Supplemental file

Contents

s1. PICO questions table

Number	Population(s)	Intervention(s)	Comparator	Outcome(s)	Studies
1	patients with acute HITT or acute isolated HIT who are at average bleeding risk	discontinue heparin alone	discontinue heparin and treat with a VKA or discontinue heparin and treat with a non-heparin anticoagulant	Thromboembolism Limb Amputation Mortality Major Bleeding	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
2	patients with acute HITT or acute isolated HIT who are at average bleeding risk	treat with one non-heparin anticoagulant	another non-heparin anticoagulant (e.g. argatroban, danaparoid, bivalirudin, fondaparinux, desirudin, dabigatran, rivaroxaban, apixaban, edoxaban	Thromboembolism Limb Amputation Mortality Major Bleeding	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
3	patients with acute HITT or acute isolated HIT who are at average bleeding risk	treat with a non-heparin anticoagulant alone	Treat with a non-heparin anticoagulant in combination with an anti-platelet agent	Thromboembolism Limb Amputation Mortality Major Bleeding	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
4	patients with acute HITT or acute isolated HIT who are at average bleeding risk	insert IVC Filter	not to insert IVC filter	Pulmonary Embolism IVC Filter Failure Deep Venous Thrombosis (DVT) in the Leg Post-Thrombotic Syndrome Limb Amputation Mortality	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
5	patients with acute HITT or acute isolated HIT who are at	start oral anticoagulation (VKA) before	not to start oral anticoagulation (VKA) before platelet recovery	Thromboembolism Limb Amputation Mortality Major bleeding	Randomized trials; Non-randomized studies (cohort,

Number	Population(s)	Intervention(s)	Comparator	Outcome(s)	Studies
	average bleeding risk	platelet recovery		Increased duration of hospitalization	case-control, cross-sectional, case report)
6	patients with acute HITT or acute isolated HIT who are at average bleeding risk	start oral anticoagulation (dabigatran, rivaroxaban, apixaban, edoxaban) before platelet recovery	not to start oral anticoagulation before platelet recovery	Thromboembolism Limb Amputation Mortality Major Bleeding Increased Duration of Hospitalization	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
7	patients with acute HITT or acute isolated HIT who are at average bleeding risk	platelet transfusion	not to provide platelet transfusion	Thromboembolism Limb Amputation Mortality Major Bleeding Delay of intervention	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
8	patients with the acute isolated HIT to detect silent DVT	perform a 4-limb ultrasound	Perform lower extremity ultrasound OR no ultrasound	Thromboembolism (symptomatic) Limb amputation Mortality Major Bleeding	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
9	patients with the acute isolated HIT	treat with a therapeutic intensity	prophylactic intensity non-heparin anticoagulant	Thromboembolism Limb Amputation Mortality Major Bleeding	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
10	patients with the isolated HIT	continue anticoagulation until platelet recovery	anticoagulation for 4-6 weeks OR anticoagulation for 3 months	Thromboembolism Limb Amputation Mortality Major Bleeding	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
11	patients with HIT who will be receiving anticoagulation in the recovery phase	treat with VKA	other oral anticoagulants	Major Bleeding Thromboembolism Limb Amputation Mortality	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)

