Hospital-Acquired Venous Thromboembolism or Bleeding Following Total Joint Arthroplasty: A Systematic Review and meta-analysis for the Association of the Gene Polymorphism.

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Hospital-Acquired Venous Thromboembolism or Bleeding Following Total Joint Arthroplasty: A Systematic Review and meta-analysis for the Association of the Gene Polymorphism.

Michael Debeau, Mohamed E Awad MD, Adel Hijazi, Ahmad I Hasan, Mariana Roldan, Justin Hruska MD, Gamal Mostafa MD, Khaleed J. Saleh MD.

Data Collection & Analysis
A total of 23 publications were identified from the literature search specific to Hospital-Acquired Venous Thromboembolism or Bleeding Following Total Joint Arthroplasty. Table 1: Literature Search

<table>
<thead>
<tr>
<th>Publication</th>
<th>Year</th>
<th>Country</th>
<th>Study Type</th>
<th>Patients</th>
<th>Control</th>
<th>Outcome</th>
<th>Method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

Introduction
The estimated rates of total hip arthroplasties (THA) and total knee arthroplasties (TKA) are projected to increase in the United States. Data obtained from the U.S. Census Bureau and US National Inpatient Sample projects the rate of THA to increase by 34%, 75%, 129%, and 284% by 2025, 2030, and 2040, respectively. Moreover, the rate of TKA is projected to increase by 56%, 110%, 182%, and 401%, respectively. Data from the National Inpatient Sample determine that 1.3% of the patients who received THA from 2009 and 2011 develop a hospital acquired infection (HAC)(3): Thromboembolic events, including pulmonary embolism (PE) and deep vein thrombosis (DVT) are common, life-threatening but preventable HACs that occur following TJA(1). Thromboembolism has multifactorial etiology and so contributing risk factors are environmental and genetic. Some environmental risk factors are provoking e.g. cancer, surgery, trauma, immobilization, pregnancy, long distance travel, hospitalization, catheterization, and acute infections. Other environmental risk factors are intrinsic to the patient e.g. age, sex, ethnicity, body mass index, oral contraceptive use, corticosteroid use, diabetes mellitus, and air pollution(4). There are many risk factors that specifically contribute to VTE following TJA. A metaanalysis of 14 case-control cohort studies provided significant relationship between VTE following TJA and prior history of VTE (RR = 10.6), varicose veins (RR = 3.2), and congenital cardiac defects (RR = 2.1). There was a VTE risk ranging from 8-10% for other factors which are listed in order of increasing risk: female gender, age > 80, hypertension, active cancer, BMI > 30, black ethnicity(5). Many genetic risk factors have also been identified, including factor V Leiden mutation and prothrombin gene polymorphism(6). Moreover, Wang et al. applied genetic risk scoring to known genetic polymorphisms associated with hemostatic disease provided 70.8% precision in identifying patients with VTE(s), which further supports a genetic role in VTE development.

Methods
This systematic review and meta-analysis were conducted according to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines (11) and the Cochrane Handbook(12).

Using the previously mentioned keywords, 304 relevant articles were obtained from the 3 online databases (PubMed, MEDLINE via Ovid, and Web of Science) as well as through manual retrieving. After screening and assessing eligibility, 23 clinical studies that investigated the association of genetic polymorphism and the incidence of venous thromboembolism following hip and knee arthroplasties were included. Only one of these 23 studies was randomized controlled trial. However, the remaining studies were prospective cohort (5 trials), retrospective cohort (2 trials) and case-control trials (15 trials). A flow chart demonstrating the study selection, inclusion, and exclusion process is shown in Figure 1 (Study Characteristics). One Randomized Controlled trial (RCT), two retrospective cohort, five prospective cohort, and 17 case-control studies of the study period between 1997 and 2018 have examined the genetic association with the incidence of VTE. 8908 patients were enrolled in the 23 studies. A total of 69.5% (16/23) trials have studies these association in Caucasian population. However, Asian population were the subjects in 7 trials. The mean age of the VTE group across all studies was 66.3, while that in the non-VTE group was 65.1. A total of 36.3% (8/23) trials have been conducted in the United States, three trials in China, two trials in (2/23) and Korea (2/23) While the other six trials came from Japan (1/23), Sweden (1/23), Hungary(1/23), Germany (1/23), India (1/23), and Australia (1/23).

