Incidence, Outcomes and Risk Factors of Heparin-Induced Thrombocytopenia after Total Joint Arthroplasty: An Analysis of the National Inpatient Sample Database

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Research article

Keywords: Heparin-induced thrombocytopenia, National Inpatient Sample, Total knee and hip arthroplasty

DOI: https://doi.org/10.21203/rs.3.rs-40244/v1

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Abstract

Background Heparin-induced thrombocytopenia (HIT) is a severe immune-mediated complication of heparin exposure, leading to negative consequences after total hip (THA) and knee arthroplasty (TKA). However, the incidence and risk factors of HIT remain to be elucidated. This study aimed to identify the incidence, outcomes, and risk factors of HIT after THA and TKA. 

Methods A retrospective study was conducted using the National Inpatient Sample (NIS) database from 2005 to 2014. The incidence and outcomes of HIT after THA or TKA were documented. Logistic regression analysis was performed to identify the postoperative HIT risk factors. 

Results A total of 593,045 patients who underwent THA and 1,228,707 patients who underwent TKA were identified. The cumulative incidences were 0.02% and 0.01%, respectively. The HIT group presented significantly higher Charlson Comorbidity Index (CCI) and Elixhauser Comorbidity Index (ECI) scores, longer hospital stays (LOS), and higher medical costs. HIT led to a significantly higher mortality rate after THA (2.17% vs. 0.16%, p =0.0091). Although not statistically significant, the HIT mortality rate after TKA was also increased (0.58% vs. 0.07%; p =0.1178). In THA, the risk factors of HIT were racial minority, AIDS, pulmonary circulation disorders (PCD), psychoses, and hypertension; the protective factors were large-scale and teaching hospitals. In TKA, the HIT risk factors were racial minority, PCD, and weight loss. Teaching hospitals served as protective factors. 

Conclusions The incidence of HIT after THA and TKA is relatively low; however, HIT significantly increases inpatient mortality, LOS, and medical cost. Therefore, HIT warrants considerable attention and further investigation.

Introduction

Heparin-induced thrombocytopenia (HIT) is a severe immune-mediated complication caused by heparin drugs during anticoagulant therapy. It is characterized by the formation of antibodies against the complex of heparin and platelet factor 4 (PF4). Such immune complexes further initiate coagulation. The clinical signs and symptoms include a significant decline in the platelet count (thrombocytopenia), thrombosis, and ulcerating skin lesions. These all lead to financial and health burdens. Anti-PF4/heparin antibodies have been uncommonly detected in healthy individuals with an incidence of only 0.3–0.5%. In cases of infection and surgical inflammation, HIT might occur without heparin exposure. This is known as spontaneous HIT and is an infrequent clinical disorder. However, most HIT cases usually occur after heparin exposure—especially unfractionated heparin (UFH)—either prophylactically or therapeutically.

Patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA) are recommended to receive routine chemical thromboprophylaxis to prevent severe complications. These include deep vein thrombosis (DVT) and pulmonary embolism (PE). Although the incidence of thrombotic complications after THA or TKA have decreased substantially, the use of heparin carries a risk of potentially resulting to HIT. Therefore, HIT after THA or TKA has become increasingly common and has lead to a higher risk of hemorrhage and thrombosis.
Currently, there is no large-scale study on HIT in post-THA and post-TKA patients. Hence, the aim of this study was to investigate the incidence and risk factors of HIT in patients after TKA or THA using the National Inpatient Sample (NIS) database. To the best of our knowledge, this is the first study based on a large sample size that focuses on HIT after THA or TKA.

Methods

This retrospective cohort study was conducted using the NIS database. This database has been recognized as the largest national database in the United States since 1998.\(^9\)\(^,\)\(^13\) We investigated patients who underwent either THA or TKA in the United States from 2005 to 2014. The patients were identified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) procedure codes 81.51 and 81.54. For each procedure, the identified patients were divided into two groups, according to the presence of postoperative HIT (ICD-9 code 289.84). Those who were diagnosed with thrombocytopenia unrelated to heparin exposure were excluded. Studies on the baseline characteristics, hospital conditions, and risk factors of HIT were performed.