Number	Population(s)	Intervention(s)	Comparator	Outcome(s)	Studies
12	patients with the subacute HIT-I who require urgent cardiovascular surgery	treat with a non- heparin anticoagulant	Treat with heparin with plasma exchange OR with heparin and antiplatelet agent	Major Bleeding Thromboembolism Limb amputation Mortality Heparin-induced thrombocytopenia (recurrent acute)	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
13	patients with the subacute HIT-I or subacute HIT-II who require urgent cardiovascular surgery	treat with one non-heparin anticoagulant	another non-heparin anticoagulant	Major Bleeding Thromboembolism Limb amputation Mortality	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
14	patients with subacute HIT-II who require urgent cardiovascular surgery	treat with heparin	treat with a non-heparin anticoagulant OR with heparin with plasma exchange OR with heparin and an antiplatelet agent	Heparin-induced thrombocytopenia (recurrent acute) Major Bleeding Thromboembolism Limb amputation Mortality	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
15	patients with acute HIT or subacute HIT-I or subacute HIT-II who require urgent percutaneous cardiovascular intervention	treat with one non-heparin anticoagulant	treat with another non-heparin anticoagulant	Major Bleeding Thromboembolism Limb amputation Mortality	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
16	patients with acute HIT or subacute HIT-I or subacute HIT-II or remote HIT who require renal replacement therapy (e.g. hemodialysis, CVVD, CVVH)	treat with one non-heparin anticoagulant	Treat with another non-heparin anticoagulant	Major bleeding Thromboembolism Limb amputation Dialysis access thrombosis (write-in) Mortality	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)

Number	Population(s)	Intervention(s)	Comparator	Outcome(s)	Studies
17	pregnant patients with acute HIT or subacute HIT-I or subacute HIT-II or remote HIT	treat with one non-heparin anticoagulant	another non-heparin anticoagulant	Pregnancy loss Congenital malformation Neonatal Bleeding Major Bleeding Thromboembolism Mortality	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
18	patients with remote HIT who require percutaneous cardiovascular intervention	treat with heparin/LMWH	Treat with a non-heparin anticoagulant	Major Bleeding Thromboembolism Limb amputation Heparin-Induced Thrombocytopenia (recurrent acute) Mortality	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
19	patients with remote HIT who require VTE prophylaxis or treatment	treat with heparin/LMWH	treat with a non-heparin anticoagulant	Major Bleeding Heparin-Induced Thrombocytopenia (recurrent acute) Thromboembolism Limb amputation Mortality	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
20	patients with remote HIT who require VTE prophylaxis or treatment	treat with one non- heparin anticoagulant	treat with another non-heparin anticoagulant	Major Bleeding Thromboembolism Mortality	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)
21	In patients with a history of HIT	carry an emergency pass (e.g. Medic-Alert bracelet)	not to carry an emergency pass (e.g. Medic-Alert bracelet)	Heparin-Induced Thrombocytopenia (Recurrent, acute)	Randomized trials; Non-randomized studies (cohort, case-control, cross-sectional, case report)

s2. Search Strategy

Database: Embase <1974 to 2016 December 30>, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations,
Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials
< November 2016>
Search Strategy:

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1 ((hit or hitt) and (prothromb* or thromb* or heparin*)).tw. (5492)
2 remove duplicates from 1 (3513)
3 ((thrombocytopaen* or thrombocytopen*) adj2 Heparin).tw. (9011)
4 2 or 3 (9651)
5 4 and anticoagulant*.mp. (4532)
6 remove duplicates from 5 (3107)
7 4 not 5 (5119)
8 remove duplicates from 7 (3929)
9 6 or 8 (7036)
10 exp platelet transfusion/ or exp thrombocyte transfusion/ (22305)
11 thrombocyte transfusion*.mp. (15651)
12 platelet transfusion*.mp. (16855)
13 or/10-12 (26516)
14 9 and 13 (191)
15 exp vena cava filters/ (7254)
16 (IVC adj filter).mp. (2155)
17 inferior vena cava filter.mp. (2328)
18 or/15-17 (8405)
19 9 and 18 (87)
20 exp ultrasonography, doppler/ (101375)
21 ultrasonography.mp. (369084)
22 exp echography/ (959070)
23 echography.mp. (376668)
24 or/20-23 (1083820)
25 9 and 24 (326)
26 renal.mp. (1419670)
27 kidney*.mp. (2007410)
28 dialys*.mp. (334564)
29 (hemodialys* or haemodialys*).mp. (208963)
30 (CVVHD or CAVHD or CVVHDF or CAVHDF or CVVHF or CAVHF or CRRT or SCUF or CVVH or CAVH).tw. (6365)
31 citrate*.mp. (134798)
32 or/26-31 (2638898)
33 9 and 32 (1193)
34 plasma exchange.mp. or exp Plasmapheresis/ or plasmapheresis.tw. (55939)
35 9 and 34 (185)
36 pregnan*.mp. (1890842)
37 (prenat* or pre nat*).mp. (399266)
38 (perinat* or peri nat*).mp. (198340)
39 (antenat* or ante nat*).mp. (77549)
40 maternal.mp. (610355)

