

New Oral Anticoagulants for the Management of Heparin Induced Thrombocytopenia: A Focused Literature Review

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Abstract: *Objective:* Drugs currently in use for the management of heparin-induced thrombocytopenia (HIT) have their limitations. Several new oral anticoagulants (NOACs) such as dabigatran, rivaroxaban and apixaban may offer attractive therapy options for HIT. Although the clinical data are sparse on this topic, we have summarized the available clinical data, discussed pertinent *in-vitro* studies and provided the rationale and advantages of using NOACs in patients with suspected or confirmed HIT. We have also reviewed the safety and efficacy of these NOACs in patients with HIT based on published literature.

Methods: We reviewed all suspected or confirmed HIT cases treated with NOACs and indexed in English language in MEDLINE and EMBASE by July 2015. The bibliography of each relevant article was searched for additional reports. *In-vitro* studies and other pertinent literature were briefly discussed.

Results: A total of 36 HIT patients were treated with the following NOACs: rivaroxaban (50%), dabigatran (36%) and apixaban (14%). Sixty-one percent of patients received argatroban bolus before NOACs and 3% received rivaroxaban after a lack of response with three-day course of fondaparinux. Three percent (n=1) received rivaroxaban after the patient responded to intravenous immunoglobulin for 2 days, following a lack of response to fondaparinux and bivalirudin. In another 3% (n=1), prophylactic dose of rivaroxaban was used for 21 days and then changed to dabigatran because of persistent thrombocytopenia. All cases responded with early signs of clinical improvement and increase in platelet counts. A follow-up after a median 47 days (range 4- 450) reported no bleeding or thrombotic complications.

Conclusion: In this review, all patients with HIT treated with NOACs responded without any bleeding or thrombotic complication. Although the argatroban bolus might have contributed to a response in some patients, response to NOAC alone in other patients and *in-vitro* studies provide a proof of principle that NOACs can be effective in the management of HIT. Additionally, properties such as rapid onset of action, oral administration, ease of use and a lack of need for monitoring make these drugs attractive options for HIT. However, given several limitations of prior reports, further confirmation of the results are desirable.

Keywords: Apixaban, argatroban, dabigatran, heparin-induced thrombocytopenia, new oral anticoagulants, rivaroxaban.

INTRODUCTION

Heparin-induced thrombocytopenia (HIT), a life threatening complication of heparin, is reported to occur in 0.2% to 5% of adults treated with unfractionated heparin (UFH) [1]. It is immune-mediated and results from platelet activation by anti-platelet factor (PF)4/heparin antibodies [2, 3]. Immediate withdrawal of heparin and prompt initiation of non-heparin anti-coagulants are the standard of care in HIT [3, 4]. Drugs such as argatroban, bivalirudin, fondaparinux, lepirudin and danaparoid may be used for treatment of HIT

but have their own pitfalls. Argatroban is one of the most commonly utilized drugs for HIT in the US. However, features such as parenteral administration, complex transition to oral warfarin [5] and higher risk of adverse effects in liver dysfunction [6] make it a less preferable agent in many instances. Fondaparinux, a frequently used drug for HIT (off-label) [7], may possibly have a small risk of HIT [8, 9], does not have an antidote and is not recommended in renal dysfunction because of its long half-life and renal elimination [10]. Bivalirudin is only approved in patients undergoing percutaneous coronary intervention [6], and lepirudin and danaparoid are not available in the US.

Recently, several new oral anticoagulants (NOACs) such as dabigatran, rivaroxaban and apixaban, approved for other thromboembolic conditions, have been used in patients with

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HIT. A few *in-vitro* studies have shown that NOACs do not interact with or release PF4 to cause activation or aggregation of platelets [11-13], thus making them a potentially good treatment option for HIT. Although the clinical data are sparse on this topic, in this review, we have summarized the available clinical data, discussed pertinent *in-vitro* studies and provided the rational and advantages of using NOACs in patients with suspected or confirmed HIT. We have analyzed published cases to review the safety and efficacy of the NOACs in suspected or confirmed HIT.

METHODS

This is a retrospective review of published cases of NOACs use in patients with suspected or confirmed HIT.