A chi-square test was used to evaluate the categorical variables which included grouped age and gender. A rank-sum test was used to assess the continuous variables including age, Charlson Comorbidity Index (CCI), Elixhauser Comorbidity Index (ECI), length of hospital stay (LOS), and total medical cost. CCI aggregated the prognostic burden of comorbid diseases. This index was used as an indicator to predict 1-year mortality. The ECI was applied to identify elevated mortality or hospital readmission risks. In addition, a logistic regression analysis was conducted to analyze the potential predictors of HIT. The odds ratios (OR) and 95% confidence intervals (CI) were calculated. The level of statistical significance was defined as \(p < 0.05\).\(^9\)\(^,\)\(^14\) All analyses were performed using the SPSS version 23 software (IBM; Armonk, New York).

Results

A total of 593,045 patients undergoing THA and 1,228,707 patients undergoing TKA were identified (Fig. 1). The annual incidence of HIT from 2005 to 2014 is shown in Fig. 2. The baseline characteristics and hospital conditions are presented in Table 1. The predictors for postoperative HIT are summarized in Table 2 below.
Table 1
Baseline and hospital-level characteristics of patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA).

|                           | The THA group |         |         | The TKA group |         |         |
|---------------------------|---------------|---------|---------|---------------|---------|---------|
|                           | No HIT        | HIT     | P value | No HIT        | HIT     | P value |
| **Median age**            | 66 (57–74)    | 68 (59–77) | 0.0597 | 67 (59–74)    | 71 (62–77) | 0.0001 |
| **Age group (%)**         |               |         |         |               |         |         |
| ≤ 50                      | 69,675 (11.76%) | 7 (7.61%) | 0.5287 | 78,669 (6.41%) | 6 (3.49%) | 0.0001 |
| 51–60                     | 136,098 (22.97%) | 20 (21.74%) |        | 280,564 (22.85%) | 31 (18.02%) |        |
| 61–70                     | 175,122 (29.56%) | 27 (29.35%) |        | 433,428 (35.29%) | 46 (26.74%) |        |
| ≥ 71                      | 211,572 (35.71%) | 38 (41.30%) |        | 435,356 (35.45%) | 89 (51.74%) |        |
| **Female (%)**            | 331,637 (56.07%) | 47 (51.09%) | 0.3914 | 770,975 (62.87%) | 88 (51.16%) | 0.0019 |
| **Race (%)**              |               |         |         |               |         |         |
| White                     | 430,983 (86.45%) | 70 (82.35%) | 0.2014 | 857,654 (83.88%) | 115 (75.66%) | 0.0335 |
| Black                     | 35,296 (7.08%) | 6 (7.06%) |         | 75,661 (7.36%) | 12 (7.89%) |         |
| Hispanic                  | 16,098 (3.23%) | 4 (4.71%) |         | 54,640 (5.31%) | 13 (8.55%) |         |
| Asian or Pacific Islander | 4,525 (0.91%) | 0 (0.00%) |         | 12,885 (1.25%) | 3 (1.97%) |         |
| Native American           | 1,650 (0.33%) | 0 (0.00%) |         | 4,918 (0.48%) | 1 (0.66%) |         |
| Other                     | 9,996 (2.01%) | 5 (5.88%) |         | 22,801 (2.22%) | 8 (5.26%) |         |
| **CCI***                  | 3 (2–4)       | 4 (3–6) | < 0.0001 | 4 (3–4)       | 4 (3–5) | < 0.0001 |
| **ECI†**                  | 0 (-1–0)      | 4 (3–9) | < 0.0001 | 0 (-2–0)      | 3 (1–8) | < 0.0001 |

*: Charlson Comorbidity Index; †: Elixhauser Comorbidity Index; ‡: the length of hospital stay. The impact of HIT on mortality was evaluated by the Fisher’s exact test.
|                        | The THA group | The TKA group | P value |
|------------------------|---------------|---------------|---------|
| **LOS‡**               | 3 (3–4)       | 5 (3–7)       | <0.0001 |
| **Total medical cost** | 44,288        | 67,706        | <0.0001 |
|                        | (32719–61371) | (45081–106011)|         |
| **Mortality**          | 926 (0.16%)   | 2 (2.17%)     | 0.0091  |
|                        | 899 (0.07%)   | 1 (0.58%)     | 0.1178  |

*: Charlson Comorbidity Index; †: Elixhauser Comorbidity Index; ‡: the length of hospital stay. The impact of HIT on mortality was evaluated by the Fisher’s exact test.
Table 2
Predictors of HIT in patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA).