41 peripartum.mp. (9618)
42 (antepart* or ante part*).mp. (14025)
43 or/36-42 (2313281)
44 9 and 43 (319)

Database: Embase <1974 to 2020 April 27>, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

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3 1 or 2 (60637)
4 prothromb*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (110631)
5 thromb*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (1493203)
6 heparin*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (304224)
7 4 or 5 or 6 (1688154)
8 3 and 7 (7075)
9 thrombocytopen*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (248708)
10 thrombocytopaen*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (2400)
11 9 or 10 (249620)
12 ((thrombocytopen* or thrombocytopaen*) adj2 heparin).mp. (12234)
13 8 or 12 (13742)
14 anticoagulant*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (288453)
15 13 and 14 (6132)
16 13 not 15 (7610)
17 platelet transfusion.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (14718)
18 thrombocyte transfusion.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (18545)
19 exp platelet transfusion/ (25613)
20 exp thrombocyte transfusion/ (18497)
21 17 or 18 or 19 or 20 (28165)
22 16 and 21 (229)
23 remove duplicates from 22 (207)
24 exp vena cava filter/ (8578)
25 (ivc adj filter).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (2985)
26 inferior vena cava filter.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (3130)
27 24 or 25 or 26 (10200)
28 16 and 27 (90)
29 remove duplicates from 28 (80)
30 exp ultrasonography, doppler/ (109531)
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32 exp echography/ (1211116)
33 echography.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (414532)
34 30 or 31 or 32 or 33 (1324802)
35 16 and 34 (417)
36 remove duplicates from 35 (393)
37 renal.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (1522225)

