G. Carli[1], A. Farsi[1], F. Chiarini[1], D. Lippolis[2], G. Cortellini[2]

Hypersensitivity reactions to non-vitamin K oral anticoagulants - a review of literature and diagnostic work-up proposal

[1]SOS Allergologia e Immunologia, Prato, Azienda USL Toscana Centro, Italy
[2]UOC Medicina Interna e Reumatologia, Allergologia, Ospedale Infermi, Rimini, Italy

Key words

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Corresponding author
Giulia Carli, MD
SOS Allergologia e Immunologia, Prato
Azienda USL Toscana Centro , Italy
Phone: +39 334 335 8388
E-mail: giulia.carli@uslcentro.toscana.it

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Summary

Non-vitamin K antagonist oral anticoagulants (NOACs) are increasingly being used in hospital and outpatient settings as safe alternatives to warfarin. Hypersensitivity reactions have been described for NOACs and can be classified according to Gell and Coombs. We reviewed case reports of possible drug hypersensitivity reactions, noticing a predominance of delayed reactions (both mild and severe) and the absence of cross-reactions to warfarin and low molecular weight heparins. International experience on diagnostic tests is lacking. The vast majority of authors refer to probability scores and rely on biopsy to classify vasculitis and rule out differential diagnoses. We propose to adapt available tests to confirm the patient's reactivity to new anticoagulants. Among in vivo tests, patch testing revealed promising in delayed reactions.

Introduction

Non-vitamin K antagonist oral anticoagulants or novel oral anticoagulants (NOACs) are increasingly being used in the prevention of stroke in atrial fibrillation (AF) and in the prevention and treatment of venous thromboembolism (VTE) (**table I**). NOACs include direct thrombin inhibitor dabigatran and factor Xa inhibitors apixaban, edoxaban and rivaroxaban (1). They are generally considered as a safe alternative to vitamin K antagonists, overcoming the need of closely INR (international normalized ratio) monitoring and the risk of drug-food and drug-drug interactions. In addition, they have the advantage of a fixed dose and a relatively quick onset of action. Since their introduction from the early phase III studies, increasing numbers of patients have been treated with novel oral anticoagulants, which are now exceeding those treated with warfarin (2). As with warfarin therapy, most drug-related side effects are type A reactions (3), which are predictable pharmacological effects, linked to the mechanism of action: in this case, anticoagulation and bleeding risk increase. Among type B adverse drug reactions, which are unpredictable (also called "bizarre") reactions, hypersensitivity reactions have been described in patients treated with NOACs.
Aim of this review is to collect data about novel anticoagulant hypersensitivity reports, to classify the reactions and to define a possible approach for their diagnostic management.

Materials and methods

A medline search with the terms "novel anticoagulants OR DTI OR NOAC OR apixaban OR edoxaban OR rivaroxaban OR dabigatran AND dermatitis OR hypersensitivity OR reaction OR allergy OR urticaria OR angioedema OR vasculitis OR rash OR exanthema" was performed, leading to 33 results (last search: July 2018). Among the results, 25 articles matched

Table I *- Non-vitamin K anticoagulants indications.*

	VTE prevention	VTE treatment	NVAF
rivaroxaban	x (in hip and knee replacement surgery)	x	x
apixaban	x (in hip and knee replacement surgery)	x	x
edoxaban	-	x	x
dabigatran	x (in hip and knee replacement surgery)	x	x

VTE, venous thromboembolism; NVAF, non valvular atrial fibrillation.

with the purpose of this study. A thorough evaluation of in-label safety data and of clinical trials published provided further information. We attempted to classify the hypersensitivity reactions according to the Gell and Coombs classification (4), taking into account the immunopathogenetic mechanism predominantly involved: type I reactions are immediate (occurring within the first hour) and IgE-mediated; type II reactions are antibody-dependent cytotoxicity reactions; type III reactions depend on immune complex formation and deposition; type IV reactions are delayed type cellular hypersensitivity reactions.