|                         | The THA group | The TKA group |
|-------------------------|---------------|---------------|
|                         | OR*           | 95% CI†       | P value | OR           | 95% CI       | P value     |
| Age(≥ 61)               | 0.72          | 0.42–1.23     | 0.2286  | 0.80         | 0.53–1.21    | 0.3003      |
| Female                  | 1.01          | 0.63–1.60     | 0.9761  | 1.04         | 0.74–1.45    | 0.8360      |
| Race                    |               |               |         |             |              |             |
| White                   | 1.00          | 0.42–2.38     | 0.9989  | 1.25         | 0.68–2.32    | 0.4707      |
| Black                   | 1.34          | 0.48–3.78     | 0.5784  | 1.52         | 0.85–2.74    | 0.1596      |
| Hispanic                | 2.65          | 1.02–6.63     | 0.0452  | 2.33         | 1.12–4.83    | 0.0228      |
| Asian or Pacific Islander| 0.01          | 0.00-Inf      | 0.9966  | 1.56         | 0.49–4.97    | 0.4554      |
| Native American         | 0.01          | 0.00-Inf      | 0.9980  | 1.89         | 0.26–13.88   | 0.5316      |
| Other                   |               |               |         |             |              |             |
| Hospital bed size       |               |               |         |             |              |             |
| Small                   | 0.72          | 0.40–1.30     | 0.2731  | 0.66         | 0.38–1.15    | 0.1407      |
| Medium                  | 0.46          | 0.27–0.80     | 0.0059  | 1.07         | 0.69–1.68    | 0.7616      |
| Large                   |               |               |         |             |              |             |
| Teaching status of hospital |          |               |         |             |              |             |
| Non-teaching hospital   |               |               |         |             |              |             |
| Teaching hospital       | 0.58          | 0.36–0.91     | 0.0182  | 0.68         | 0.48–0.96    | 0.0280      |
| Location of hospital    |               |               |         |             |              |             |
| Rural                   |               |               |         |             |              |             |

*: Odds Ratios; †: 95% Confidence Intervals; ‡: Acquired Immune Deficiency Syndrome; §: rheumatoid arthritis or collagen vascular diseases; ||: weight loss. Weight loss is not strictly defined per ICD-9 coding criteria; rather, it is determined by the discretion of the health care provider.
| Condition                                | The THA group | The TKA group |
|------------------------------------------|---------------|---------------|
| Urban                                    | 1.33          | 0.72          |
| AIDS‡                                    | 5.86          | 0.00-Inf      |
| Alcohol abuse                            | 1.70          | 0.68          |
| Deficiency anemias                       | 0.81          | 0.97          |
| RA or CV§                                | 1.42          | 0.97          |
| Chronic blood loss anemia                | 0.35          | 0.32          |
| Congestive heart failure                 | 0.68          | 1.52          |
| Chronic pulmonary disease                | 0.82          | 0.91          |
| Coagulopathy                             | < 0.01        | < 0.01        |
| Depression                               | 1.42          | 0.87          |
| Diabetes (uncomplicated)                 | 1.14          | 1.06          |
| Diabetes with chronic complications      | 2.38          | 0.83          |
| Drug abuse                                | 2.26          | 3.17          |
| Hypertension                             | 2.57          | 1.02          |
| Hypothyroidism                           | 1.61          | 0.82          |
| Liver disease                            | 0.78          | 0.48          |
| Lymphoma                                 | 1.85          | 0.84          |

*: Odds Ratios; †: 95% Confidence Intervals; ‡: Acquired Immune Deficiency Syndrome; §: rheumatoid arthritis or collagen vascular diseases; ||: weight loss. Weight loss is not strictly defined per ICD-9 coding criteria; rather, it is determined by the discretion of the health care provider.
| Condition                                | The THA group        | The TKA group        |
|------------------------------------------|----------------------|----------------------|
| Fluid and electronic disorder            | 0.66 0.37–1.16       | 0.97 0.65–1.45       |
| Metastatic cancer                        | 0.01 0.00-Inf        | 0.01 0.00-Inf        |
| Other neurological disorders             | 0.90 0.36–2.29       | 1.14 0.59–2.19       |
| Obesity                                  | 0.86 0.46–1.63       | 1.13 0.76–1.66       |
| Paralysis                                | 1.74 0.23–13.35      | 1.28 0.17–9.45       |
| Peripheral vascular disorders            | 0.85 0.30–2.39       | 1.56 0.81–3.01       |
| Psychoses                                | 2.63 1.08–6.40       | 0.41 0.10–1.67       |
| Pulmonary circulation disorders          | 4.14 1.83–9.40       | 4.38 2.50–7.65 <0.0001|
| Renal failure                            | 0.79 0.38–1.65       | 1.05 0.61–1.80       |
| Solid tumor without metastasis           | 0.01 0.00-Inf        | 0.01 0.00-Inf        |
| Peptic ulcer disease excluding bleeding  | 0.01 0.00-Inf        | 0.01 0.00-Inf        |
| Valvular disease                         | 1.38 0.67–2.82       | 0.99 0.53–1.84       |
| Weight loss†                             | 1.57 0.47–5.23       | 2.75 1.08–6.99       |

