Am J Blood Res 2023;13(6):198-206
www.AJBlood.us /ISSN:2160-1992/AJBR0152876

Original Article

A retrospective analysis of the frequency of heparin-induced thrombocytopenia in the intensive care unit at a tertiary care center in Riyadh, Saudi Arabia

Ali H Mushtaq[1,2], Abdulrahman W Rasheed[2], Mouhamad G Jamil[3], Khalid Maghrabi[3], Osama Khoja[3], Muhammad R Sajid[1], Hani Tamim[1], Mohammad Hijazi[3], Tarek Owaidah[1,3]

[1]Al Faisal University, Riyadh, Saudi Arabia; [2]Department of Internal Medicine, Cleveland Clinic Foundation, Cleveland, Ohio, The United States of America; [3]Department of Hematology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Received August 11, 2023; Accepted December 21, 2023; Epub December 25, 2023; Published December 30, 2023

Abstract: Background: Heparin-induced thrombocytopenia (HIT) is an extremely serious and potentially fatal condition that can develop in patients taking heparin-based medications, such as unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). The incidence and risk factors for HIT in critically ill patients, however, are not well defined. Methods: We retrospectively collected data on HIT test results, route of heparin administration, age, sex, heparin type (UFH or LMWH), and date of illness from patients admitted to the intensive care unit (ICU) and regular nursing floor (non-ICU) at our hospital between January 2011 and December 2014. We screened patients for HIT using the 4T score and confirmed the diagnosis through laboratory testing (direct enzyme immunoassay immunoglobulin G [IgG] or a platelet-activating antibody). Results: We screened a total of 946 patients, 56 (5.9%) of whom were positive for HIT. Among 776 patients receiving UFH and 180 receiving LMWH, 2.8 and 6.6% developed HIT, respectively (P = 0.051). We then classified our patients into two groups: ICU, and non-ICU. In the non-ICU group (n = 317), 4 (2.7%) patients receiving LMWH and 25 (5.1%) receiving UFH were positive for HIT (P = 0.221). In the ICU group (n = 639), 1 (3.1%) patient receiving LMWH and 26 (9.1%) receiving UFH were positive for HIT (P = 0.249). The ICU group, therefore, had a higher cumulative incidence rate of HIT than the non-ICU group (8.5 vs. 4.5%). Conclusion: HIT was more common in ICU patients than non-ICU patients and in more patients receiving UFH than LMWH, although the differences were not statistically significant. Early diagnosis and appropriate treatment are essential to prevent adverse outcomes in patients with HIT.

Keywords: Heparin-induced thrombocytopenia, heparin, intensive care unit, critical illness, low molecular weight heparin

Introduction

Heparin and its derivatives are widely used as anticoagulants for the prevention and treatment of various medical conditions. Among the most common applications of heparin are prophylaxis and treatment of deep venous thrombosis [1-4]. While hemorrhagic episodes are the prevailing adverse effects associated with heparin, some individuals are prone to developing thrombotic complications secondary to heparin-induced thrombocytopenia (HIT) [1]. HIT is a severe and potentially fatal immunologically mediated adverse drug reaction to heparin-based medications, unfractionated heparin (UFH), and low-molecular-weight heparin (LMWH). Medical professionals need to be more aware of the presence of HIT to ensure its detection, treatment, and prevention of its serious repercussions, especially considering relevant literature reports. HIT-related mortality is estimated to be 20-30% [5]. The morbidity and mortality of HIT are affected by the misdiagnosis of the condition, along with the misunderstanding of the course of the illness [1].

The incidence of HIT is significantly reduced in patients receiving LMWH (0.1-0.5%) than in

https://doi.org/10.62347/GPME5540

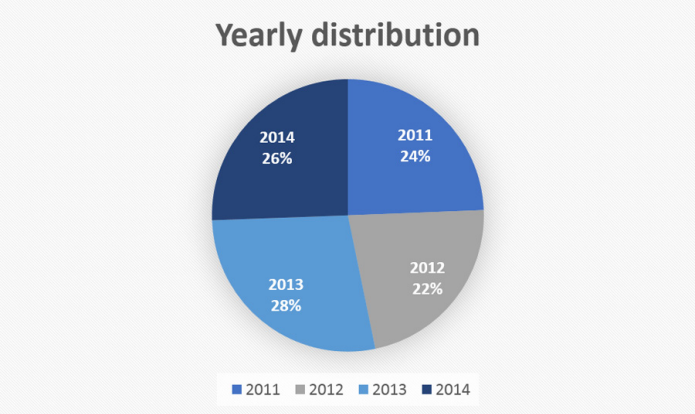

Figure 1. Depicts the annual development of HIT from January 2011 to December 2014.

those receiving UFH (0.5-1%) [2, 4-8]. Numerous patient and drug related factors influence the likelihood of someone developing HIT, although the factors most closely linked to an increased likelihood of developing HIT include the length of heparin therapy, type and dose of heparin used, underlying indications for heparin treatment, and patient sex [8-10].