Results

Through the literature search mentioned above we were able to identify 29 case reports of possible hypersensitivity reactions to NOACs (**table II**). The culprit drugs were mostly rivaroxaban

Table II *- Summary of reported drug hypersensitivity reactions (DHR) to novel oral anticoagulants.*

	rivaroxaban	apixaban	edoxaban	dabigatran
type I DHR	1 (U/AE + bronchospasm) *(Altin et al, 2014)*	< 1% *(product label)*	< 0.01% *(product label)*	< 0.1% *(RE-LY study)*
type II DHR	2 (thrombocytopenia) *(Mima et al, 2014; Pop et al, 2018)*	-	-	-
type III DHR	5 (leukocytoclastic vasculitis) *(Sainz-Gaspar et al, 2018; Dean et al, 2017; Hasbal et al, 2017; Chaaya et al, 2016; ROCKET trial 2011)* 1 (serum sickness) *(Snyder et al, 2015)*	1 (IgA leukocytoclastic vasculitis) *(Nasir et al, 2018)*	-	3 (leukocytoclastic vasculitis) *(An et al, 2016; Potolidis et al, 2015; Cakmak et al, 2014)*
type IV DHR	4 (DRESS or HES) *(Prasannan et al, 2013; Chiasson et al, 2017; Radu et al, 2016; Barrett et al, 2015)* 2 (MPE) *(Rudd et al, 2018, Sasson et al, 2017)* 2 (toxic skin eruptions) *(ROCKET trial 2011)* 1 (SJS/GBFDE) *(Vernon et al, 2016)* 1 (AGEP-like) *(Yates et al, 2013)* 2 (erythema multiforme/exfoliative rash) *(ROCKET trial 2011)*	1 (psoriasiform exanthem) *(Veliyev et al, 2016)* 1 (eczematous dermatitis) *(Cortellini et al, 2018)*	2 (skin rash) *(Kuroda et al, 2013; Cortellini et al, 2018 in press)* 1-10% (rash) (product label)	4 (MPE) *(Winkle er al, 2012; To et al, 2013; Eid e al, 2011; Cucurull et al, 2010)* 1 (TEN) (Tsoumpris et el, 2013) 5.3% (skin disorders) *(post-marketing data)*

U, urticaria; AE, angioedema; DRESS, drug rash with eosinophilia and systemic symptoms; HES, hypereosinophilic syndrome; MPE, maculopapular exanthema; SJS, Stevens Johnson syndrome; GBFDE, generalized bullous fixed drug eruption; AGEP, acute generalized exanthematous pustolosis; TEN, toxic epidermal necrolysis.

(16 cases) and dabigatran (8 cases). Of note, these drugs were the first to be introduced on the market in 2008 (**table III**). As for rivaroxaban, 5 cases were also described in the ROCKET trial (5). After a further analysis of data provided, a case of neurologic adverse reaction to edoxaban (6) was considered an idiosyncratic reaction and therefore excluded from the total of hypersensitivity reactions collected.

Table III *- Novel oral anticoagulants.*

	drug name	approval in Europe
direct thrombin inhibitors	dabigatran	2008
factor Xa inhibitors	rivaroxaban	2008
	apixaban	2011
	edoxaban	2015

Hypersensitivity reactions to rivaroxaban

Rivaroxaban is a factor Xa inhibitor indicated for the prophylaxis of stroke and systemic embolism in nonvalvular AF, for the prophylaxis of deep vein thrombosis (DVT) in patients undergoing knee or hip replacement surgery, for the treatment of DVT and pulmonary embolism (PE) and for the secondary prophylaxis of DVT and/or PE (7). Prescribing information leaflet reports skin and subcutaneous tissue disorders (pruritus and blisters) as side effects described by more than 1% (2.1%, 1.4%, respectively) of 4487 rivaroxaban-treated patients in RECORD 1-3 studies. Pruritus was also recorded in EINSTEIN DVT and EINSTEIN PE studies in 2.2% of patients. Immune system disorders as hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema, Stevens Johnson syndrome and thrombocytopenia have also been identified during post-marketing experience, but an estimation of the incidence of these side effects lacks. In real-world prospective observational study XANTUS the authors do not mention hypersensitivity reactions as side effects (8). In the ROCKET trial comparing rivaroxaban to warfarin, 2 patients experienced toxic skin eruption, one patient suffered from cutaneous vasculitis, one patient developed erythema multiforme and one patient had an exfoliative rash following rivaroxaban therapy, 2 patients had anaphylactic reactions (the latter proved unrelated to the drug by the investigators) (5). In a comparative study of rivaroxaban and dabigatran in Poland (9), in the group of patients receiving rivaroxaban 25% experienced pruritus, 8.3% experienced rash. Although anaphylactic reactions and angioedema are reported as possible side effects, we were able to find only one case describing urticaria and angioedema in addition to bronchospasm (10) after the fourth dose of rivaroxaban. The clinical picture calls back to an IgE mechanism, but the reaction has occurred upon first known contact with this drug. A possible explanation for this event may be a cross-reaction with IgE antibodies generated by previous contact with apparently unrelated and up to now unidentified chemicals. The patient received antihistaminic drugs, methylprednisolone and oxygen treatment, but neither blood tests (in particular no tryptase) nor other diagnostic tests, nor rechallenge were performed. Two cases of possible drug induced thrombocytopenia were described, acute and delayed. Acute thrombocytopenia occurred 48 hours after first drug exposure, resolved after withdrawal and developed again on rechallenge (11). A possible antibody-dependent mechanism may be postulated (12), in which the drug, by binding reversibly to platelet membrane proteins, induces structural changes in the membrane proteins resulting in new antigen exposure. Delayed-onset thrombocytopenia was associated with purpuric lesions 4 months after starting rivaroxaban therapy, which gradually resolved six days after discontinuation (13). Of note, a 3-day course of high dose intravenous immunoglobulins probably contributed to rapid improvement of platelet count.