*: Odds Ratios; †: 95% Confidence Intervals; ‡: Acquired Immune Deficiency Syndrome; §: rheumatoid arthritis or collagen vascular diseases; ||: weight loss. Weight loss is not strictly defined per ICD-9 coding criteria; rather, it is determined by the discretion of the health care provider.

**HIT after THA**

The inpatient mortality was significantly higher in patients with HIT after THA (2.17% vs. 0.16%, \( p = 0.091 \)). Patients in the HIT group had significantly higher CCI and ECI scores, longer hospital stays, and more burdensome medical costs (\( p < 0.0001 \)).

Racial minorities (OR = 2.60, 95% CI 1.02–6.63, \( p = 0.0452 \)), AIDS (OR = 5.86, 95% CI 1.27–27.12, \( p = 0.0236 \)), pulmonary circulation disorders (OR = 4.14, 95% CI 1.83–9.40, \( p = 0.0007 \)), psychoses (OR = 2.63, 95% CI 1.08–6.40, \( p = 0.0326 \)), and hypertension (OR = 2.57, 95% CI 1.47–4.50, \( p = 0.0010 \)) were identified.
as independent risk factors of postoperative HIT. The protective factors were large-scale hospitals (OR = 0.46, 95% CI 0.27–0.80, \( p = 0.0059 \)) and teaching hospitals (OR = 0.58, 95% CI 0.36–0.91, \( p = 0.0182 \)).

**HIT after TKA**

The median ages (71 vs. 67 years, \( p < 0.0001 \)) and the proportions of patients over 70 years (51.74% vs. 35.45%, \( p < 0.0001 \)) in the HIT group were significantly higher. Races other than Caucasians earned higher percentages in the HIT group as well (\( p = 0.0335 \)). The proportion of females in the HIT group was significantly lower (51.16% vs. 62.87%, \( p = 0.0019 \)). Although not statistically significant, HIT was demonstrated to result in a higher death rate after TKA (0.58% vs. 0.07%; \( p = 0.1178 \)). Additionally, the HIT group presented significantly higher CCI and ECI scores, longer hospital stays, and more burdensome medical costs (\( p < 0.0001 \)).

Patients from other minor racial ethnicities (OR = 2.33; 95% CI 1.12–4.83; \( p = 0.0228 \)), pulmonary circulation disorders (OR = 4.38; 95% CI 2.50–7.65; \( p < 0.0001 \)), and weight loss (OR = 2.75; 95% CI 1.08–6.99; \( p = 0.0332 \)) were identified as risk factors for HIT. The protective factors were teaching hospitals (OR = 0.68; 95% CI 0.48–0.96; \( p = 0.0280 \)).

**Discussion**

THA and TKA are the most frequently performed joint replacement surgeries. The annual demands for primary THA and TKA are estimated to reach 174% and 673% by the year 2030, respectively.\(^{15,16} \) Patients undergoing total joint arthroplasty (TJA) have a high risk of developing thrombotic complications due to reduced blood flow, thrombophilia, and damage to the venous linings.\(^{17–20} \) Thus, after TJA, patients are recommended to routinely receive prophylactic anticoagulation.\(^{19} \) However, HIT — one of the most dangerous pro-thrombotic disorders — may occur during anti-thrombotic prophylaxis.\(^{1,12,21} \) HIT patients have a higher risk of developing paradoxical thrombotic syndrome.\(^{22–24} \) Hence, it is critical to understand the incidence and risk factors of HIT.