HIT should be suspected in patients who have new complaints of new-onset thrombocytopenia, development of venous or arterial thromboses, or necrotic skin lesions at heparin injection sites after receiving prolonged LMWH treatment or starting heparin within the preceding 5-10 days [11, 12]. Thrombocytopenia affects 95% of all patients with HIT and is caused by platelet removal and consumption [13, 14]. HIT is a highly prothrombotic state, and as a result, 25-64% of individuals with HIT develop arterial or venous thromboses [2, 3, 5]. Thrombotic disorders can affect any part of the vasculature; however, venous thrombosis is most commonly observed and can cause gangrene, adrenal hemorrhage, skin necrosis, and/or pulmonary embolism [12, 15-17].

Diagnosing HIT can be challenging, especially in critically ill patients in the intensive care unit (ICU), where thrombocytopenia and thromboses are common for a variety of reasons [18-22]. The overall incidence of HIT reported in ICU patients is estimated to be between 0.4-3% [23, 24]. In a German study of 12,528 medical-surgical ICU patients, Selleng et al. [25] reported an incidence of HIT of 0.21%. Another large, randomized trial of 3,764 patients found the overall incidence of HIT to be 0.4% [6].

There is a paucity of studies analyzing the frequency of HIT in Saudi Arabia, particularly in critically ill ICU patients. The present study, therefore, aimed to retrospectively evaluate and compare the risk of developing HIT in association with the use of UFH and LMWH, specifically in patients admitted to medical wards and ICUs. The present study was a retrospective analysis of data from a large tertiary care center in Riyadh, Saudi Arabia.

Materials and methods

We conducted a retrospective study of all patients who received heparin (UFH or LMWH) and were diagnosed with HIT between January 2011 and December 2014 at King Faisal Specialist Hospital and Research Center (KFSHRC), Riyadh, Saudi Arabia (**Figure 1**). The data we collected included the HIT test results, enzyme-linked immunosorbent assay (ELISA) confirmation test results, age, sex, ICU status, type of heparin (UFH or LMWH), and route of administration (**Table 1**). We obtained a total of 1190 patient records to include in our study based on the following inclusive and exclusive criteria.

Inclusive criteria: Patients admitted to our hospital between January 2011 and December 2014 who received preventative or therapeutic doses of LMWH or UFH and underwent a HIT test due to clinical suspicion. Thrombocytopenia was defined as a >50% drop in platelet count from baseline or ≥2 consecutive platelet counts of <150,000 per mm^3.

Exclusive criteria: Patients who received both UFH and LMWH within 10 days of the test date or had a negative result within a week of the initial positive result were excluded.

Hospital guidelines recommend the use of the 4T scoring system to confirm clinical suspicion of HIT, as prompt initiation of treatment is of paramount importance in effective treatment. However, data regarding the 4T score were not collected in the present study. We instead used the results of a sensitivity and specificity assay for heparin immunoglobulin G (IgG) antibodies via an ELISA (Asserachrom HPIA-IgG, Stago Diagnostica STA®, Cedex, France) Tecan EVOlyzer machine to confirm the diagnosis of

Table 1. Patient demographics for all patients

	Frequency	Percentage
Sex		
Male	461	48.2
Female	495	51.8
ELISA Result		
Negative	900	94.1
Positive	56	5.9
Route		
IV	302	31.6
SC	543	56.8
Both	111	11.6
Type of Heparin		
LMWH	180	18.8
UFH	776	81.2
ICU		
Yes	317	33.2
No	639	66.8
Year of study		
2011	231	24.2
2012	212	22.2
2013	274	28.7
2014	239	25.0

ELISA: Enzyme-linked immunosorbent assay; IV: Intravenous; SC: Subcutaneous; LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; ICU: Intensive Care Unit.