Results
Meta-analysis: 1. Factor V Leiden (FVL) G1691A polymorphism Seventeen clinical trials (15-30) investigated the association of FVL (G1691A polymorphism) in Caucasian (14 trials) and Asian (3 trials) populations with VTE following TJA. The pooled results showed that FVL-G1691A polymorphism, in Caucasian populations, is statistically significant associated with the incidence of VTE following TJA. (OR = 1.295955, CI: 1.01-1.80; p value = 0.035) Asian population showed no association between FVL polymorphism and the incidence of VTE.

2. Angiotensin Converting Enzyme (ACE) deletion/ deletion (D/D) genotype Three trials(31) investigating the association of Angiotensin Converting Enzyme (ACE) (D/D) genotype in Caucasian populations with VTE following TJA. The pooled results showed that there is no statistically significant association between ACE-D/D polymorphism, the population- and the incidence of VTE. (OR = 1.49 (95% CI 0.92-2.29; p value = 0.15) [figure 3]

3. Prothrombin gene (G20210A): Twelve clinical trials(32, 17, 20-22, 27-29, 31, 32) investigated the association of Prothrombin (G20210A) polymorphism in Caucasian (7 trials) and Asian (5 trials) populations with VTE following TJA. The pooled results showed that Prothrombin G20210A polymorphism, in Caucasian populations, is statistically significant associated with the incidence of VTE following TJA. (OR = 2.24 (95% CI 1.73-2.86; p value = 0.0005) [figure 4] Asian population showed no association between FVL polymorphism and the incidence of VTE.

4. Methylene tetrahydrofolate Reductase (C677T/TT) genotype Eight trials (16, 20-22, 24, 29, 32, 33) investigated the association of Methylene tetrahydrofolate Reductase (C677TT) in Caucasian (5 trials) and Asian (3 trials) with VTE following TJA. The pooled results showed that there is no statistically significant association between MTHFR polymorphism-regardless the population- and the incidence of VTE. (OR= 0.97 (95% CI 0.69-1.38; p value = 0.83) [figure 4]

5. Plasma proconvertin activator inhibitor-1 (PAI-1) G4G4 genotype Four trials (16, 24, 27, 34) investigated the association of PAI-1 G4G4 polymorphism in Caucasian populations with VTE following TJA. The pooled results showed that PAI-1 G4G4 polymorphism in Caucasian populations, is statistically significant associated with the incidence of VTE following TJA. (OR = 1.72 (95% CI 1.01-2.93; p value = 0.05) [figure 4]

Figure 1: Strengthening the Reporting of Genetic Association Studies (STREGA)

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVL</td>
<td>1.295955</td>
<td>0.035</td>
</tr>
<tr>
<td>ACE</td>
<td>1.49</td>
<td>0.15</td>
</tr>
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<td>Proth</td>
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<tr>
<td>PAI-1</td>
<td>1.72</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Conclusion
In conclusion, we do recommend that physicians screen TJA patients peri-operatively for Factor V Leiden mutation, G20210A prothrombin mutation, and PAI-1 G4G4 genotype. Detecting these genetic polymorphisms could be a good step to prevent the incidence of postoperative venous thromboembolism following TJA. Moreover, the ACe delee/ deletion genotype are similarly unlikely to be associated with VTE. Moreover, patients that develop DVT might benefit from perioperative screening for PAI-1 G4G4 to determine if they are likely to be resistant to anticoagulation therapy. Patients would benefit from a screen for MTHFR polymorphisms; however, orthopedic surgeons should be aware that only compound heterozygotes for C677T and A1298C polymorphisms have shown to be resistant to anticoagulation protocols.

References

The studies included in this meta-analysis contained an average STREGA score of 8 with a median of 7, mode of 7, and range of 1-11. Many of the studies stated the objectives and hypothesis, provided case eligibility criteria, defined all variables, contained replicable statistical methods, provided sufficient descriptive data (e.g. age, gender), and stated genotype frequencies. However, many of the studies lacked an assessment of study. Sensitivity analyses and/or meta-regression. The authors also did not present a flow chart of the study selection process (Table 2). The methodological quality of the 5-STAR meta-analysis score was plotted against year of publication in order to assess the methodological quality (Figure 3). There is a negative correlation (R2 = 0.8008, slope = -0.068)