Rivaroxaban was also considered responsible of four cases of leukocytoclastic vasculitis (14,15,16,17) which developed respectively 4, 7, 10 and approximately 90 days after the start of anticoagulation. Common characteristics were the appearance of purpuric papules with diffuse distribution and in particular involving the limbs, symmetrically. On histopathologic evaluation infiltration was mainly consisting of neutrophils with erythrocyte extravasation and vessel wall fibrin deposition. In all cases vasculitic lesions disappeared approximately one week after stopping rivaroxaban. Two patients were prescribed systemic steroids, two patients did not receive any treatment.

Anticoagulation with rivaroxaban was also linked with serum sickness (18), characterized by fatigue, arthralgia, rash with wheals, generalized swelling, hypertransaminasemia and bilirubin elevation, fever (38.6 °C), leukocytosis, low C3 and C4, occurring 10 days after starting the drug and responsive to supportive treatment together with rivaroxaban withdrawal.

Among delayed type IV hypersensitivity reactions, most cases were mild to moderate, requiring steroids and supportive therapy, as well as culprit drug discontinuation.

Nevertheless, a case of fatal hypereosinophilic syndrome (19) was reported in a patient treated with rivaroxaban (the authors do not mention the duration of treatment), who presented with hypereosinophilia with eosinophilic lung disease, dyspnea, bleeding, transverse sinus thrombosis, cerebral infarcts with hemorrhages and subsequently coma, myocardial infarction leading to multi-organ failure and death. Neither rash nor fever were described, therefore a diagnosis of DRESS cannot be made.

A drug-induced hypersensitivity syndrome (20) not fullfilling criteria for DRESS was experienced by a patient one day after restarting rivaroxaban: the patient presented with mild pruritic papular rash, elevated transaminases, mild anemia, C reactive protein elevation and biopsy revealed acute spongiotic dermatitis with perivascular lymphocytes and eosinophilic infiltrates. No treatment was required and signs and symptoms disappeared 48 hours after discontinuing drug. The patient tolerated enoxaparin as switch-therapy.
A case of possible AGEP developed in a surgical patient on the second day of rivaroxaban treatment, consistent of a diffuse maculopapular itchy rash with pustolosis and peripheral blood neutrophilia and eosinophilia (21). Rivaroxaban was taken off and concomitant oral antihistamines and topical steroid treatment contributed to rapid resolution of symptoms. Switch to tinzaparin was tolerated.
Two definite diagnoses of drug rash with eosinophilia and systemic symptoms (DRESS) were made in relation to rivaroxaban intake: the first occurred 10 days after drug introduction (22), and resolved after stopping rivaroxaban, with supportive therapy and long tapering of oral steroids. The second case developed after 6 months of rivaroxaban treatment (23) with a particular liver involvement, responding to corticosteroids and drug withdrawal. The patient subsequently tolerated switch to warfarin.
Milder delayed hypersensitivity reactions included drug-induced rashes described as morbilliform eruption (24) or urticarial rash (25) without systemic symptoms and internal organs' involvement, fading after steroids and drug discontinuation. These reactions developed within the first week of treatment (day 2 and day 7, respectively). Patients could tolerate enoxaparin and apixaban as alternative drugs.
Rivaroxaban has also been implied as culprit drug in a hypersensitivity reaction characterized by an itchy rash, desquamating skin and blistering (26) after the first dose, accompanied by renal function impairment and inflammatory markers, resolving with hyperpigmentation after prompt rivaroxaban discontinuation, topical steroids and switch to enoxaparin. A diagnosis of generalised bullous fixed drug eruption (GBFDE) or an initial form of Steven Johnsons syndrome was postulated. Switch to enoxaparin was tolerated.