Despite the performance of TJA soaring from 2005 to 2014, the incidence of HIT after TJA has remained at 0.01–0.03%. This is consistent with the results reported by Craik.\(^{10} \) In 2008, the American Academy of Orthopedic Surgeons (AAOS) released a guideline recommending thromboprophylaxis after TJA.\(^{17} \) Thereafter, chemoprophylaxis has been done more routinely.\(^{10,12,25} \) Although it has not been commonly diagnosed, HIT has been recognized as one of the thromboembolic complications of patients after TJA. HIT has resulted to negative effects on surgical outcomes. Interestingly, compared with the incidence of postoperative HIT to other procedures, Dhakal et al.\(^{26} \) reported that the risk of HIT after TJA was lower. A possible explanation might be the application of low molecular weight heparin (LMWH) rather than UFH. Thus, routine laboratory monitoring was not recommended for HIT after TJA.\(^{10,25,27} \) However, according to our study, the cases of inpatient mortalities in post-THA patients were 13.75 times higher (2.2% vs. 0.16%) and 8.3 times higher than in post-TKA patients (0.58% vs. 0.07%), respectively. It is critical to identify the HIT risk factors and keep in mind that HIT may take place during LMWH exposure.
There have been controversial conclusions about the risk factors of HIT. In contrast to our results, Warkentin et al.\textsuperscript{28} and Chaudhry et al.\textsuperscript{29} found the female gender as a risk factor to HIT. This may be due to the different immune responses after various surgeries\textsuperscript{29}, or the different thromboprophylactic therapies employed.\textsuperscript{28} The racial differences\textsuperscript{30} and polymorphism variabilities\textsuperscript{31} have also been reported by other researchers. For example, non-Caucasians had higher thrombotic risks of HIT development after undergoing any procedure on their current admission.\textsuperscript{30} Furthermore, large-scale and teaching hospitals served as protective factors after THA.

The study of preoperative comorbidities may be valuable in preventing HIT. For THA, AIDS, hypertension, psychoses, and pulmonary circulation disorders increased the risk of postoperative HIT. In TKA patients, pulmonary circulation disorders and weight loss were identified as risk factors. To date, there is no established mechanism able to explain the above findings. One possible explanation is the formation of nonspecific and dysregulated antibodies triggered by pathological processes.\textsuperscript{32} Specially, in the case of psychoses, the combined use of heparin and psychotropic medications may result in adverse hematologic effects.\textsuperscript{33}

The application of novel anticoagulants may provide a good opportunity of decreasing HIT. Argatroban and lepirudin, both direct thrombin inhibitors, have been estimated to have comparative efficacy and safety in the management of HIT.\textsuperscript{34} Danaparoid has been found to have less influence on platelets compared with other anticoagulants because it inhibits factor Xa selectively.\textsuperscript{35} However, given the low incidence of HIT after TJA, LMWH is still the preferred chemoprophylaxis after TJA in patients without a history of HIT.\textsuperscript{17,19,20}

This study had several limitations. First, as a retrospective study utilizing the NIS database, coding and data-entry errors may have existed and led to an erroneous estimation of the HIT. Second, the limited elements and absence of follow-up in the NIS database made it impossible to analyze the long-term HIT outcomes. For instance, we were unable to accurately select patients with heparin therapy through the ICD-9 code. This made it inevitable to rule out patients without heparin admission. Finally, the different risk factors of HIT after THA and TKA were identified without established mechanisms. Bias in the medical records, utilization of tourniquet in the TKA, and the different seroconversion rates of anti-PF4/heparin antibodies between the two procedures\textsuperscript{36} might have contribute to the difference in the results. Further prospective, evidence-based studies are needed to determine the exact causalities between comorbidities and HIT.

**Conclusion**

According to our study based on a large sample size, the incidence of HIT in patients undergoing THA and TKA is relatively low. However, HIT significantly increases inpatient mortality. Thus, considerable attention and further investigations regarding HIT are warranted. Orthopedic surgeons should remain
vigilant to the occurrence of HIT during postoperative anticoagulant therapy. They should also be aware of the risk factors of HIT to further improve patient outcomes.