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39 dialys*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (352437)
40 (hemodialys* or haemodialys*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (229127)
41 (CVVHD or CAVHD or CVVHDF or CVVHF or CAVHF or CRRT or SCUF or CVVH or CAVH).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (8239)
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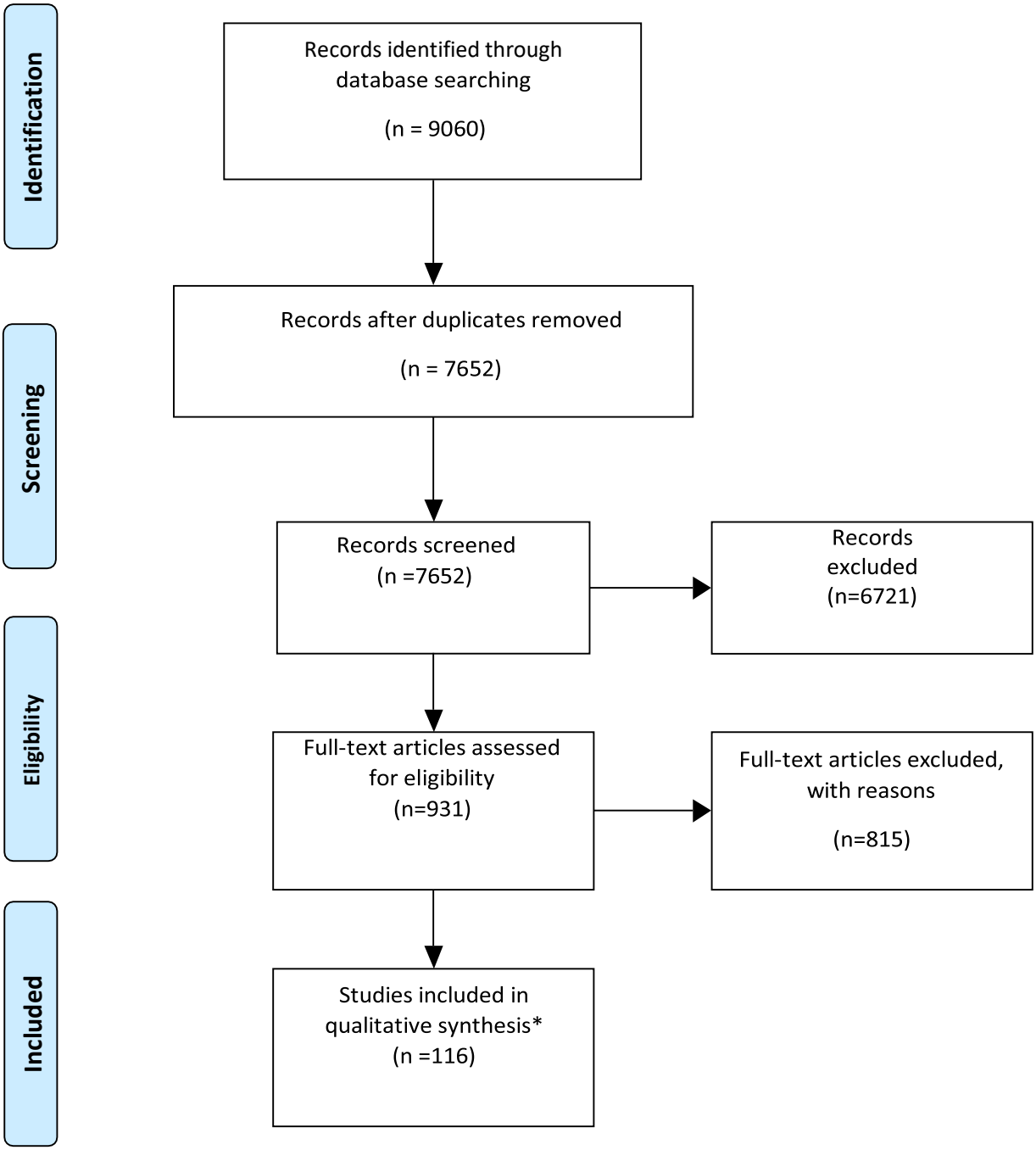
43 or/37-42 (2782400)
44 16 and 43 (1092)
45 remove duplicates from 44 (954)
46 plasma exchange.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (25290)
47 exp plasmapheresis/ (54858)
48 plasmapheresis.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (50712)
49 46 or 47 or 48 (64902)
50 16 and 49 (221)
51 remove duplicates from 50 (191)
52 pregnan*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (1921523)
53 (prenat* or pre nat*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (418953)
54 (perinat* or peri nat*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (221343)
55 (antenat* or ante nat*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (91505)
56 maternal.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (689981)
57 peripartum.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (12517)
58 (antepart* or ante part*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] (15585)
59 or/52-58 (2388110)
60 16 and 59 (298)
61 remove duplicates from 60 (265)

s3. PRISMA

Heparin-Induced Thrombocytopenia Management and Treatment Systematic Review



*Studies included in quantitative synthesis (meta-analysis)