Hypersensitivity reactions to apixaban

Apixaban is a factor Xa inhibitor indicated for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF), for the prophylaxis of DVT and PE in patients who have undergone hip or knee replacement surgery, for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy (27). Worldwide experience with apixaban is relatively small in contrast to rivaroxaban. According to product informative documents, hypersensitivity reactions (skin rash, anaphylactic reactions, allergic edema, etc.) and syncope were reported in less than 1% of patients treated.
Our literature search included a case of reversible neurologic symptoms (6) after the first apixaban dose confirmed by re-challenge, in which the authors suggest a type I hypersensitivity reaction although the symptoms - dizziness, loss of balance, diplopia, confusion - were not consistent with a histamine- or eicosanoid-mediated mechanism, but rather with an idiosyncratic event. Furthermore, the patient was not clinically evaluated and symptoms were merely reported subjectively. The patient was successfully switched to rivaroxaban.
One case of leukocytoclastic vasculitis was described after 10 days of apixaban (28), appearing as an erythematous rash of lower limbs quickly evolving into purpuric itchy and burning rash. On biopsy evaluation IgA and C3 stained positive at a perivascular level; infiltration of neutrophils was described around and inside the superficial vascular plexus together with focal fibrinoid vessel wall necrosis and in association with erythrocyte extravasation. This clinical picture resolved after stopping apixaban and introducing oral steroids. Switch to rivaroxaban was tolerated.
Apixaban was also linked to the development of a palmoplantar psoriasiform eruption (29), three days after its start. The relationship between the thick, scaly, hyperkeratotic, erythematous, and desquamative plaques and the drug was supported by histopathological features of skin biopsy consistent with those of drug-related psoriasiform eruptions. The patient improved after drug withdrawal and topical steroid therapy.
Interestingly, a case of widespread eczematous dermatitis (30) developed 7 days after graded challenge with apixaban in a patient with delayed drug hypersensitivity reaction (DHR) to edoxaban, suggesting a possible cross-reactivity between Fxa inhibitors.

Hypersensitivity reactions to edoxaban

Edoxaban is a factor Xa inhibitor with approved indication for the prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors according to CHADS2 score and for the treatment of DVT and PE as well as for the prevention of recurrent DVT and PE in adults (31). Product information label reports the results of safety evaluations in the ENGAGE AF-TIMI 48 and Hokusai VTE studies including 21105 patients exposed to edoxaban. Anaphylactic reactions and allergic edema are listed as rare (≥ 1/10,000 to < 1/1,000), hypersensitivity reactions and urticaria as uncommon (≥ 1/1,000 to < 1/100), while rash and pruritus affect a considerable proportion of patients (1-10%). No further information about the timing and characteristics of reactions is provided.
During post-marketing surveillance one patient experienced rash (32) with edoxaban in Japan but more details are lacking.

Recently, another delayed hypersensitivity skin reaction was described (30), occurring as a widespread erythematous rash ten days after the start of edoxaban therapy. Symptoms resolved after stopping edoxaban. The authors provide the first attempt to diagnostic evaluation of skin reactions to novel oral anticoagulants as other T cell-mediated drug reactions: skin tests with heparins were negative; a galenic preparation at 10% and 30% concentration in vaseline was used to perform patch test. Cross-reactivity between edoxaban and dabigatran was demonstrated by patch tests. Subsequent use of apixaban was unsuccessful too, due to the occurrence of a delayed eczematous rash but the patient tolerated warfarin.

