Non-vitamin K antagonist oral anticoagulants for heparin-induced thrombocytopenia. A systematic review of 54 reported cases

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Dear Sirs,

Heparin-induced thrombocytopenia (HIT) results from the formation of antibodies to the complex of heparin and platelet factor (1, 4) and result in high rates of thrombosis (> 50 %) and mortality if untreated (10–30 %) (2, 3). The initiation of direct thrombin inhibitors after the detection of HIT has been suggested to improve clinical outcomes as compared to historical controls (4). Current guidelines recommend immediate cessation of heparin and initiation of a non-heparin anticoagulant including argatroban, lepirudin, and danaparoid at the time of diagnosis or adequate suspicion of HIT (grade 1C), although lepirudin and danaparoid are no longer available in the United States and Europe (5).

Non-vitamin K antagonist oral anticoagulants (NOACs) have recently been approved in numerous settings and in pooled analysis have proven to have lower overall rates of bleeding, breakthrough thrombosis, and mortality as compared to vitamin K antagonists (6, 7). They offer many other potential benefits, including ease of administration, no required monitoring, and competitive cost to other anticoagulants. While a clinical trial was underway evaluating the use of rivaroxaban in patients with HIT, the study was terminated early due to poor recruitment (8). There is currently no available prospective data determining the efficacy and safety of NOACs in patients with HIT. Despite this, numerous reports of HIT being effectively treated with NOACs have begun to emerge in the literature. We performed a systematic review attempting to find all reported cases of NOACs used in the treatment of HIT in an attempt to assess rates of breakthrough thrombosis, bleeding, and HIT related mortality.

We performed a systematic review of English language reports of HIT treated with NOACs, searching three databases: PubMed, Google Scholar, and Embase as well as reviewing accepted abstracts from the American Society of Hematology annual meeting, in an attempt to find all reported cases of NOAC use in the treatment of HIT within the past three years (January 1, 2012 – December 1, 2015). Exact search criteria are reported in Suppl. Table 1 (available online at www.thrombosis-online.com). We included all English language reports of HIT being managed with NOACs either alone or in combination with other non-heparin anticoagulants in human subjects. All articles were selected for relevance based on title and independently reviewed by two authors for relevance and inclusion.

Our search yielded eight articles and two abstracts reporting outcomes in patients with HIT treated with NOACs, which in total encompassed 54 unique patients (mean age 68.4 years, 68 % male), of which 94 % had laboratory proven HIT by either platelet factor four ELISA or Serotonin release assay, and 48 % of reported cases had thrombosis present at the diagnosis of HIT (▶Table 1). The most commonly used NOAC was rivaroxaban (59 %), followed by apixaban (28 %) and dabigatran (13 %). In total, 78 % of patients received a non-heparin anticoagulant considered appropriate for use in HIT (argatroban, bivalrudin, or fondaparinux) prior to initiation of NOAC. 22 % of patients received NOAC alone. In total, only 1/54 reported cases had thrombus progression after the initiation of NOAC (a catheter-related thrombus which expanded despite NOAC use, and responded to catheter removal and continued NOAC administration). In total, 3/54 reported cases described instances of clinically relevant bleeding, with no reported bleeding related mortality. There was no reported HIT related mortality.

This report has compiled the largest series of HIT patients treated with NOACs to date, with no reported cases of HIT-related mortality, and only one reported case of thrombosis progression despite NOAC administration. Previous *in vitro* data has suggested that NOACs do not cause platelet activation or aggregation in the presence of HIT antibodies, implying NOACs to be efficacious therapeutics for patients with HIT (9). This has in part lead to the developments of a prospective trial evaluating rivaroxaban for the treatment of HIT, which unfortunately was stopped early due to poor recruitment (8).

Further studies are needed to determine if NOACs are indeed as effective as the current report suggests and if they are a safe alternative for the initial treatment for HIT, as this would likely revolutionise therapy for patients with HIT due to the ease of administration, lack of requirement for monitoring, and decreased rates of bleeding - compared to traditional anticoagulants.