1. Heparin discontinuation vs parenteral non-heparin anticoagulant (n=26)
2. DOAC vs DOAC (n=4)
3. Therapeutic vs prophylactic dosing (n=3)
4. DOAC vs DOAC plus platelets (n=2)
5. IVC filter (n=2)
6. Oral anticoagulation (VKA) be initiated before platelet recovery (n=3)
7. Platelet vs no platelet (n=4)
8. Limb ultrasound vs no limb ultrasound (n=5)
9. Continue anticoagulation until platelet recovery or for 4-6 weeks or for 3 months in patients with isolated HIT (n=1)
10. DOAC vs VKA among patients with subacute HIT A (n=1)
11. Anticoagulation with a non-heparin anticoagulant or preoperative plasma exchange with heparin or heparin with an antiplatelet agent for patients with acute HIT or subacute HIT who require urgent cardiovascular surgery (n=15)
12. Anticoagulation with a non-heparin anticoagulant or preoperative plasma exchange with heparin or heparin with an antiplatelet agent for patients with subacute HIT B or remote HIT who require urgent cardiovascular surgery (n=11)
13. Anticoagulation with a non-heparin anticoagulant for patients with acute HIT or subacute HIT A who require urgent percutaneous cardiovascular interventions (n=5)
14. Anticoagulation with a non-heparin anticoagulant or unfractionated heparin for patients with subacute HIT B or remote HIT who require urgent percutaneous cardiovascular interventions (n=11)
15. Renal replacement therapy for acute HIT, subacute HIT or remote HIT (21).
16. VTE prophylaxis in patients with Remote HIT (n=1)
17. Emergency identification (n=1)

s4. Additional Systematic Review Results

What are the effects of oral anticoagulation initiating VKA prior to platelet recovery

In a small series of 6 patients initiating VKA, 5 had skin necrosis and 2 (33%) had limb gangrene Srinivasan et al., report on 6 patients with HIT(Srinivasan et al., 2004). Of those patients, the study reported 5 (83%) events of skin necrosis and 2 (33%) events of limb gangrene. Warfarin was withdrawn in 2 patients. One patient (17%) required limb amputations and one patient (17%) died. Warkentin et al. conducted a retrospective chart review of patients with HIT who experienced venous limb gangrene(Warkentin et al., 1997). Eight of 66 patients (12%) with HIT and deep venous thrombosis who received warfarin developed venous limb gangrene. Warkentin and Kelton reported on 21 patients with isolated HIT who were treated with discontinuation of heparin and initiation of warfarin(Warkentin & Kelton, 1996). Of those patients, 10 (48%) developed thrombosis.

Duration of anticoagulation (platelet recovery, 4-6 weeks, or 3 months)

Warkentin & Kelton followed 62 patients with isolated HIT who were treated with discontinuation of heparin, with or without warfarin(Warkentin & Kelton, 1996). The majority of events (52%) occurred within the first 10 days following diagnosis of HIT, which corresponds to the expected period of platelet count recovery.

DOAC vs. VKA among patients with subacute HIT A

No randomized or observational studies were identified comparing DOACs with VKA for patients with HIT following platelet recovery or that compared DOACs following platelet recovery. We identified one systematic review and case-series that reported on patients with HIT treated with DOACs following platelet recovery(Warkentin et al., 2017). Out of 46 patients, 11 received DOACs following platelet count recovery from HIT (rivaroxaban, n = 7; apixaban, n = 3; edoxaban, n = 0; dabigatran, n = 1). One patient (9%) reported a major hemorrhage secondary to known varices.

VTE treatment and prophylaxis in patients with remote HIT

Warkentin & Kelton 2001 followed 3 patients with serologically confirmed HIT who received a second course of heparin more than 100 days post initial HIT (Warkentin & Kelton, 2001). None of the patients developed recurrent HIT.