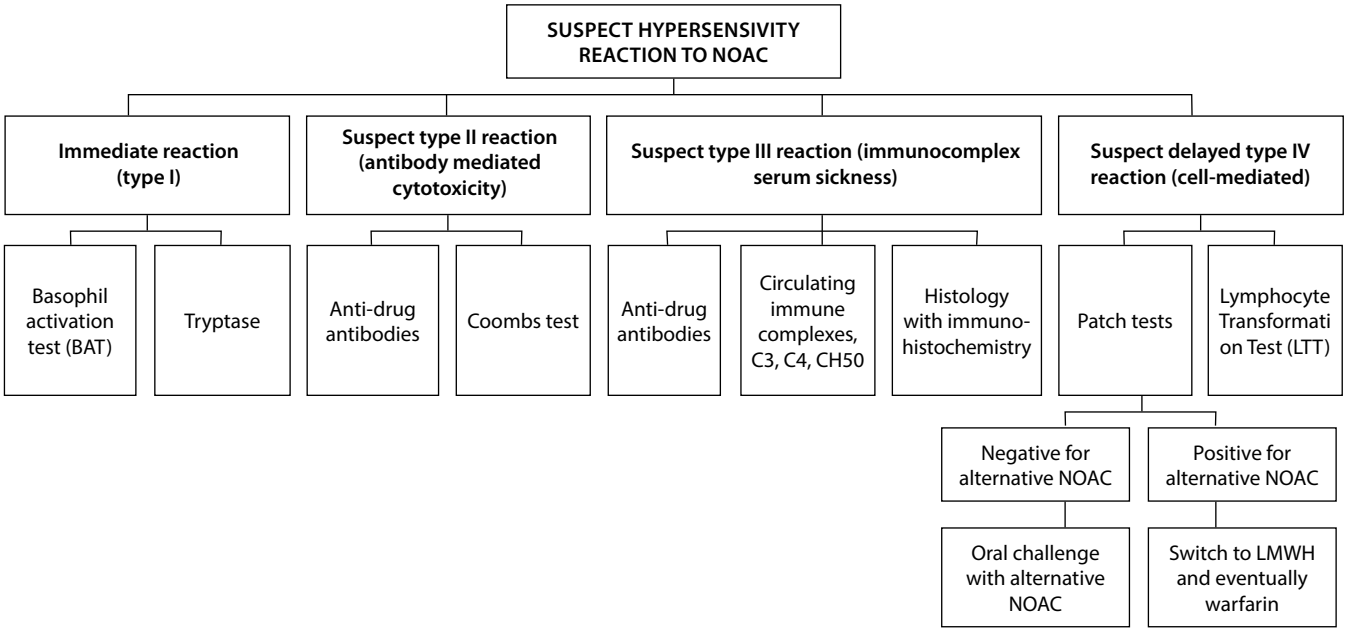
Hypersensitivity reactions to dabigatran

Dabigatran is a direct thrombin inhibitor indicated to prevent stroke and systemic embolism in patients with non-valvular atrial fibrillation, in the prophylaxis of VTE in patients who have undergone elective total hip or knee replacement surgery and in the treatment of DVT and PE and prevention of their recurrence (33,34). As reported in product information, in the RE-LY study drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema and anaphylactic reactions occurred in less than 0.1% of patients. During post marketing safety surveillance skin and subcutaneous tissue disorders were notified with an incidence of 5.3% (35). A possible explanation for this relatively frequent side effect may be related to drug chemical structure as an aromatic amine (36).
Three leukocytoclastic vasculitis case reports were found (37,38,39) developing within the first week of treatment with dabigatran with typical purpuric macules, distribution to limbs, back and trunk, and shared histopathologic findings of neutrophilic infiltration, red cell extravasation and fibrin deposition within vessel walls. In the case described by An J. and colleagues (37) cutaneous vasculitis was associated with peripheral blood eosinophilia and elevation of inflammatory markers. Patients tolerated alternative anticoagulation (enoxaparin and warfarin) and resolution was generally rapid after dabigatran withdrawal and antinflammatory treatment (prednisolone, colchicine).
Four distinct cases of diffuse rash were clinically described as diffuse maculopapular rash (40), non pruritic maculopapular rash (41), diffuse, full-body pruritic rash (42) and urticarioid dermatitis (43). In the latter case, histologic data revealed an infiltration of lymphocytes, eosinophils with dermis vacuolization. The onset of symptoms ranged from 24 hours to 9 days after drug start. In all cases dabigatran discontinuation was sufficient for resolution.
The most severe reaction is a case of toxic epidermal necrolysis (45), in which dabigatran is one of the two possible culprits. The hypersensitivity reaction developed on restarting the drug after a brief discontinuation due to bleeding. Clinically, the patient presented with influenza-like symptoms and three days after erythematous symmetrical macules evolving into painful, burning vesicles and flaccid bullae with extensive sloughing, positive Nikolsky sign in approximately 70% of body surface (skin and conjunctiva). Treatment consisted of high dose intravenous immunoglobulins, antibiotics and wound care, together with culprit drugs interruption.