While direct thrombin inhibitors have become guideline therapy for HIT, there are shortcomings to their use which should be addressed. Limitations on the data leading to the use of argatroban have been pointed out by other authors, including no requirement for positive antibody testing in the initial studies (10). Furthermore, an inherent difficulty with argatroban is the requirement for activated partial thromboplastin time (aPTT) monitoring. Patients with critical illness often have an associated coagulopathy for a variety of reasons which

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Included studies	Kunk et al. (12)	Ng et al. (14)	Linkins et al. (13)	Mirdamadi et al. (15)	Hantson et al. (16)	Sartori et al. (17)	Larsen et al. (18)
Number of patients	11	3	12	1	1	1	1
Mean patient age	na	58	na	67	36	68	72
# male	na	2	na	0	1	1	0
Type of DOAC used							
rivaroxaban	2	3	12	0	1	1	0
edoxaban	0	0	0	0	0	0	0
dabigatran	0	0	0	1	0	0	0
apixaban	9	0	0	0	0	0	1
not reported	0	0	0	0	0	0	0
DOAC given after a period of non-heparin anticoagulation.	11 (argatroban or bivalirudin)	0	6 (fondaparinux)	0	1 (fondaparinux)	1 (fondaparinux)	0
DOAC given as the primary non-heparin anticoagulant	0	3	6	1	0	0	1
HIT-related outcomes							
HIT PF4 and/or Serotonin Release Assay Confirmed	11	3	12	0	1	1	1
Thrombosis present at HIT diagnosis	na	3	na	1	1	1	1
Type of thrombosis	na	venous (3)	na	venous	arterial	venous	venous
Recurrent thrombus after NOAC	0	0	1	0	0	0	0
Reported bleeding	2	0	1	0	0	0	0
Mortality							
HIT-related mortality	0	0	0	0	0	0	0
Bleeding-related mortality	0	0	0	0	0	0	0
Other reported mortality	0	0	0	0	0	0	0
Treatment characteristics							
Patient setting	not reported	medical	not reported	surgery	surgery	surgery	medical
Duration of anticoagulation	1–18 months (avg 8.25)	2.5–15 months (avg 7.8)	30 days	10 days	> 21 days	3 months	3.5 months
PLT count recovery	not reported	5–18 days (avg 9.67 days)	avg reported 9 days	„few days“	12 days	6 days	10 days

can lead to baseline aPTT prolongation making argatroban dosing difficult. This phenomenon, known as "aPTT confounding," may lead to underdosing during critical periods of therapy (11). Non-monitored anticoagulants such as NOACs may have an advantage in this setting as they are more likely to provided adequate levels of anticoagulation (8).

Despite the favourable outcomes seen in the studies reported in this analysis, it should also be pointed out that the vast majority of patients received a course of argatroban or fondaparinux preceding the use of NOAC. It remains unproven if NOAC trough levels are sufficient to overcome the prothrombotic state of HIT during the initial phase of treatment. This report suggests that transitioning to a NOAC after initial therapy is safe.

This study has important limitations that should be addressed, of which publication bias is the greatest. Incidences of NOAC failure were less likely to be reported and as such the real incidence of failure may be underreported in this study. Some of the included reports were incom-

	Sharifi et al. (19)	Abouchakra et al. (20)	Kopolovic et al. (21)	Total
	22	1	1	54
	72	53	67	68.4 years (31/54)
	15	1	1	21 (68%) (31/54)
	11	1	1	32 (59%)
	0	0	0	0 (0%)
	6	0	0	7 (13%)
	5	0	0	15 (28%)
	0	0	0	0 (0%)
	22 (argatroban)	0	1 (fondaparinux)	42 (78%)
	0	1	0	12 (22%)
	20	1	1	51 (94%)
	7	1	0	15 (52%) (31 of 54)
	venous (7)	arterial	na	Of the reported 15 thrombi: arterial 2 (13%); venous 13 (87%) (41/54 reported)
	0	0	0	1 (2%)
	0	0	0	3 (6%)
	0	0	0	0 (0%)
	0	0	0	0 (0%)
	6 (2 cancer, 2 heart failure, 1 systemic sclerosis, 1 renal failure)	0	0	6 (11%)
	surgery 4; medical 18	surgery	surgery	medicine 22 (71%); surgery 9 (29%) (31/54)
	3–6 months	not reported	not reported	
	no reported	not reported	not reported	Average 9 days (18/54)