Emergency identification

We identified one study among children with hemophilia that reported on current practices wearing and not wearing EMI(Gorlin, Hooke, & Leonard, 2011). Adverse effects reported from persons wearing an EMI include rashes and bruising (reported among 3%-6% of the population). Undesirable consequences from not wearing an EMI can include mortality (among hemophiliacs treated with contraindicated regimens).

s5. Study Characteristics

Separate file

s6. Risk of Bias Assessment for Non-heparin Parenteral Anticoagulants

Randomized controlled trials

Studies	Randomization	Allocation	Blinding of participants/ personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Other bias
Chong 2001							

Low	Unclear	High

Non-randomized comparative studies

Studies	Confounding	Selection	Measurement of Exposure	Departures from Interventions	Missing Data	Measurement of Outcomes	Reported Results
Lewis 2003							
Kang 2015							
Al-Rossaies 2011							

Low	Moderate	Serious	Critical

s7. GRADE Evidence Profiles

Danaparoid compared to dextran 70 for treatment in patients with acute HITT or acute isolated HIT who are at average bleeding risk

Setting: Inpatient

References: Chong BH, Gallus AS, Cade JF, et al. Prospective randomised open-label comparison of danaparoid with dextran 70 in the treatment of heparin-induced thrombocytopaenia with thrombosis: A clinical outcome study. Thrombosis and Haemostasis. 2001;86(5):1170-1175.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	danaparoid	dextran 70	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	4/25 (16.0%)	4/17 (23.5%)	RR 0.68 (0.20 to 2.35)	75 fewer per 1,000 (from 188 fewer to 318 more)	⊕◯◯◯ VERY LOW	CRITICAL
Limb amputation (follow up: median 14 days)												
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	1/24 (4.2%)	3/17 (17.6%)	RR 0.24 (0.03 to 2.08)	134 fewer per 1,000 (from 171 fewer to 191 more)	⊕◯◯◯ VERY LOW	CRITICAL
New thromboembolic complications (follow up: median 14 days)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	danaparoid	dextran 70	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	3/24 (12.5%)	7/17 (41.2%)	RR 0.30 (0.09 to 1.01)	288 fewer per 1,000 (from 4 more to 375 fewer)	⨁⨁◯◯ LOW	CRITICAL
Major bleed												
1	randomised trials	not serious	not serious	serious [a]	very serious [c]	none	0/24 (0.0%)	0/17 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (vomiting, flushing) (follow up: median 14 days)												
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	4/24 (16.7%)	4/17 (23.5%)	RR 0.71 (0.21 to 2.44)	68 fewer per 1,000 (from 186 fewer to 339 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio

a. Patients in both treatment arms also receive warfarin.

b. 95% CI crosses line of no effect and includes both benefit and harm.

c. No events reported.

Argatroban compared to historical controls for treatment for patients with acute HITT or acute isolated HIT who are at average bleeding risk

Setting: Inpatient

References: Lewis BE, Wallis DE, Berkowitz SD, et al. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation. 2001;103(14):1838-1843. Lewis BE, Wallis DE, Leya F, Hursting MJ, Kelton JG. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. Archives of Internal Medicine. 2003;163(15):1849-1856.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	argatroban	standard of care	Relative (95% CI)	Absolute (95% CI)		
Thrombosis-related mortality (follow up: 37 days)												
2	observational studies	not serious	not serious	very serious [a,b]	not serious	none	7/373 (1.9%)	7/46 (15.2%)	RR 0.12 (0.05 to 0.34)	134 fewer per 1,000 (from 100 fewer to 145 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
New thromboembolic complications (follow up: 37 days)												
2	observational studies	not serious	not serious	very serious [a,b]	not serious	none	58/373 (15.5%)	16/46 (34.8%)	RR 0.45 (0.28 to 0.71)	191 fewer per 1,000 (from 101 fewer to 250 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Limb amputation (follow up: 37 days)												
2	observational studies	not serious	not serious	very serious [a,b]	serious [c]	none	51/373 (13.7%)	5/46 (10.9%)	RR 1.26 (0.53 to 2.99)	28 more per 1,000 (from 51 fewer to 216 more)	⊕◯◯◯ VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	argatroban	standard of care	Relative (95% CI)	Absolute (95% CI)		
Major bleed (follow up: 37 days)												
2	observational studies	not serious	not serious	very serious [a,b]	serious [c]	none	30/373 (8.0%)	1/46 (2.2%)	RR 3.70 (0.52 to 26.50)	59 more per 1,000 (from 10 fewer to 554 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. Diagnosis of HIT is based on a platelet count < 100 X 10^9/L or a 50% reduction in platelet count relative to the preheparin treatment value after heparin therapy with no explanation besides HIT. HIT may be over-diagnosed in this patient population.

b. Lewis 2001 & 2003 use historical controls, which may not reflect the comparator of interest: discontinuation of heparin and/or initiation of VKA.

c. 95% CI crosses line of no effect and includes important benefit and harm.