HIT in all patients who experienced thrombocytopenia after receiving heparin. We did not use a serotonin release assay to confirm the diagnosis even though these assays have a higher specificity, given they are not always readily available and do not produce results quickly enough to help with the initial diagnostic clinical framework.

The HIT results were represented in optical density (OD) units, and based on the manufacturer's range, a value of >0.4 was regarded as positive. We excluded patients who received both UFH and LMWH within 10 days of the test date, or who had a negative result within a week of the initial positive result.

Statistical analysis

A statistical analysis was then performed to compare the incidence of positive results for each of the variables of interest. Multiple Pearson's chi-squared tests were conducted to assess the differences among numerous variables in the LMWH and UFH groups. These variables included HIT test results, mean platelet count, mean age, sex, and route of administration. Our patients were then split into two groups, ICU and non-ICU, and the same analysis was repeated within each of these groups to assess for a difference in the effect of heparin type in an ICU and non-ICU setting. Each Pearson's chi-squared was two-sided, with a *P*-value ≤0.05 considered statistically significant. Statistical analyses were performed using SPSS v25 software.

Results

Patient demographics

During the 4 years encompassing the present study, we analyzed the data of 956 patients, 461 (48.2%) of whom were men vs. 495 (51.8%) women. 639 (66.8%) were admitted to the regular nursing floors (non-ICU) vs. 317 (33.2%) to the ICU. The mean age of the patients was 54.7 years (standard deviation of 22.3 years), with a median age of 59.5 years and a median platelet count of 76 × 10^9/L. Most of the patients (81.2%) received UFH, while the rest (18.8%) received LMWH. Heparin was administered intravenously in 31.6% of the patients, subcutaneously in 56.8%, and through both routes in 11.6%. The overall incidence rate of positive heparin-PF4 antibody tests by ELISA was 5.9% (56 out of 946). **Table 2** shows the characteristics of all the patients who received LMWH and UFH. **Table 3** shows the characteristics of the non-ICU patients receiving LMWH and UFH. **Table 4** shows the characteristics of the ICU patients who received LMWH and UFH.

Incidence of HIT

The overall incidence of a positive heparin-PF4 antibody test was higher in those receiving UFH compared to LMWH. This finding was consistent when the patients were split into ICU and non-ICU patients. However, none of these findings were of statistical significance. Overall, the incidence of HIT in UFH vs. LMWH was 2.4 × higher (6.6 vs. 2.8%, respectively; $P = 0.051$). In the non-ICU setting, the incidence was 1.9 × higher (5.1 vs. 2.7%, respectively; $P = 0.221$). In the ICU setting, the incidence was 2.9 × higher (9.1 vs. 3.1%, respectively; $P = 0.249$). The overall incidence rate of HIT cases in the ICU

Table 2. Patient characteristics for all patients who received LMWH and UFH

	LMWH (n = 180)	UFH (n = 776)	*P*-value
Age, years, mean (SD)	50.4 (21.4)	55.8 (22.5)	0.004
Platelets, mean (SD)	103.8 (110)	84.9 (60.6)	0.002
Sex			
Males (%)	69 (38.3%)	392 (50.5%)	0.003
Females (%)	111 (61.7%)	384 (49.5%)	0.003
HIT testing results			
Negative, n (%)	175 (97.2%)	725 (93.4%)	0.051
Positive, n (%)	5 (2.8%)	51 (6.6%)	0.051
Heparin Route			
Intravenous, n (%)	0 (0.0%)	302 (38.9%)	<0.001
Subcutaneous, n (%)	179 (99.4%)	364 (46.9%)	<0.001
Both, n (%)	1 (0.6%)	110 (14.2%)	<0.001

LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; HIT: Heparin induced thrombocytopenia. We compared the differences between the 2 groups (UFH and LMWH) using chi squared tests for categorical variables (sex, HIT testing results, Heparin Route) and using T-test for continuous variables (age and platelets).