Table 1: Reported Cases of HIT treated with NOACs.

plete in terms of patient data, which limited the analysis. Two of the reported studies have not yet been published, and were reported as abstracts only, so are lacking in multiple data points including age, sex and setting (12, 13). The retrospective nature of these reports is also a significant limitation, although it is worthwhile to report that one included abstract, encompassing 12 patients, had prospective accrual (13). Nevertheless, this study suggests that NOACs seem to be safe therapy for HIT after a short course of parenteral treatment with a non-heparin anticoagulant, suggests that further trials of NOACs in this population are warranted, and suggests that clinical trials are likely to find efficacy.

Author contributions
Joseph J. Shatzel MD: Project conception and design, data accumulation and interpretation and manuscript drafting, Meg Crapster-Pregont BS: Data accumulation and interpretation and manuscript drafting. Thomas Deloughery MD, MACP, FAWM data interpretation, manuscript drafting, and critical edits.

Conflicts of interest
None declared.

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L-homoarginine administration reduces neointimal hyperplasia in balloon-injured rat carotids

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Dear Sirs,

Identifying new players in cardiovascular health is crucial to improve risk prediction and to establish novel targets of treatment (1). Recent studies have indicated a particular relevance of homoarginine metabolism in cardiovascular health (2–4). Homoarginine is an arginine homologue whose physiological role is unknown, that differs from arginine by an additional methylene group. Because of this structural similarity, homoarginine may be a substrate, alternative to arginine, for nitric oxide synthase (NOS) (5). Additionally, it may also indirectly increase nitric oxide (NO) production by inhibiting arginase activity, thus raising arginine availability (6). In support of these evidences, homoarginine levels have been associated with endothelial function (3, 7). Data from clinical studies have indicated that low homoarginine concentrations independently predict mortality from cardiovascular disease, including sudden cardiac death, heart failure, and fatal ischaemic stroke (4, 8–11). Two independent Genome-Wide Association Studies (GWAS) documented a strong association between serum homoarginine concentration and the region on chromosome 15 containing the arginine:glycine amidinotransferase (AGAT) gene (12, 13). AGAT plays a central role in energy metabolism by catalysing the conversion of arginine and glycine to ornithine and guanidinoacetate, which is subsequently methylated to creatine. However, when AGAT uses lysine instead of glycine, homoarginine is formed (14). Interestingly, AGAT knockout mice are characterised by extremely low levels of homoarginine and, when experimental ischemic stroke was induced, these mice had larger infarct volumes and worse neurological deficits compared to controls. Importantly, these features were attenuated by homoarginine supplementation (12).

The possible role of homoarginine on smooth muscle cell proliferation and migration that can occur after arterial balloon angioplasty has never been explored. To this aim, balloon injury was performed in the left carotid artery of Sprague-Dawley rats, followed by the insertion of a cannula into the right jugular vein for continuous i.v. drug administration (15). Thirty-six male Sprague-Dawley rats were randomly divided into three treatment groups: group 1, infused with saline (CTR); group 2, infused with L-arginine (30 mg/kg/day in saline, ARG); group 3, infused with L-homoarginine (30 mg/kg/day in saline, HOMO). The intravenous infusion lasted 14 days, starting from the day of arterial injury, and was achieved by connecting the cannula to an osmotic infusion pump containing 2 ml of the solutions described above. Systolic blood pressure was measured by tail cuff volume-oscillometric method in conscious animals, before and 14 days after balloon injury. At the end of drug treatments, blood was collected, rats were humanly sacrificed and carotids harvested for analyses (see

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