The major goal of this review was to analyze the safety and efficacy of the NOACs in patients with HIT based on published literature. The diagnosis of HIT, as reported by the authors of the original articles, was accepted. We reviewed all cases published and indexed in English language in MEDLINE and EMBASE database by July 2015. Search terms included “heparin induced thrombocytopenia,” “HIT,” “rivaroxaban,” “dabigatran,” “apixaban,” “edoxaban.” Specific search strategies are shown below Fig. (1). The bibliography of each relevant article was searched for additional related reports. A total of 12 articles meeting the eligibility criteria were included in this study Fig. (1). The quality of the articles was not strong since all the reports were case reports and case series without a control group. Additionally, we have discussed *in-vitro* studies and other pertinent literature

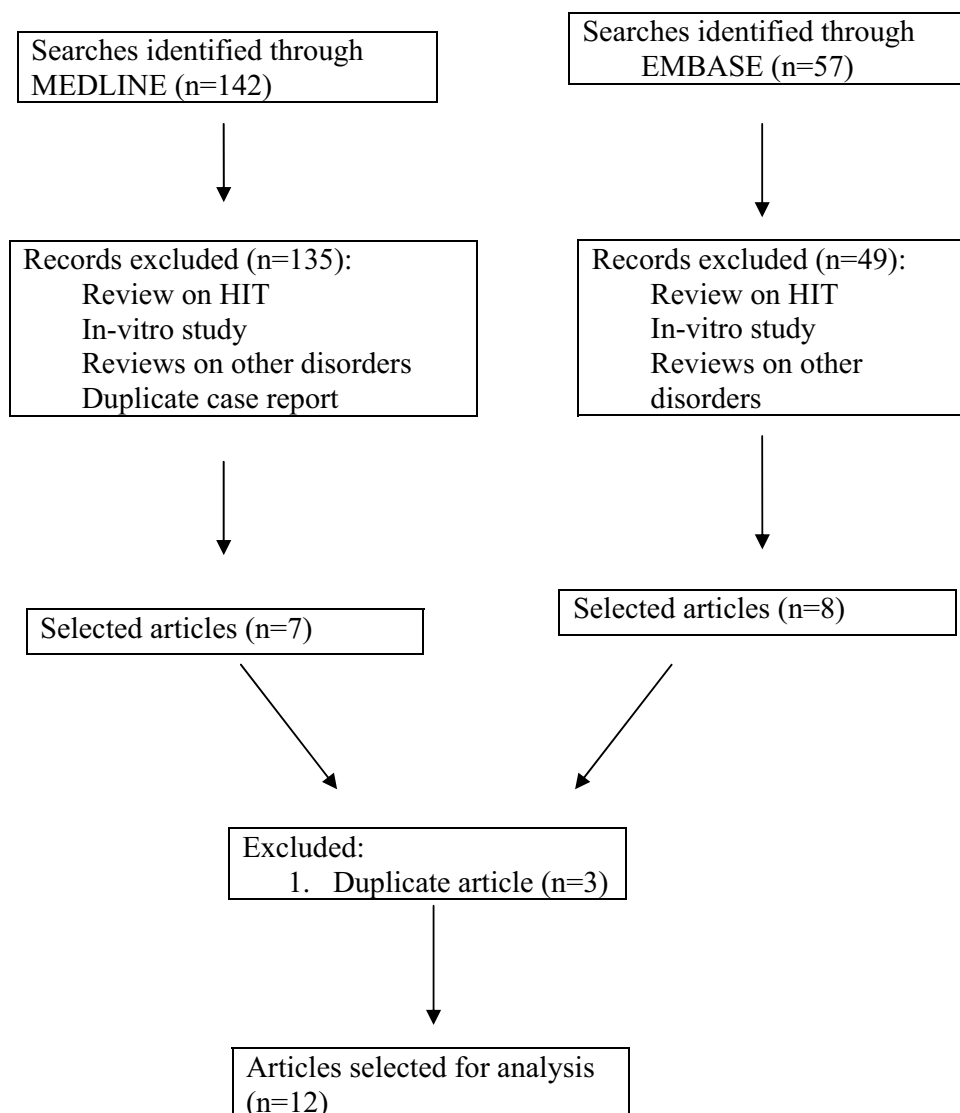


Fig. (1). Flow diagram for selection of the articles. For MEDLINE search, the following strategy was used ((heparin induced thrombocytopenia OR HIT)) AND (((rivaroxaban) OR dabigatran) OR apixaban) OR edoxaban). For EMBASE search, the following strategy was used ('heparin induced thrombocytopenia'/exp) AND ('rivaroxaban'/exp OR 'dabigatran'/exp OR 'dabigatran etexilate'/exp OR 'apixaban'/exp OR 'edoxaban'/exp). Search was limited to: [embase]/lim NOT [medline]/lim 'case report'/de OR 'clinical study'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'human'/de OR 'major clinical study'/de OR 'phase 2 clinical trial (topic)'/de OR 'phase 3 clinical trial (topic)'/de OR 'randomized controlled trial (topic)'/de OR 'systematic review'/de).

to provide broader perspectives of the scientific rationale for using NOACs and the potential advantages of NOACs over other agents.