Table 3. Patient characteristics for non-ICU patients who received LMWH and UFH

	LMWH (n = 148)	UFH (n = 491)	*P*-value
Age, years, mean (SD)	49.87 (21)	53.24 (22.4)	0.105
Platelets, mean (SD)	105.81 (118.5)	88.78 (61.7)	0.021
Sex			
Males (%)	56 (37.8%)	253 (51.5%)	0.003
Females (%)	92 (62.2%)	238 (48.5%)	0.003
HIT testing results			
Negative, n (%)	144 (97.3%)	466 (94.9%)	0.221
Positive, n (%)	4 (2.7%)	25 (5.1%)	0.221
Heparin Route			
Intravenous, n (%)	0 (0.0%)	154 (31.4%)	<0.001
Subcutaneous, n (%)	147 (99.3%)	270 (55%)	<0.001
Both, n (%)	1 (0.7%)	67 (13.6%)	<0.001

LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; HIT: Heparin induced thrombocytopenia; ICU: Intensive Care Unit. We compared the differences between the 2 groups (UFH and LMWH) in non-ICU patients using chi squared tests for categorical variables (sex, HIT testing results, Heparin Route) and using T-tests for continuous variables (age and platelets).

group was higher than that in the non-ICU group (8.5 vs. 4.5%, respectively).

Platelet count

The overall mean platelet count was significantly lower in those receiving UFH than in those receiving LMWH (84.9 vs. 103.8; $P = 0.002$). This was also true in the non-ICU setting (88.78 vs. 105.81, respectively; $P = 0.021$). These results were also consistent in the ICU setting, but not statistically significant (78.2 vs. 94.3, respectively; $P = 0.136$). The mean platelet count was lower in the ICU setting compared to the non-ICU setting (79.8 vs. 93.7; respectively).

Route of heparin administration

There was a significant difference in the route of heparin administration between the patients receiving UFH and LMWH, with significantly more patients in the UFH group receiving the drug via an intravenous or combined route (38.9 and 14.2% vs. 0 and 0.6%, respectively; $P<0.001$). This trend remained consistent when analyzing ICU and non-ICU settings separately. Specifically, the intravenous administration of heparin was more prevalent in the ICU group compared to the non-ICU group (46.7% vs. 24.1%, respectively).

Age and gender

The mean age of the patients receiving UFH was significantly higher than that of those receiving LMWH (55.8 vs. 50.4 years; $P = 0.004$). There was a significant difference in sex distribution between the patients receiving UFH and LMWH, with significantly more females in the LMWH group (49.6 vs. 61.7%; $P = 0.003$).

Discussion

The present study aimed to compare the incidence and risk factors of HIT in patients admitted to the regular nursing floors (non-ICU) versus those in the ICU. Our findings are consistent with previously published studies, affirming the accuracy and practicality of the clinical pathways used for diagnosing and treating HIT [1, 2, 10, 11, 26, 27]. We observed an overall incidence of positive heparin-PF4 antibody tests at 5.9%, which

Table 4. Patient characteristics for ICU patients who received LMWH and UFH

	LMWH (n = 32)	UFH (n = 285)	*P*-value
Age, years, mean (SD)	53.09 (23.1)	60.14 (22.0)	0.089
Platelets, mean (SD)	94.34 (55.5)	78.20 (58.2)	0.136
Sex			
Males (%)	13 (40.6%)	139 (48.8%)	0.382
Females (%)	19 (59.4%)	146 (51.2%)	0.382
HIT testing results			
Negative, n (%)	31 (96.6%)	259 (90.9%)	0.249
Positive, n (%)	1 (3.1%)	26 (9.1%)	0.249
Heparin Route			
Intravenous, n (%)	0 (0.0%)	148 (51.9%)	<0.001
Subcutaneous, n (%)	32 (100%)	94 (33%)	<0.001
Both, n (%)	0 (0.0%)	43 (15.1%)	<0.001

LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; HIT: Heparin induced thrombocytopenia; ICU: Intensive Care Unit. We compared the differences between the 2 groups (UFH and LMWH) in non-ICU patients using chi squared tests for categorical variables (sex, HIT testing results, Heparin Route) and using T-tests for continuous variables (age and platelets).

aligns with the reported range of 0.1-5% in previous studies [23, 24, 28-30].

HIT incidence in patients receiving UFH vs. LMWH

We primarily investigated the impact of heparin type (UFH versus LMWH) on the incidence of HIT and found a higher incidence in those receiving UFH versus LMWH, although the difference was not statistically significant (6.6 vs. 2.8%, respectively; $P = 0.051$) aligning with previous literature [27, 31, 32]. However, a meta-analysis indicated comparable rates of clinical HIT with both medications at therapeutic levels (UFH, 1.5% vs. LMWH, 1.2%) [33, 34].