**Abbreviations**

| Abbreviation | Description                        |
|--------------|------------------------------------|
| AAOS         | American Academy of Orthopedic Surgeons |
| CCI          | Charlson Comorbidity Index         |
| CI           | Confidence intervals               |
| DVT          | Deep vein thrombosis               |
| ECI          | Elixhauser Comorbidity Index       |
| HIT          | Heparin-induced thrombocytopenia   |
| LMWH         | Low molecular weight heparin       |
| LOS          | Length of hospital stay            |
| NIS          | National Inpatient Sample          |
| OR           | Odds ratios                        |
| PCD          | Pulmonary circulation disorders    |
| PE           | Pulmonary embolism                 |
| THA          | Total hip arthroplasty             |
| TJA          | Total joint arthroplasty           |
| TKA          | Total knee arthroplasty            |

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and materials**
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This research did not receive any funding or financial support.

**Authors’ contributions**

YH.C, J.W, and Y.Z performed this study, analyzed and interpreted data; J.W, Y.Z and YH.C designed the study; QF.Y, YC.X. carried out data collection; and YH.C and Y.Z wrote the manuscript.

**Acknowledgments**

Not applicable.

**References**

1. Arepally GM. Heparin-induced thrombocytopenia. Blood 2017;129:2864-72.
2. Spyropoulos AC, Magnuson S, Koh SK. The use of fondaparinux for the treatment of venous thromboembolism in a patient with heparin-induced thrombocytopenia and thrombosis caused by heparin flushes. Ther Clin Risk Manag. 2008;4:653-7.
3. Haffner M, Heyrani N, Meehan JP, Giordani M. Enoxaparin-induced skin necrosis at injection site after total knee arthroplasty. Arthroplasty Today. 2018;4:10-4.
4. Krauel K, Pötschke C, Weber C, Kessler W, Fürll B, Ittermann T, et al. Platelet factor 4 binds to bacteria, inducing antibodies cross-reacting with the major antigen in heparin-induced thrombocytopenia. Blood. 2011;117:1370-8.
5. Hursting MJ, Pai PJ, McCracken JE, Hwang F, Suvama S, Lokhnygina Y, et al. Platelet factor 4/heparin antibodies in blood bank donors. Am J Clin Pathol. 2010;134:774-80.
6. Elshoury A, Khedr M, Abousayed MM, Mehdi S. Spontaneous heparin-induced thrombocytopenia presenting as bilateral adrenal hemorrhages and pulmonary embolism after total knee arthroplasty. Arthroplasty Today. 2015;1:69-71.
7. Warkentin TE, Basciano PA, Knopman J, Bernstein RA . Spontaneous heparin-induced thrombocytopenia syndrome: 2 new cases and a proposal for defining this disorder. Blood 2014;123:3651-4.
8. Poudel DR, Ghimire S, Dhital R, Forman DA, Warkentin TE. Spontaneous HIT syndrome post-knee replacement surgery with delayed recovery of thrombocytopenia: a case report and literature review. Platelets. 2017;28:614-20.
9. Telila T, Akintoye E, Ando T, Merid O, Mallikethi-Reddy S, Briasoulis A, et al. Incidence and outcomes of heparin-induced thrombocytopenia in patients undergoing transcatheter aortic valve replacement. American Journal of Cardiology. 2017;120:300-3.

10. Craik JD, Cobb AG. Heparin-induced thrombocytopenia following hip and knee arthroplasty. Brit J Haematol. 2013;161:255-61.

11. Hill J, Treasure T. Reducing the risk of venous thromboembolism in patients admitted to hospital: summary of NICE guidance. BMJ. 2010;340:c95.

12. Chow VW, Abnousi F, Huddleston JI, Lin LH. Heparin-induced thrombocytopenia after total knee arthroplasty with subsequent adrenal hemorrhage. The Journal of Arthroplasty. 2012;27:1413-5.

13. Chung AS, Campbell DH, Hustedt JW, Olmscheid N, Chutkan N. Inpatient outcomes in dialysis-dependent patients undergoing elective lumbar surgery for degenerative lumbar disease. Spine. 2017;42:1494-501.

14. Kumar R, Bhandari S, Singh SRK, Malapati S, Cisak KI. Incidence and outcomes of heparin-induced thrombocytopenia in solid malignancy: an analysis of the national inpatient sample database. Br J Haematol 2020;189:543-50.

15. Hochman MG, Melenevsky YV, Metter DF, Roberts CC, Bencardino JT, Cassidy RC, et al. ACR appropriateness criteria imaging after total knee arthroplasty. J Am Coll Radiol. 2017;14:S421-48.

16. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007;89:780-5.