Argatroban compared to danaparoid for treatment in patients with acute HITT or acute isolated HIT who are at average bleeding risk

Setting: Inpatient

References: Kang M, Alahmadi M, Sawh S, Kovacs MJ, Lazo-Langner A. Fondaparinux for the treatment of suspected heparin-induced thrombocytopenia: a propensity score-matched study. Blood. 2015;125(6):924-929.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	argatroban	danaparoid	Relative (95% CI)	Absolute (95% CI)		
New thrombosis and thrombosis-related mortality												
1	observational studies	not serious [a]	not serious	not serious	very serious [b]	none	5/20 (25.0%)	8/40 (20.0%)	RR 1.25 (0.47 to 3.33)	50 more per 1,000 (from 106 fewer to 466 more)	⨁◯◯◯ VERY LOW	CRITICAL
Bleeding and bleeding-related mortality												
1	observational studies	not serious [a]	not serious	not serious	not serious	none	7/20 (35.0%)	5/40 (12.5%)	RR 2.80 (1.02 to 7.72)	225 more per 1,000 (from 3 more to 840 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. Kang et al., 2015 present results from a propensity-score matched patient cohort based on age, gender, creatinine, 4T scores, and comorbidity index.

b. 95% CI crosses line of no effect; few events reported

Argatroban compared to fondaparinux for treatment of patients with acute HITT or acute isolated HIT who are at average bleeding risk

Setting: Inpatient

References: Al-Eidan, F. A., Alrawkan, S., Alshammary, H., & Crowther, M. A. (2018). Comparison of argatroban and fondaparinux for the management of patients with isolated heparin-induced thrombocytopenia. Annals of hematology, 97(11), 2055-2059. Kang M, Alahmadi M, Sawh S, Kovacs MJ, Lazo-Langner A. Fondaparinux versus argatroban and danaparoid for the treatment of suspected or confirmed heparin-induced thrombocytopenia: A propensity score analysis. *Blood.* 2012;120(21):no pagination.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	argatroban	fondaparinux	Relative (95% CI)	Absolute (95% CI)		
Thrombosis and thrombosis-related mortality												
1	observational studies	very serious [a]	not serious	not serious	very serious [b]	none	5/20 (25.0%)	22/133 (16.5%)	RR 1.51 (0.65 to 3.53)	84 more per 1,000 (from 58 fewer to 418 more)	⨁◯◯◯ VERY LOW	CRITICAL
Bleeding and bleeding-related mortality												
1	observational studies	very serious [a]	not serious	not serious	very serious [b]	none	7/20 (35.0%)	28/133 (21.1%)	RR 1.66 (0.84 to 3.29)	139 more per 1,000 (from 34 fewer to 482 more)	⨁◯◯◯ VERY LOW	CRITICAL
Length of hospital stay												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	argatroban	fondaparinux	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	very serious [c]	not serious	not serious	very serious [b]	none	56	39	-	MD 14.5 days higher (10.15 higher to 18.85 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. Kang et al., 2015 present results from a propensity-score matched patient cohort based on age, gender, creatinine, 4T scores, and comorbidity index; however, concerns with residual and unmeasured confounding.

b. 95% CI crosses line of no effect; few events reported

c. Al-Eidan et al., 2018 has concerns with residual confounding from baseline characteristics and unmeasured confounding.