The formation of heparin-platelet 4 complexes is responsible for HIT, and its most common association is with the use of UFH, a finding consistent with other studies [2, 10, 27, 31, 35]. However, our study did not reveal a statistically significant difference in HIT development between LMWH and UFH in both ICU (P = 0.249) and non-ICU patients (P = 0.221). Nevertheless, a multicenter, randomized controlled study comparing the development of deep venous thrombosis with UFH and Dalteparin in an ICU setting reported a reduced HIT prevalence with Dalteparin (P = 0.046) [6]. In a subsequent sub-study of 17 trial participants who acquired HIT, it was discovered that those receiving Dalteparin had lower rates of seroconversion, thrombocytopenia, or thrombosis development. In addition, patients who were serologically tested for HIT and randomly assigned to Dalteparin had a 50% lower chance of testing positive for anti-PF4/heparin IgG antibodies (13 vs. 27%, $P = 0.001$) [36]. The use of Dalteparin at prophylactic dosages is particularly advantageous in critically ill patients with chronic kidney disease, including end-stage renal disease, as it does not bioaccumulate [37]. This is crucial when selecting thromboprophylaxis therapy for critically ill patients who often have underlying kidney dysfunction.

Platelet count in patients receiving UFH vs. LMWH

Regarding platelet count, our study detected a statistically significant reduction in the UFH group compared to the LMWH group. The difference may be explained by the increased age of the UFH group, as platelet counts are known to decrease with age [38]. Our study did not examine the clinical consequences of this thrombocytopenia and its possible role in increasing the likelihood of thrombosis. Consequently, further research is necessary to investigate these clinical ramifications. While our study found a greater frequency of HIT with UFH, the platelet count in the LMWH group, when stratified based on the ICU setting, was not significantly different (P = 0.136). The lower platelet counts in the ICU setting may be ascribed to the heightened prevalence of thrombocytopenia, affecting up to 41.3% of ICU patients [39]. Patients with positive HIT assay findings typically have other, more prevalent causes of thrombocytopenia than patients with negative HIT assay results, which adds another layer of complexity to the diagnosis [40]. Another critical consideration in the ICU setting is drug-induced thrombocytopenia, which is often mistaken for HIT. It typically presents with a platelet count drop 7-20 days after initiating the offending drug and identifying the causative agent can be challenging in critically ill patients receiving multiple medications simultaneously. Unlike thrombosis, drug-induced thrombocytopenia often results in significant reduction in platelet counts, falling below 20 ×

10^9/L, which can lead to increased problems with bleeding [25].

HIT incidence in an ICU vs. non-ICU setting

Our study also revealed that ICU patients demonstrated a higher likelihood of testing positive for HIT. This discrepancy may reflect the higher severity and complexity of illnesses in ICU patients, as well as greater and prolonged exposure to heparin [25, 41, 42]. Furthermore, our findings showed that HIT is more likely to occur via the intravenous route than via the subcutaneous route [43]. This corresponds with a study conducted by Crow et al. [43], indicating that patients who tested positive for HIT were more prone to have received heparin through both intravenous and subcutaneous routes, while the likelihood of HIT occurrence was lower when heparin was administered subcutaneously.

While the incidence of HIT was higher in an ICU setting (8.5% vs. 4.5% in a non-ICU setting), both LMWH and UFH remain optimal choices for anticoagulation in critically ill patients. Their familiarity among healthcare practitioners, the ability to directly measure their levels using anti-factor Xa levels, and the swift reversibility of their effects with protamine sulfate underscore their suitability. On the contrary, introducing non-heparin anticoagulants in patients with coagulopathy poses challenges due to uncertainties about their safety and effectiveness, especially in critically ill individuals.

HIT risk scores have not been thoroughly verified in critically ill patients; therefore, care must be taken when utilizing them to exclude HIT in the ICU population. The 4T score, for instance, has demonstrated low sensitivity and specificity in a cardiac surgery population. Prompting the proposal of alternative scoring systems such as the HIT Expert Probability (HEP) score to enhance diagnostic accuracy, especially in surgical ICU patients [43-45]. Patients with an ongoing clinical suspicion of HIT who initially have a low-risk 4T score should be re-evaluated to determine if their risk score has changed. Moreover, for patients with a moderate risk of HIT, consulting a hematologist is advised to navigate the challenges associated with halting heparin therapy and transitioning to potentially more detrimental and less effective anticoagulants.