Discussion and proposal for a diagnostic work-up

Dealing with patients who presented a possible reaction to novel oral anticoagulants implies taking into account their need to be safely and rapidly anticoagulated and to monitor anticoagulation's side effects. In fact, although all NOACs have a predictable onset and offset of effect, not needing for routinal anticoagulation monitoring, kidney function should be assessed regularly to allow dose adaptation.
Data reported above highlight some common features of hypersensitivity reactions to Fxa inhibitors and DTI, particularly with respect to the majority of them, which belong to delayed type III and IV reactions. The possibility to switch patients to other anticoagulants is of utmost importance while performing the allergological diagnostic evaluation and the first evidence our search provides is that patients who reacted to NOACs, could afterwards tolerate warfarin and/or low molecular weight heparins (LMWH). The second observation arises from the case reports from Sasson et al. (25) and Cortellini et al. (30,unpublished), who stated that two patients reacting to edoxaban could tolerate rivaroxaban and that the patient with a previous reaction to rivaroxaban tolerated apixaban: rivaroxaban appears not to cross-react with other factor Xa inhibitors, whereas the same patient presented clinical and/or cutaneous reactivity to both factor Xa inhibitors (edoxaban, apixaban) and DTI (dabigatran).
We hence propose to manage a patient with a suspect reaction to NOAC as in **figure 1** in order to confirm diagnosis, according to time of onset and type of reaction, adapting available in vivo and/or in vitro tests, which are already being used in other drug allergies. After prompt discontinuation of the culprit drug, the patient should be switched to low molecular weight heparin to allow proper in-hospital drug hypersensitivity evaluation and diagnostic tests. The patient's indication for anticoagulation may then direct the choice and dose of alternative drugs.
We suggest using patch tests for the culprit drug and for other novel anticoagulants in the case of mild or moderate and delayed reactions. In vivo tests should be avoided in severe systemic reactions (i.e. SJS, TEN, HES), in which in vitro tests like lymphocyte transformation test (LTT) with the culprit drug may be experimentally performed in experienced laboratories. Patch tests should be prepared with whole tablets crushed in a mortar and mixed with vaseline at 30%. Readings are to be scheduled at 48 h, 72 h and 96 h. A graded challenge should be

Figure 1 *- Proposed diagnostic algorithm.*



performed with an alternative NOAC which resulted negative to patch tests. Due to the possibility of late reactions, we suggest a very slow challenge schedule (**table IV**), starting with a quarter of the total dose at day 1, then half dose at day 3 and a full dose from day 7 and subsequently daily, with concomitant close clinical and laboratory monitoring of side effects. Parallel heparin administration should be continued until 12 hours after reaching the full dose of NOAC.

Conclusions and research agenda

Novel oral anticoagulants appear to be most commonly responsible of delayed reactions, in particular type III and IV drug hypersensitivity reactions. Most cases of severe reactions are described for rivaroxaban, which has been used for longer. Although hypersensitivity was a relatively rare side effect, it is important to keep in mind the possibility, as well as for other anticoagulants, that NOACs may induce skin and also systemic reactions, particularly because they are being extensively and increasingly used as an alternative to warfarin. In addition, the lack of clinicians' awareness might underestimate the real incidence of hypersensitivity.
There is still scarce international experience on diagnostic tests to be performed in order to confirm the suspect of DHR to these novel drugs. The vast majority of authors refer to probability scores (e.g. Naranjo score, WHO-UMC Causality categories) to assess a correlation between the reaction and the use of the drug.

Table IV *- Challenge test proposed schedule.*

	day 1	***day 2***	***day 3***	***day 4***	***day 5***	***day 6***	***day 7***	***day 8 - 13***	***day 14***
graded challenge with NOAC (dose)	¼		½				1	1	1
LMWH anticoagulation							(last dose 12 h after reaching 1 dose NOAC)		
clinical evaluation	x	x	x	x	x	x	x		x
blood count	x		x		x		x		x
creatinine	x		x		x		x		x
PT, aPTT, fibrinogen	x		x		x		x		x

NOAC, novel oral anticoagulant; LMWH, low molecular weight heparin; PT, prothrombine; aPTT, activated partial thromboplastin time.