RESULTS

A total of 36 patients received NOACs for treatment of HIT [14-25] including a patient with anti-platelet factor (PF)4/heparin antibodies but without a high clinical suspicion of HIT [15] (Table 1). The median age was 64 years (range 30-85), and 34% were females. Sharifi *et al.* reported mean age of 72 years; 32% were females in their study [23]. The median interval between heparin exposure and HIT was 7 days (range 3-13). The mean interval was 5 days, and the mean nadir platelet count was $68 \times 10^9/L$ in Sharifi study (23). We calculated the median nadir platelet count to be $59 \times 10^9/L$ (range 3- 161 $\times 10^9/L$) in all other reports. The 4T score was high in 66% of patients [14, 16,

20, 22], HIT antibodies were present in 91% [14-16, 19, 20, 22, 24, 25], and 35% of patients had thrombotic complications [14, 18-20, 23]. The drugs included rivaroxaban (50% of total patients) [16, 19, 20, 22, 23, 25], dabigatran (36%) [14, 15, 17, 18, 21, 24], and apixaban (14%) [23]. Among them, 60% of patients received intravenous argatroban bolus before utilizing NOACs (23). Five percent received rivaroxaban after a lack of response with three-day course of fondaparinux [16]. In one case report of delayed-onset or spontaneous HIT, dabigatran was used after persistent thrombocytopenia despite the use of prophylactic dose of rivaroxaban [24]. Intravenous immunoglobulin (IVIG) for 2 days was followed by treatment with rivaroxaban in a patient, who did not respond to fondaparinux or bivalirudin [25].

In the majority of patients, the NOACs were used at the following approved doses for venous thromboembolism: dabigatran 150 mg twice daily; rivaroxaban 15 mg twice

Table 1. Published studies of novel oral anticoagulants in heparin-induced thrombocytopenia.

Author, Year	Age (Years)/Sex	Interval between Heparin use and Thrombocytopenia (Days)	Nadir Platelet ($\times 10^9/L$)	Presence of Thrombosis at the Time of HIT Diagnosis	Drug Used	Duration of Treatment (Days)	Follow-up
Abouchakra <i>et al.</i> (2015)	53/M	5	25	Arterial clot	Rivaroxaban	NR	30
Anniccherico <i>et al.</i> (2012)	NR	7	120	PE	Dabigatran	NR	NR
Eshraghi <i>et al.</i> (2015)	65/M	6	75	NR	Dabigatran	4	4
	30/F	5	67	NR	Dabigatran	12	12
Fieland <i>et al.</i> (2012)	70/M	4	80	NR	Dabigatran	7	14
Hantson <i>et al.</i> (2014)	36/M	9	25	Arterial clot	Rivaroxaban	NR	60
Lee <i>et al.</i> (2013)	70/M	5	59	NR	Dabigatran	4	32
Mirdamadi <i>et al.</i> (2013)	67/F	11	32	VTE	Dabigatran	10	NR
Ng <i>et al.</i> (2014)	63/F	9	61	VTE	Rivaroxaban	22	180
	46/M	13	18	PE, VTE, Arterial clot	Rivaroxaban	450	450
Sartori <i>et al.</i> (2015)	66/M	3*	28	None	Rivaroxaban	70	120
	68/M	6	161	None	Rivaroxaban	90	180
Sharifi <i>et al.</i> (2014)	(n=22) mean of 72 years, 15 M/ 7 F	5 (mean)	68(mean)	5 cases with VTE	Argatroban bolus, then Rivaroxaban, Dabigatran or Apixaban	>90	570
Tardy- Poncet <i>et al.</i> (2015)	71/F	10	56	NR	Rivaroxaban then Dabigatran	14	35
Tvito <i>et al.</i> (2015)	85/F	8	3	NR	IVIG over 2 days before Rivaroxaban	180	180

HIT indicated Heparin-induced thrombocytopenia; IVIG Intravenous immunoglobulin; NR Not reported; PE Pulmonary embolism; VTE Venous thromboembolism

*Prior hospitalization 1 month earlier with heparin exposure

All cases responded with early signs of clinical improvement and increase in platelet counts. During the period of follow-up, there was no reported thrombotic or bleeding complication related to the use of new oral anticoagulant.