Sex distribution among patients receiving UFH vs. LMWH

HIT represents a significant clinical adverse reaction, with research suggesting a higher prevalence, particularly among women, especially in cases involving UFH compared to LMWH [46]. Our findings revealed a greater proportion of females in the LMWH group compared to the UFH group (61.7% vs. 49.5%, P = 0.003). However, we did not conduct a subgroup analysis to assess whether this female-dominant population had a greater susceptibility to developing HIT compared to males. It is noteworthy that the distribution of males and females in ICU patients was not statistically significant.

Limitations

The present study had limitations that merit consideration. Despite being conducted at a large academic medical facility, its single-center design may limit its external validity. The retrospective nature of the study posed challenges in capturing a comprehensive dataset, potentially resulting in missing information on crucial variables and outcomes, including HIT-related confounders and HIT-induced thrombosis. Additionally, the study did not explore the impact of subgroup analyses based on heparin dosage, age, indications, or drug interactions introducing a potential gap in our understanding. These limitations highlight the need for future multi-center studies to enhance external validity and address these data-related challenges.

Conclusion

HIT poses a serious risk to patients in both ICU and non-ICU settings if not promptly identified and treated. Our study suggests that HIT is a frequent adverse effect of UFH and LMWH treatments in both ICU and non-ICU patients. Although we did not find a statistically significant difference between the UFH and LMWH groups in either setting, a lower incidence of HIT in the LMWH group implies potential benefits. Therefore, we recommend using LMWH over UFH for thromboprophylaxis in critically ill patients whenever possible. Further studies are needed to confirm our findings, explore the optimal dose, duration, indication, and reversal strategies in this population, and accurately

assess the risk of HIT in patients requiring prolonged courses of these medications.

Disclosure of conflict of interest

None.

Address correspondence to: Tarek Owaidah, Department of Hematology, King Faisal Specialist Hospital and Research Center, Al Mathar Ash Shamali, Riyadh 11564, Saudi Arabia. Tel: +966-11-464-7272; E-mail: towaidah@gmail.com

References

[1] Younes MA, Corrales JP, Mattour A, Rana J, Karam M, Shah S and Kuriakose P. Heparin induced thrombocytopenia: descriptive analysis of diagnosis and management. Blood 2011; 118: 1168.

[2] Kuter DJ, Konkle BA, Hamza TH, Uhl L, Assmann SF, Kiss JE, Kaufman RM, Key NS, Sachais BS, Hess JR, Ness P, McCrae KR, Leissinger C, Strauss RG, McFarland JG, Neufeld E, Bussel JB and Ortel TL. Clinical outcomes in a cohort of patients with heparin-induced thrombocytopenia. Am J Hematol 2017; 92: 730-738.

[3] Zhou CZ, Feng DJ, Fang Y, Zha FY, Wang EH, Li YZ, Wei MX and Wen JM. Research on clinical characteristics and prognostic analysis of heparin-induced thrombocytopenia after surgery for acute type a aortic dissection. J Cardiothorac Surg 2021; 16: 96.

[4] Dhakal B, Kreuziger LB, Rein L, Kleman A, Fraser R, Aster RH, Hari P and Padmanabhan A. Disease burden, complication rates, and health-care costs of heparin-induced thrombocytopenia in the USA: a population-based study. Lancet Haematol 2018; 5: e220-e231.

[5] Salter BS, Weiner MM, Trinh MA, Heller J, Evans AS, Adams DH and Fischer GW. Heparin-induced thrombocytopenia: a comprehensive clinical review. J Am Coll Cardiol 2016; 67: 2519-2532.

[6] PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group; Cook D, Meade M, Guyatt G, Walter S, Heels-Ansdell D, Warkentin TE, Zytaruk N, Crowther M, Geerts W, Cooper DJ, Vallance S, Qushmaq I, Rocha M, Berwanger O and Vlahakis NE. Dalteparin versus unfractionated heparin in critically ill patients. N Engl J Med 2011; 364: 1305-1314.

[7] Girolami B, Prandoni P, Stefani PM, Tanduo C, Sabbion P, Eichler P, Ramon R, Baggio G, Fabris F and Girolami A. The incidence of heparin-induced thrombocytopenia in hospitalized medical patients treated with subcutaneous unfractionated heparin: a prospective cohort study. Blood 2003; 101: 2955-2959.

[8] Linkins LA. Heparin induced thrombocytopenia. BMJ 2015; 350: g7566.

[9] Aguayo E, Sanaiha Y, Seo YJ, Mardock A, Bailey K, Dobaria V and Benharash P. Heparin-induced thrombocytopenia in cardiac surgery: incidence, costs, and duration of stay. Surgery 2018; 164: 1377-1381.