Biopsy is useful to confirm and classify the type of vasculitis. Other blood tests (e.g. serum autoantibodies, serology for infectious diseases...) are used to rule out other possible diagnoses. Taking into account the probable pathogenetic mechanism underlying the drug hypersensitivity reaction, we suggest to use available tests, in particular in vitro tests, to confirm the patient's reactivity to culprit drug. As for in vivo tests, there are no reports of attempts with skin prick tests or intradermal tests; patch testing revealed as a promising tool in one study instead. In fact, epicutaneous tests may be used in the future to evaluate alternative non-vitamin K antagonist oral anticoagulants and to guide subsequent oral drug tolerance test with a non-cross-reactive one in patients with mild delayed hypersensitivity reactions. Further studies might therefore confirm our preliminary observation of an absence of cross-reactivity between rivaroxaban and other NOACs.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Kirchhof P, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37.
2. Van den Heuvel JM et al. NOACs Replace VKA as Preferred Oral Anticoagulant among New Patients: A Drug Utilization Study in 560 Pharmacies in The Netherlands. Thrombosis Journal 2018; 16:7.
3. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000; 356:1255-1259.
4. Coombs PRGP. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell RR, editor. Clinical Aspects of Immunology. Oxford: Oxford Univ Pr; 1968: 575-596.
5. Beasley N, Dunnmon P, Rose M. Clinical Review Application type: Standard, NDA 22-439 Xarelto (rivaroxaban). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202439Orig1s000MedR.pdf
6. Josyln JA, Khattak FH, Geraci SA. A Case of a Reversible Neurologic Adverse Reaction to Apixaban Confirmed by Re-Challenge. J Clin Med Res 2018; 10(6):523-526.
7. Xarelto Package Insert. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022406s015lbl.pdf (accessed: August 9, 2018)
8. Camm AJ et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. European Heart Journal 2016; 37(14):1145-1153.
9. Gorzelak-Pabiś P, Duraj I, Szlagowska L, Ciastkowska A, Broncel M. [Comparison of the safety of rivaroxaban versus dabigatran therapy in patients with persistent atrial fibrillation]. Pol Merkur Lekarski 2014; 37(221):261-264.
10. Altin C, Ozturkeri OA, Gezmis E, Askin U. Angioedema due to the new oral anticoagulant rivaroxaban. Ann Card Anaesth 2014; 17(2):173-174.
11. Mima Y, Sangatsuda Y, Yasaka M, Wakugawa Y, Nagata S, Okada Y. Acute Thrombocytopenia after Initiating Anticoagulation with Rivaroxaban. Internal Medicine 2014; 53(21):2523-2527.
12. Aster RH, Curtis BR, McFarland JG, Bougie DW. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. J Thromb Haemost 2009; 7:911-918.
13. Pop MK, Farokhi F, Iduna L. Drug-induced thrombocytopenia after anticoagulation with rivaroxaban. Am J Emerg Med 2018; 36(3):531.e1-531.e2.
14. Dean R, Messer AM, Pickett M, Jahan-Tigh R. A case of leukocytoclastic vasculitis caused by novel anticoagulant rivaroxaban. Dermatol Online J 2017; 15:23(11).
15. Chaaya G, Jaller-Char J, Ghaffar E, Castiglioni A. Rivaroxaban-induced leukocytoclastic vasculitis: A challenging rash. Ann Allergy Asthma Immunol 2016; 116(6):577-8.
16. Hasbal NB, Baştürk T, Koç Y, Sahutoğlu T, Bayrakdar Çağlayan F, Ünsal A. Leukocytoclastic Vasculitis Associated with a New Anticoagulant: Rivaroxaban. Turk J Haematol 2017;34(1):116-117.
17. Sainz-Gaspar L, Pita da Veiga G, Suárez-Peñaranda JM, Vázquez-Veiga H, Sánchez-Aguilar D. Leukocytoclastic vasculitis associated with rivaroxaban. Int J Dermatol 2018; 57(5):622-624.
18. Snyder DJ, Matusik FB. Rivaroxaban-induced serum sickness after total knee arthroplasty. Am J Health Syst Pharm 2015; 72(18):1567-1571.
19. Prasannan N, Soultati A, Harrison C, Yeghen T, Radia D. 2 cases of idiopathic hypereosinophilic syndrome: a rare disorder with severe thrombohaemorrhagic complications [abstract]. Haematologica 2013; 98 Suppl1:627.
20. Chiasson CO, Canneva A, Roy FO, Doré M. Rivaroxaban-Induced Hypersensitivity Syndrome. Can J Hosp Pharm 2017; 70(4):301-304.
21. Yates J, Choudhry M, Keys G. A case report describing a suspected rivaroxaban hypersensitivity reaction in a surgical patient. J Clin Pharm Ther 2013; 38(2):159-161.
22. Radu C, Barnig C, de Blay F. Rivaroxaban-Induced Drug Reaction With Eosinophilia and Systemic Symptoms. J Investig Allergol Clin Immunol 2016; 26(2):124-6.
23. Barrett P, Vuppalanchi R, Masuoka H, Chalasani N. Severe drug-induced skin and liver injury from rivaroxaban. Dig Dis Sci 2015; 60: 1856-1858.
24. Rudd KM, Panneerselvam N, Patel A. Rash associated with rivaroxaban use. Am J Health Syst Pharm 2018; 75(6):347-349.
25. Sasson E, James M, Russell M, Todorov D, Cohen H. Probable Rivaroxaban-Induced Full Body Rash: A Case Report. J Pharm Pract. 2017:897190017722872.
26. Vernon HM, Nielsen AK, O'Bryan EC. Hypersensitivity reaction after administration of rivaroxaban (Xarelto). Am J Emerg Med 2016; 34(7):1325.e1-2.
27. Eliquis Package Insert. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf (access: July 26, 2018)
28. Nasir UB, Kumar A, Easwar A. Apixaban Causing Leukocytoclastic Vasculitis. J Allergy Clin Immunol Pract 2018. pii: S2213-2198(17)31025-5.
29. Veliyev V. A rare side effect seen due to the use of apixaban: Palmoplantar psoriasiform drug eruption. Anatol J Cardiol 2016; 16:212-215.
30. Cortellini G, Rossi F, Lippolis D, Cortellini F, Gavioli B, Ballardini G. Delayed hypersensitivity to new oral anticoagulants. Demon-