17. Parvizi J, Azzam K, Rothman RH. Deep venous thrombosis prophylaxis for total joint arthroplasty: American Academy of Orthopedic Surgeons guidelines. J Arthroplasty. 2008;23:2-5.

18. Azboy I, Groff H, Goswami K, Vahedian M, Parvizi J. Low-dose aspirin is adequate for venous thromboembolism prevention following total joint arthroplasty: a systematic review. J Arthroplasty 2020;35:886-892

19. Mont M, Jacobs JJ, Boggio LN, Bozic KJ, Valle CJD, Goodman SB, et al. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. J Am Acad Orthop Surg. 2011;19:768-76.

20. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e278S-325S.

21. Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. New Engl J Med. 1995;332:1330-5.

22. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. Am J Med. 1996;101:502-7.

23. Greinacher A, Farner B, Kroll H, Kohlmann T, Warkentin TE, Eichler P. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis: a retrospective analysis of 408
patients. Thromb Haemost 2005;94:132-5.

24. Fabris F, Luzzatto G, Soini B, Ramon R, Scandellari R, Randi ML, et al. Risk factors for thrombosis in patients with immune mediated heparin-induced thrombocytopenia. J Intern Med;252:149-54.

25. Linkins L, Dans AL, Moores LK, Bona R, Davidson BL, Schulman S, et al. Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e495S-e530S.

26. Dhakal B, Kreuziger LB, Rein L, Kleman A, Fraser R, Aster RH, et al. Disease burden, complication rates, and health-care costs of heparin-induced thrombocytopenia in the USA: a population-based study. Lancet Haematol. 2018;5:e220-31.

27. Haughton B, Haughton J, Norman JG, Navid A, Allport K, Andrews M, et al. Routine monitoring for heparin-induced thrombocytopenia following lower limb arthroplasty: is it necessary? A prospective study in a UK district general hospital. Orthop Traumatol Surg Res 2019;105:497-501.

28. Warkentin TE, Sheppard JJ, Sigouin CS, Kohlmann T, Eichler P, Greinacher A. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. Blood 2006;108:2937-41.

29. Chaudhry R, Wegner R, Zaki JF, Pednekar G, Tse A, Kukreja N, et al. Incidence and outcomes of heparin-induced thrombocytopenia in patients undergoing vascular surgery. J Cardiothorac Vasc Anesth. 2017;31:1751-7.

30. Lewis BE, Wallis DE, Hursting MJ, Levine RL, Leya F. Effects of argatroban therapy, demographic variables, and platelet count on thrombotic risks in heparin-induced thrombocytopenia. Chest. 2006;129:1407-16.

31. Hursting MJ, Jang I. Dosing patterns and outcomes in African American, Asian, and Hispanic patients with heparin-induced thrombocytopenia treated with argatroban. J Thromb Thrombolys. 2009;28:10-5.

32. Thompson GR, Lawrence VA, Crawford GE. HIV infection increases the risk of heparin-induced thrombocytopenia. Clin Infect Dis. 2007;45:1393-6.

33. Aksoy A, Erduran E, Gedik Y. A case of imipramine-associated immune thrombocytopenia. Turk J Pediatr. 2009;51:275-8.

34. Sun Z, Lan X, Li S, Zhao H, Tang Z, Xi Y. Comparisons of argatroban to lepirudin and bivalirudin in the treatment of heparin-induced thrombocytopenia: a systematic review and meta-analysis. Int J Hematol. 2017;106:476-83.

35. Nakase J, Toribatake Y, Mouri Y, Seki H, Kitaoka K, Tomita K. Heparin versus danaproid for prevention of venous thromboembolism after hip surgery. J Orthop Surg (Hong Kong). 2009;17:6-9.

36. Bito S, Miyata S, Migita K, Nakamura M, Shinohara K, Sato T, et al. Mechanical prophylaxis is a heparin-independent risk for anti-platelet factor 4/heparin antibody formation after orthopedic surgery. Blood. 2016;127:1036-43.
Figure 1

Flow diagram of the study population. NIS®National Inpatient Sample; ICD-9 CM: International Classification of Diseases, Ninth Revision, Clinical Modification; HIT: heparin-induced thrombocytopenia.

Figure 2

Incidence of HIT in patients undergoing THA and TKA from 2005 to 2014. HIT: heparin-induced thrombocytopenia; THA: total hip arthroplasty; TKA: total knee arthroplasty.