[10] Lovecchio F. Heparin-induced thrombocytopenia. Clin Toxicol (Phila) 2014; 52: 579-583.

[11] Pishko AM, Lefler DS, Gimotty P, Paydary K, Fardin S, Arepally GM, Crowther M, Rice L, Vega R, Cines DB, Guevara JP and Cuker A. The risk of major bleeding in patients with suspected heparin-induced thrombocytopenia. J Thromb Haemost 2019; 17: 1956-1965.

[12] Warkentin TE, Roberts RS, Hirsh J and Kelton JG. Heparin-induced skin lesions and other unusual sequelae of the heparin-induced thrombocytopenia syndrome: a nested cohort study. Chest 2005; 127: 1857-1861.

[13] Greinacher A, Farner B, Kroll H, Kohlmann T, Warkentin TE and Eichler P. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis. A retrospective analysis of 408 patients. Thromb Haemost 2005; 94: 132-135.

[14] Arepally GM. Heparin-induced thrombocytopenia. Blood 2017; 129: 2864-2872.

[15] Hong AP, Cook DJ, Sigouin CS and Warkentin TE. Central venous catheters and upper-extremity deep-vein thrombosis complicating immune heparin-induced thrombocytopenia. Blood 2003; 101: 3049-3051.

[16] Ernest D and Fisher MM. Heparin-induced thrombocytopaenia complicated by bilateral adrenal haemorrhage. Intensive Care Med 1991; 17: 238-240.

[17] Baroletti SA and Goldhaber SZ. Heparin-induced thrombocytopenia. Circulation 2006; 114: e355-356.

[18] Guinat M and Vincent JL. Thrombocytopenia in the critically ill patient. Rev Med Brux 2011; 32: 513-522.

[19] Thiele T, Selleng K, Selleng S, Greinacher A and Bakchoul T. Thrombocytopenia in the intensive care unit-diagnostic approach and management. Semin Hematol 2013; 50: 239-250.

[20] Thachil J and Warkentin TE. How do we approach thrombocytopenia in critically ill patients? Br J Haematol 2017; 177: 27-38.

[21] Hui P, Cook DJ, Lim W, Fraser GA and Arnold DM. The frequency and clinical significance of thrombocytopenia complicating critical illness:

a systematic review. Chest 2011; 139: 271-278.
[22] Ostadi Z, Shadvar K, Sanaie S, Mahmoodpoor A and Saghaleini SH. Thrombocytopenia in the intensive care unit. Pak J Med Sci 2019; 35: 282-287.
[23] Crowther MA, Cook DJ, Albert M, Williamson D, Meade M, Granton J, Skrobik Y, Langevin S, Mehta S, Hebert P, Guyatt GH, Geerts W, Rabbat C, Douketis J, Zytaruk N, Sheppard J, Greinacher A and Warkentin TE; Canadian Critical Care Trials Group. The 4Ts scoring system for heparin-induced thrombocytopenia in medical-surgical intensive care unit patients. J Crit Care 2010; 25: 287-293.
[24] Sakr Y, Haetscher F, Gonsalves MD, Hoffman M, Theis B, Barz D, Reinhart K and Kortgen A. Heparin-induced thrombocytopenia type II in a surgical intensive care unit. J Crit Care 2012; 27: 232-241.
[25] Selleng K, Warkentin TE and Greinacher A. Heparin-induced thrombocytopenia in intensive care patients. Crit Care Med 2007; 35: 1165-1176.
[26] Vakil NH, Kanaan AO and Donovan JL. Heparin-induced thrombocytopenia in the pediatric population: a review of current literature. J Pediatr Pharmacol Ther 2012; 17: 12-30.
[27] Martel N, Lee J and Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 2005; 106: 2710-2715.
[28] McGowan KE, Makari J, Diamantouros A, Bucci C, Rempel P, Selby R and Geerts W. Reducing the hospital burden of heparin-induced thrombocytopenia: impact of an avoid-heparin program. Blood 2016; 127: 1954-1959.
[29] Hogan M and Berger JS. Heparin-induced thrombocytopenia (HIT): review of incidence, diagnosis, and management. Vasc Med 2020; 25: 160-173.
[30] Solanki J, Shenoy S, Downs E, Palkimas S, Goldman S and Sharma AM. Heparin-induced thrombocytopenia and cardiac surgery. Semin Thorac Cardiovasc Surg 2019; 31: 335-344.
[31] Junqueira DR, Zorzela LM and Perini E. Unfractionated heparin versus low molecular weight heparins for avoiding heparin-induced thrombocytopenia in postoperative patients. Cochrane Database Syst Rev 2017; 4: CD007557.
[32] Warkentin TE, Greinacher A, Koster A and Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). Chest 2008; 133 Suppl: 340S-380S.
[33] Stein PD, Hull RD, Matta F, Yaekoub AY and Liang J. Incidence of thrombocytopenia in hospitalized patients with venous thromboembolism. Am J Med 2009; 122: 919-930.
[34] Morris TA, Castrejon S, Devendra G and Gamst AC. No difference in risk for thrombocytopenia during treatment of pulmonary embolism and deep venous thrombosis with either low-molecular-weight heparin or unfractionated heparin: a metaanalysis. Chest 2007; 132: 1131-1139.
[35] Junqueira DR, Perini E, Penholati RR and Carvalho MG. Unfractionated heparin versus low molecular weight heparin for avoiding heparin-induced thrombocytopenia in postoperative patients. Cochrane Database Syst Rev 2012; CD007557.
[36] Warkentin TE, Sheppard JI, Heels-Ansdell D, Marshall JC, McIntyre L, Rocha MG, Mehta S, Davies AR, Bersten AD, Crozier TM, Ernest D, Vlahakis NE, Hall RI, Wood GG, Poirier G, Crowther MA and Cook DJ; Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Heparin-induced thrombocytopenia in medical surgical critical illness. Chest 2013; 144: 848-858.
[37] Douketis J, Cook D, Meade M, Guyatt G, Geerts W, Skrobik Y, Albert M, Granton J, Hebert P, Pagliarello G, Marshall J, Fowler R, Freitag A, Rabbat C, Anderson D, Zytaruk N, Heels-Ansdell D and Crowther M; Canadian Critical Care Trials Group. Prophylaxis against deep vein thrombosis in critically ill patients with severe renal insufficiency with the low-molecular-weight heparin dalteparin: an assessment of safety and pharmacodynamics: the DIRECT study. Arch Intern Med 2008; 168: 1805-1812.
[38] Biino G, Balduini CL, Casula L, Cavallo P, Vaccargiu S, Parracciani D, Serra D, Portas L, Murgia F and Pirastu M. Analysis of 12,517 inhabitants of a Sardinian geographic isolate reveals that predispositions to thrombocytopenia and thrombocytosis are inherited traits. Haematologica 2011; 96: 96-101.
[39] Vanderschueren S, De Weerdt A, Malbrain M, Vankersschaever D, Frans E, Wilmer A and Bobbaers H. Thrombocytopenia and prognosis in intensive care. Crit Care Med 2000; 28: 1871-1876.
[40] Fiorenza MA, Frazee EN, Personett HA, Dierkhising RA and Schramm GE. Assessment of a modified 4T scoring system for heparin-induced thrombocytopenia in critically ill patients. J Crit Care 2014; 29: 426-431.
[41] Napolitano LM, Warkentin TE, Almahameed A and Nasraway SA. Heparin-induced thrombocytopenia in the critical care setting: diagnosis

and management. Crit Care Med 2006; 34: 2898-2911.
[42] Greinacher A and Selleng K. Thrombocytopenia in the intensive care unit patient. Hematology Am Soc Hematol Educ Program 2010; 2010: 135-143.
[43] Crow JR, Nam L, Chasler JE, Ong CS, Dane KE, Kickler T, Lawton J, Streiff MB, Alejo D, Canner JK and Schena S. Association of heparin dose, route, timing, and duration with heparin-induced thrombocytopenia. Ann Thorac Surg 2021; 112: 32-37.
[44] Besch G, Ilic D, Ginet M, d'Audigier C, Nguyen P, Ferreira D, Samain E, Mourey G and Pili-Floury S. Identification of heparin-induced thrombocytopenia in surgical critically Ill patients by using the HIT expert probability score: an observational pilot study. J Clin Med 2022; 11: 1515.
[45] Powell BD, Lin FC, Beach KF, Kasthuri RS and Northam KA. Accuracy of a modified 4Ts score in predicting heparin-induced thrombocytopenia in critically ill patients: a pilot study. J Crit Care 2022; 67: 88-94.
[46] Warkentin TE, Sheppard JA, Sigouin CS, Kohlmann T, Eichler P and Greinacher A. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. Blood 2006; 108: 2937-41.