CO222

Systematic Literature Review (SLR) of Direct Oral Anticoagulants (DOACs) as a Treatment Option for Acute Heparin-induced Thrombocytopenia (HIT) with or without Thrombosis

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Introduction

- DOACs are an attractive treatment option for acute HIT due to their ease of administration and reduced need for outpatient monitoring.
- Traditional HIT treatment consists of discontinuing heparin and initiating a non-heparin anticoagulant.
- Medications approved to treat acute HIT include argatroban, bivalrudin and danaparoid.
  - These medications are administered intravenously and require continuous laboratory monitoring with corresponding dosage adjustments.
- DOACs are administered orally and do not require continuous adjustments based on laboratory monitoring.
- The 2018 American Society of Hematology (ASH) HIT treatment guidelines conditionally recommend DOAC use due to very low certainty in the evidence about effects.[1]

Objective

Our systematic literature review of published studies assessed the outcomes of DOAC use in acute HIT treatment.

Methods

- MEDLINE and Embase databases were searched through July 2022 to identify studies that assessed DOAC use in acute HIT treatment.
- This search resulted in 902 published records.
- All abstracts were reviewed for relevance based on pre-determined inclusion and exclusion criteria.
  - Studies were included if they were available in English, assessed human subjects, and studied the safety or efficacy of DOACs in the treatment of acute HIT.
- Non-human studies, case reports, case series, meta-analyses, and review articles were excluded.
- Eight cohort studies met our inclusion criteria and were included in the final review.

Results

Table 1 presents a summary of included studies.[2-9]

- Zero randomized control trials (RCTs) that assessed the use of DOACs in acute HIT were identified.
- Out of eight studies included in our review, six were retrospective cohort studies and two were single-arm interventional studies.
  - Six, four, and three studies reported use of rivaroxaban,[2-4,6-8] apixaban,[3,7-9] and dabigatran,[3,5,8] respectively.
  - A moderate-to-high 4T score result was reported for all patients; a positive antibody immunoassay was reported for 115 patients; a positive serotonin release assay (SRA) was reported for 81 patients.[2-9]
  - Of 241 patients, 95 received initial parenteral acute HIT treatment.[2-4,7,8]
  - Three studies did not indicate whether an initial parenteral treatment was administered prior to the DOAC treatment.[5,6,9]

Table 2 presents a summary of baseline characteristics.

- Baseline platelet count is reported at HIT diagnosis for 189 patients and at DOAC initiation for 40 patients.
- A reported 85 patients experienced heparin-induced thrombocytopenia with thrombosis (HITT).
- Mean platelet nadir is reported in two studies and accounts for 24 patients.

Observed outcomes are reported in **Table 3**.

- Studies reported aggregate data for a total of two hundred and forty-one patients.
- Mean time to platelet recovery ranged between 4 to 13 days across all studies.
- Platelet recovery was reported in four of eight studies.
- Thrombosis, major bleeding, and clinically relevant non-major bleeding were reported in 12, 6, and 12 patients respectively.

Results

Table 1. Summary of Included Studies

Study Name	Study Design	N	Known Initial Parenteral Therapy, n	DOACs	HIT Screening and Diagnostic Tools Used, % (n)	HIT[a,b]
Linkins et al. 2016[2]	prospective cohort	12	7	rivaroxaban	4T-score, 100% (12) SRA, 100%(12)	confirmed, 100% (12)
Davis et al. 2017[3]	retrospective cohort	12	7	apixaban, dabigatran, rivaroxaban	4T-score, 100% (12) ELISA Test, 100% (12) SRA, 33% (4)	confirmed, 33% (4) suspected, 67% (8)
Warkentin et al. 2017[4]	restrospective cohort	16	DOACs prior to platelet recovery, 2 DOACs after platelet recovery, 6	rivaroxaban	4T-score, 100% (16) ELISA Test, 100% (16) SRA, 100% (16)	confirmed, 100% (16)
Nasiripour et al. 2019[5]	retrospective cohort, multicenter	40	NR	dabigatran	4T- score, 100% (40)	confirmed, 0% (0) suspected, 100% (40)
Farasatinasab et al. 2020[6]	retrospective cohort	42	NR	rivaroxaban	4T-score, 100% (42)	confirmed, 0% (0) suspected, 100% (42)
Cirbus et al. 2021[7]	retrospective cohort	12	10	rivaroxaban, apixaban	4T-score, 33.3% (4) ELISA Test, 83% (10) SRA, 58% (7)	confirmed, 33% (4) suspected, 67% (8)
Davis et al. 2022[8]	retrospective cohort, multicenter	77	63	apixaban, dabigatran, rivaroxaban	4T-score, 100% (77) ELISA Test, 100% (77) LIA, 22% (17) SRA, 58% (45)	confirmed, 58% (45) suspected, 42% (32)
Farasatinasab et al. 2022[9]	single-arm pilot intervention	30	NR	apixaban	4T-score, 100% (30)	confirmed, 0% (0) suspected, 100% (30)