Danaparoid compared to fondaparinux for treatment in patients with acute HITT or acute isolated HIT who are at average bleeding risk

Setting: Inpatient

References: Kang M, Alahmadi M, Sawh S, Kovacs MJ, Lazo-Langner A. Fondaparinux versus argatroban and danaparoid for the treatment of suspected or confirmed heparin-induced thrombocytopenia: A propensity score analysis. *Blood.* 2012;120(21):no pagination.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	danaparoid	fondaparinux	Relative (95% CI)	Absolute (95% CI)		
Thrombosis and thrombosis-related mortality												
1	observational studies	not serious [a]	not serious	not serious	very serious [b]	none	8/40 (20.0%)	22/133 (16.5%)	RR 1.21 (0.58 to 2.50)	35 more per 1,000 (from 69 fewer to 248 more)	⨁◯◯◯ VERY LOW	CRITICAL
Bleeding and bleeding-related mortality												
1	observational studies	not serious [a]	not serious	not serious	very serious [b]	none	5/40 (12.5%)	28/133 (21.1%)	RR 0.59 (0.25 to 1.44)	86 fewer per 1,000 (from 93 more to 158 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. Kang et al., 2015 present results from a propensity-score matched patient cohort based on age, gender, creatinine, 4T scores, and comorbidity index.

b. 95% CI crosses line of no effect; few events reported

Lepirudin compared to fondaparinux for treatment of patients with acute HITT or acute isolated HIT who are at average bleeding risk

Setting: Inpatient

References: Al-Rossaies A, Alkharfy KM, Al-Ayoubi F, Al-Momen A. Heparin-induced thrombocytopenia: Comparison between response to fondaparinux and lepirudin. *International Journal of Clinical Pharmacy.* 2011;33(6):997-1001.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	lepirudin	fondaparinux	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
1	observational studies	not serious [a]	not serious	not serious	very serious [b]	none	0/7 (0.0%)	2/5 (40.0%)	RR 0.15 (0.01 to 2.58)	340 fewer per 1,000 (from 396 fewer to 632 more)	⨁◯◯◯ VERY LOW	CRITICAL
Thromboembolic complications												
1	observational studies	not serious [a]	not serious	not serious	very serious [b]	none	2/7 (28.6%)	2/5 (40.0%)	RR 0.71 (0.15 to 3.50)	116 fewer per 1,000 (from 340 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Limb amputation												
1	observational studies	not serious [a]	not serious	not serious	very serious [c]	none	0/7 (0.0%)	0/5 (0.0%)	not estimatable		⨁◯◯◯ VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	lepirudin	fondaparinux	Relative (95% CI)	Absolute (95% CI)		
Major bleed												
1	observational studies	not serious [a]	not serious	not serious	very serious [b]	none	2/7 (28.6%)	1/5 (20.0%)	RR 1.43 (0.17 to 11.76)	86 more per 1,000 (from 166 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; RR: Risk ratio

a. HIT confirmation based on a positive PF4/H-ELISA immunoassay with an optical density of greater than 0.40 at 410 nm.
b. 95% CI crosses line of no effect; few events reported.
c. No events reported.

References of Included Studies:

1. Al-Rossaies A, Alkharfy KM, Al-Ayoubi F, Al-Momen A. Heparin-induced thrombocytopenia: Comparison between response to fondaparinux and lepirudin. International Journal of Clinical Pharmacy. 2011;33(6):997-1001.
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3. Kang M, Alahmadi M, Sawh S, Kovacs MJ, Lazo-Langner A. Fondaparinux for the treatment of suspected heparin-induced thrombocytopenia: a propensity score-matched study. Blood. 2015;125(6):924-929.Lewis BE, Wallis DE, Berkowitz SD, et al. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation. 2001;103(14):1838-1843.
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5. Linkins LA, Dans AL, Moores LK, 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(2 SUPPL.):e495S-e530S.
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