daily for initial 21 days followed by 20 mg once daily; and apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily. Based on the dabigatran trial [26], Lee *et al.* [17] administered dabigatran 110 mg every 12 hours *via* the feeding tube. Concomitant use of antiplatelet agent (which may increase the bleeding risk) and administration of crushed dabigatran pellets without the capsule shell (which may increase the oral bioavailability by 75%) were the other rationale for modification of dabigatran dosage. Similarly, Miramadi *et al.* [18] administered dabigatran 110 mg every 12 hours. Ng *et al.* [19] used 10 mg daily dosage of oral rivaroxaban in a female with creatinine clearance of <10mg/ml. Peak and trough levels of rivaroxaban were monitored and maintained within the 5th and 95th percentile of ranges established for patients with venous thromboembolism. Ng *et al.* [19] utilized oral rivaroxaban at 15 mg twice daily dosage in another patient because of concomitant anti-tuberculosis treatment. Tardy- Poncet *et al.* used prophylactic dose of rivaroxaban 10 mg daily for 21 days, which was changed to dabigatran 220 mg once daily because of persistent thrombocytopenia [24]. Apixaban 5mg twice daily was utilized in 5 patients by Sharifi *et al.* [23].

All cases, including those receiving only NOACs, responded with early signs of clinical improvement and increase in platelet counts. A follow-up after a median of 47 days (range 4- 450) reported no bleeding or thrombotic complications related to the use of NOAC. The mean follow-up in Sharifi study was about 19 months, and no complication was reported in any patient [23].

DISCUSSION

In this review, all patients with HIT treated with NOACs responded without any bleeding or thrombotic complication. Although the argatroban bolus might have contributed to response in some patients [23], response to NOAC alone in other patients provide a proof of principle that NOACs may be effective in the management of HIT.

A few *in-vitro* studies have assessed the properties of NOACs in the context of HIT. Fareed *et al.* [11] compared the effect of rivaroxaban, apixaban and dabigatran with UFH in platelet rich plasma of normal donors. While the use of UFH resulted in a release of PF4 from platelets and platelet aggregation, NOACs demonstrated no interaction with PF4, PF4 release or platelet aggregation. Moreover, the relative immunogenic potential of NOACs was marginal compared to UFH in rabbits. Another *in-vitro* study by Krauel and coworkers [12] also showed no effect of dabigatran or rivaroxaban on the interaction of PF4 or anti-PF4/heparin antibody with platelets. Walenga *et al.* [13] evaluated functional platelet activation with apixaban in the presence of HIT antibodies using serotonin release assay and heparin-induced platelet aggregation assay. In contrast to heparin and enoxaparin, apixaban did not cause platelet activation. In another study, rivaroxaban did not cross-react with anti-PF4/heparin antibody, mobilize PF4 from platelets or interact with PF4 [27]. These studies provide important insights towards the underlying molecular basis of the efficacy of NOACs in HIT.

An ongoing prospective, multicenter, single-arm cohort study (ClinicalTrials.gov Identifier: NCT01598168) [28] is

evaluating rivaroxaban for the treatment of patients with suspected or confirmed HIT. Rivaroxaban, with its properties such as fixed dosing and oral administration, has a number of important advantages over the current armamentarium of drugs for HIT. Although the study has limitations such as lack of a control group and a small proportion of patients with serologically confirmed HIT, this is going to be an important trial in HIT. Although the accrual of patients has been slow, the results, expected to be available in 2016, are eagerly awaited.

In conclusion, the usefulness of NOACs in HIT, as indicated by *in-vitro* studies, has been supported by several case reports summarized in this review. In our review, we have demonstrated that the use of NOACs, alone or in combination with short-course of “induction” argatroban, may be safe and efficacious in HIT. Although the number of patients are small, the results so far are at least comparable to the outcomes with other agents [3]. Additionally, properties such as rapid onset of action, oral administration, ease of use and a lack of need for monitoring make these drugs attractive options for HIT [3]. Even though concerns have been raised regarding a lack of specific antidote for NOACs in the event of any bleeding, the risk of major bleeding, fatal bleeding and deaths are similar between NOACs and other anticoagulants [29]. Although the cost of these drugs may be higher, the use of these oral drugs may expedite hospital discharge and therefore, be cost-effective. However, dose adjustments may be required in patients with hepatic or renal [30, 31] impairment. The major limitations of prior clinical data include small number of available articles on the subject and poor quality of data of the original articles. Given such limitations, the results of the aforementioned prospective study are awaited before NOACs can be routinely used for the management of patients with HIT [28].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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