ELISA, enzyme linked immunosorbent assay; LIA, latex immunoturbidimetric assay; NR, not reported.
[a]Confirmed HIT as per + SRA test; [b]Most patients with a negative functional assay do not have HIT and may be managed accordingly. However, depending on the type of functional assay and the technical expertise of the laboratory, false-negative results are possible. Therefore, a presumptive diagnosis of HIT may be considered for some patients with a negative functional assay, especially if there is a high-probability 4Ts score and a strongly positive immunoassay.

Table 2. Baseline Characteristics

Study Name	Male, % (n)	Mean Age, years	HITT, % (n)	Mean platelet count at HIT diagnosis, x10^9/L	Mean platelet count at DOAC initiation, x10^9/L	Median platelet nadir, x10^9/L
Linkins et al. 2016[2]	58.3%(7)	74	50% (6)	NR	84	NR
Davis et al. 2017[3]	50% (6)	67	41.7% (5)	NR	NR	58
Warkentin et al. 2017[4]	31.3% (5)	71	37.5% (6)	NR	97[a]	NR
Nasiripour et al. 2019[5]	40% (16)	70	NR	80	NR	NR
Farasatinasab et al. 2020[6]	28.6% (12)	67	40.5% (17)	86	NR	NR
Cirbus et al. 2021[7]	33.3% (4)	62	17% (2)	NR	206	61
Davis et al. 2022[8]	57.1% (44)	63[a]	49.4% (38)	126[a]	NR	NR
Farasatinasab et al. 2022[9]	56.7% (17)	58	36.7% (11)	99	NR	NR

HITT, heparin-induced thrombocytopenia with thrombosis; NR, not reported.
[a]Value was reported as or calculated as a median.

Results

Table 3. Observed Outcomes

Study Name	Platelet Recovery, % (n)	Mean time to platelet recovery, days	HIT-related thrombotic events, % (n)	Clinically relevant non-major bleeding, % (n)	Major bleeding, % (n)
Linkins et al. 2016[2]	92% (11)	11	8.3% (1)	0% (0)	8.3% (1)[a]
Davis et al. 2017[3]	100% (12)	7	0% (0)	NR	0% (0)
Warkentin, 2017[4]	100% (16)	13	0% (0)	0% (0)	0% (0)
Nasiripour et al. 2019[5]	95% (38)	7	2.5% (1)	5% (2)	0% (0)
Farasatinasab et al. 2020[6]	NR	4	2.4% (1)	NR	NR
Cirbus et al. 2021[7]	92% (11)	NR	0% (0)	NR	NR
Davis et al. 2022[8]	79.2% (61)	5[b]	11.7% (9)	11.7% (9)	6.5% (5)
Farasatinasab et al. 2022[9]	NR	5	0% (0)	3.3% (1)	0% (0)

NR, not reported.
[a]Unrelated to HIT; [b]Value was reported as or calculated as a median.

Conclusion

- Preliminary results indicate that rivaroxaban, apixaban, and dabigatran may possibly be used for the treatment of acute HIT.
- All published studies that were identified were observational or single arm interventional studies with few patients.
- Variation with regards to diagnostic criteria, presence of initial parenteral therapy prior to DOAC administration, choice of DOAC, baseline data collected, and outcomes of interest limits data utility and generalizability.
- More prospective observational studies are needed following a large cohort of patients and collecting meaningful outcome measures that assess efficacy and safety of DOAC use in acute HIT.

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The authors of this poster have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter presented

ISPOR Annual Meeting, May 7th- May 10th, 2023 Boston Conference & Exhibition Center, Boston, MA USA