stration of cross reactivity for the drug category and definition of non-irritant concentrations for patch tests. Eur Ann Allergy Clin Immunol 2018.
31. Lixiana Package Insert. Available at https://ec.europa.eu/health/documents/community-register/2015/20150619132091/anx_132091_en.pdf (accessed: September 2, 2018)
32. Kuroda Y, Hirayama C, Hotoda H, Nishikawa Y, Nishiwaki A. Postmarketing safety experience with edoxaban in Japan for thromboprophylaxis following major orthopedic surgery. Vasc Health Risk Manag 2013; 9(1):593-598.
33. Pradaxa Product Information FDA available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022512s007lbl.pdf (accessed: August 13, 2018)
34. Pradaxa Product Information EMA available at: https://www.ema.europa.eu/documents/product-information/pradaxa-epar-product-information_en.pdf (accessed: August 13, 2018)
35. Boehringer Ingelheim Dabigatran Briefing Document, 2010, available at https://www.researchgate.net/profile/Michael_Ezekowitz/publication/262733892_Stroke_prevention_in_atrial_fibrillation_established_oral_anticoagulants_versus_novel_anticoagulants-translating_clinical_trial_data_into_practice/links/576eea0808ae842225a8849c/Stroke-prevention-in-atrial-fibrillation-established-oral-anticoagulants-versus-novel-anticoagulants-translating-clinical-trial-data-into-practice.pdf (accessed: August 13, August)
36. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol 2010; 105:259-273.
37. An J, Garje R, Wanat KA, Leone JP. Dabigatran-related leukocytoclastic vasculitis. BMJ Case Rep 2017; Jan 4; 2017.
38. Potolidis E, Mandros C, Kotsa K, Mitsiou E, Potolidis D, Fanourgiakis P. Dabigatran Associated Leukocytoclastic Vasculitis. Case Rep Med 2015; 2015:616109.
39. Cakmak MA, Sahin S, Cinar N, Karsidag S. Adverse skin reaction caused by dabigatran. Eur Rev Med Pharmacol Sci 2014; 18(18):2595.
40. Winkle et al. Dabigatran After AF Ablation Journal of Cardiovascular Electrophysiology Vol. 23, No. 3, March 2012.
41. To K, Reynolds C, Spinler SA. Rash associated with dabigatran etexilate. Pharmacotherapy 2013; 33(3):e23-7.
42. Eid TJ, Shah SA. Dabigatran-induced rash. Am J Health Syst Pharm 2011; 68(16):1489-1490.
43. Cucurull I, Canosa J, Vega-Molpeceres S, Just Sarobe M, Escoda García M. [Dabigatran induced exanthema]. Rev Clin Esp 2010; 210(11):590-591.
44. Tsoumpris A, Tzimas T, Gkabrelas K, Akritidis N. Iron complex, dabigatran and toxic epidermal necrolysis syndrome: a case-report. J Clin Pharm Ther 2013; 38(2):177-178.