dimension to the integrity and robustness of reported conclusions.

Although several previous studies have revealed that orthopaedic literature is indeed statistically fragile, our study evaluates literature that has not been previously evaluated in large-scale fragility studies of adult reconstruction literature. In a statistical fragility-based study by Ekhtiari et al. of the hip and knee arthroplasty literature, only 3 of the 34 included RCTs evaluated RCTs concerning anticoagulation or VTE following TJA [45]. Notably, they did not include any studies from the *New England Journal of Medicine*, *The Lancet*, or the *Journal of Thrombosis and Haemostasis*, journals that are heavily cited by the AAOS guidelines to make recommendations regarding VTE prophylaxis following TJA [46]. Similarly, Herndon et al. re-evaluated the arthroplasty literature for its statistical fragility but failed to include key landmark articles from medical journals that comment on VTE prophylaxis following TJA [47]. As is suggested by previous fragility studies in the orthopaedics literature, RCTs with a larger sample size and greater power will inherently produce higher FI and FQ, optimizing their statistical rigor and the strength of the subsequent conclusions of the study. We posit that the consistent and regular reporting of FI and FQ in tandem with *P* values, as well as larger sample sizes and greater power in future RCTs, will help to specifically address previous deficiencies concerning the determination of a gold standard for VTE prophylaxis following TJA.

Although this study is the first of its kind to evaluate the statistical fragility of conclusions drawn regarding VTE prophylaxis following TJA, it does have its limitations. First, the inclusion of only high-impact medical and orthopaedic RCTs, while intentional, may

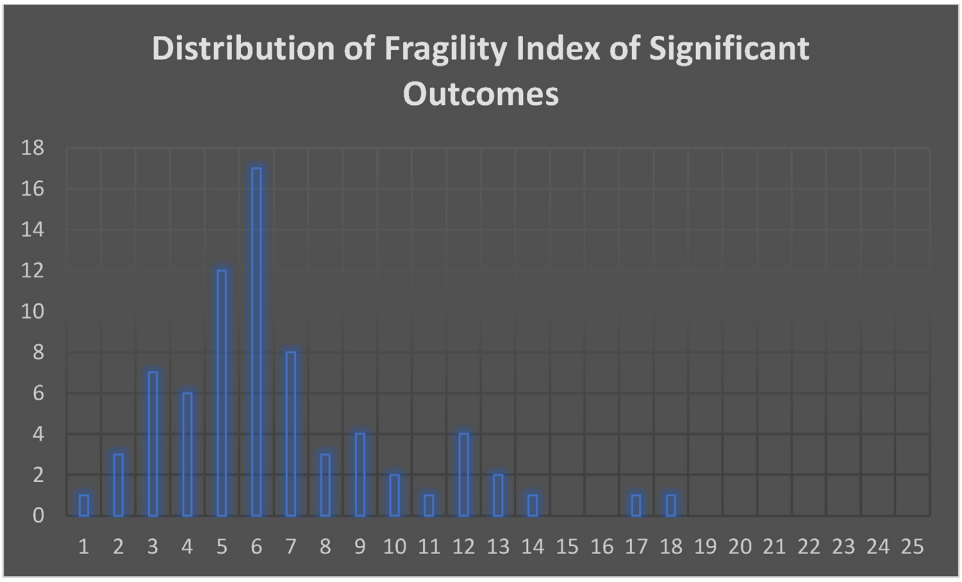

Figure 3. Distribution of fragility index among all 73 significant dichotomous outcomes.

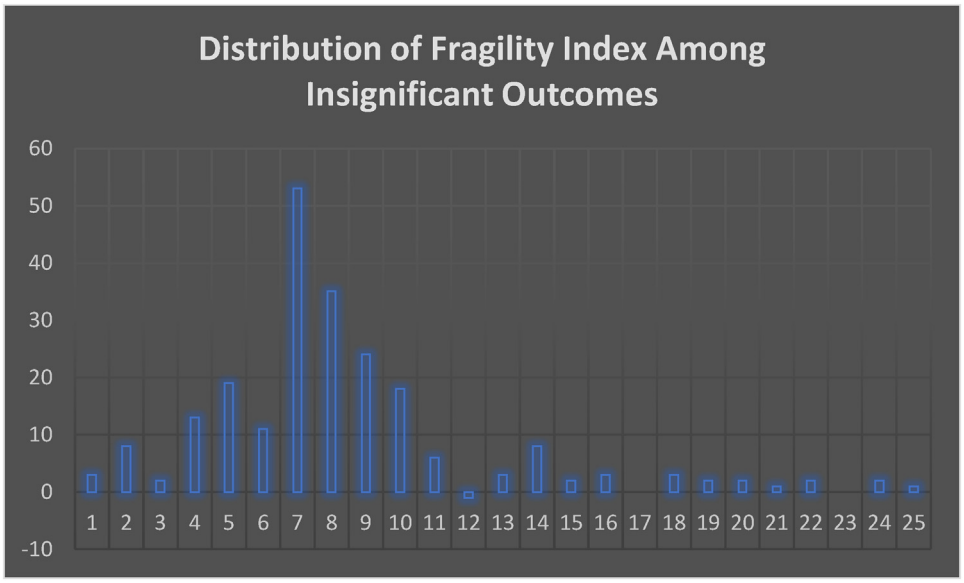

Figure 4. Distribution of fragility index among all 220 insignificant dichotomous outcomes.

have excluded RCTs that would have otherwise fit inclusion criteria. Additionally, the concept of FI has intrinsic limitations itself. FI is a standalone value with no prescribed threshold to indicate fragility or stability of the study in question and, moreover, does not incorporate the study's sample size into consideration. FQ was introduced to mitigate some of these limitations, but even FQ is limited by no true threshold to confer fragility or lack thereof. Finally, only dichotomous outcomes were included in the analysis of fragility. The inability to assess the fragility of continuous outcome variables limits the generalizability of this study's findings.

Conclusions

Our findings suggest that RCTs evaluating VTE prophylaxis following total hip arthroplasty and total knee arthroplasty may lack statistical stability as few outcome events are required to reverse the significance of outcomes. Future randomized trials should consider reporting FI and FQ along with the *P* value analysis to provide better context to the integrity of statistical stability.

Conflicts of interest

Dr. H. R. Boucher receives royalties from Innomed and Aesculap/B. Braun and is a paid consultant for Globus Medical, Inc. The other 2 authors declare no potential conflicts of interest.

For full disclosure statements refer to https://doi.org/10.1016/j.artd.2023.101111.

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Appendix

Search strategy

1. "Venous thromboembolism"/all subheadings
2. "hip arthroplasty"/all subheadings
3. "knee arthroplasty"/all subheadings
4. "hip replacement"/all subheadings
5. "knee replacement"/all subheadings
6. #1 AND (2 OR 3 OR 4 OR 5)

Search strategy for RCTs

1. Randomized control trial
2. Controlled clinical trial
3. Random allocation
4. Double blind method
5. Single blind method
6. 1 OR 2 OR 3 OR 4 OR 5 OR 6
7. Human NOT Animal
8. Clinical trial