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Recommendation on the nomenclature for anticoagulants: updated communication from the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee on the Control of Anticoagulation

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AUTHOR CONTRIBUTIONS

G.D.B. and A.C. conceived of the manuscript idea. G.D.B. drafted the manuscript. All authors read and approved the final version of the paper.

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Abstract

Oral anticoagulation therapy has evolved beyond vitamin K antagonists to include oral direct thrombin inhibitors and factor Xa inhibitors. Collectively known as “direct oral anticoagulants,” this class of medications represents the current standard of care for the prevention and treatment of common thrombotic disorders, including atrial fibrillation and venous thromboembolism. Medications that target factors XI/XIa and XII/XIIa are currently under investigation for several thrombotic and nonthrombotic conditions. Given that these emerging medications will likely have distinct risk-benefit profiles to the current direct oral anticoagulants, may have different routes of administration, and could be used for unique clinical conditions (e.g., hereditary angioedema), the International Society on Thrombosis and Haemostasis Subcommittee on Control of Anticoagulation assembled a writing group to make recommendations on the nomenclature of anticoagulant medications. With input from the broader thrombosis community, the writing group recommends that anticoagulant medications be described by the route of administration and specific targets (e.g., oral factor XIa inhibitor).

Keywords

anticoagulant; factor Xa inhibitors; factor XIa; factor XII; atrial fibrillation; venous thromboembolism

1 | INTRODUCTION

In recent decades, oral anticoagulation therapy has evolved beyond vitamin K antagonists to include oral direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban). For the initial several years, different terms were used to describe this newer class of oral anticoagulants. To minimize confusion and to harmonize classification, experts assembled global input and published recommendations on nomenclature [1]. Since that time, the term direct oral anticoagulants (DOACs) became largely used in the hematology/thrombosis community and these drugs have become the most prescribed oral anticoagulants for stroke prevention in atrial fibrillation (AF)

as well as for treatment of venous thromboembolism and other thrombotic conditions and prevention of venous thromboembolism in orthopedic procedures [2]. However, the use of alternative nomenclature persists, including target-specific oral anticoagulants, non-vitamin K antagonist oral anticoagulants, and novel oral anticoagulants (NOACs), despite these agents no longer being “novel” [3,4]. There is also a suggestion that the “NOAC” abbreviation can sometimes be misinterpreted to indicate “no anticoagulation.” Nonetheless, NOAC is still the most used abbreviation in the worldwide cardiology community. The concurrent use of several terms may, in part, reflect a lack of concerted effort to generate consensus until after the oral direct thrombin and factor Xa inhibitors were in widespread use.

The next generation of therapies target factor XI/XIa or factor XII/XIIa in the intrinsic pathway of coagulation. Several parenteral and oral factor XI inhibitors are currently being tested in phases 2 and 3 of clinical trials [5]. In some of these trials, the factor XI/XIa inhibitors are being compared head-to-head with DOACs, whereas in other trials, they are being compared with a placebo on top of antiplatelet therapy for secondary stroke prevention or for treatment of acute coronary syndrome. Regardless of the indication, factor XI/XIa inhibitors have different mechanisms of action and are expected to have a better benefit-risk profile than DOACs. They also may have different routes of administration and pharmacologic properties from the current class of DOACs. As such, the names given to classes of anticoagulants are important for both clinical and research purposes and to harmonize terms.

To ensure consistent nomenclature for the upcoming generation of anticoagulants, an expert panel was assembled to make recommendations. The global thrombosis community was then invited to provide input into the recommendation statements.

2 | METHODS

We assembled a diverse expert panel representing the global thrombosis community of clinicians and researchers, including early and established career members. The expert panel held multiple videoconference discussions to review the emerging anticoagulant medications, their properties, mechanisms of action, and potential clinical uses. The expert panel prepared a draft set of recommendations for public comment (Supplementary Appendix).

Public comment was solicited through an online survey invitation sent to approximately 1700 members of 2 different International Society on Thrombosis and Haemostasis (ISTH) Scientific Standardization Committees subcommittees (Control of Anticoagulation, factor XI, and the Contact System) as well as promoted on social media and in ISTH email newsletters. Public comments were gathered on the survey form between March 15 and April 15, 2022. Summary statistics were calculated, and free text comments were grouped on the basis of themes.

The expert panel reconvened to review public comments and revise the recommendation statement. Final input was obtained from both the thrombosis/hemostasis community and the cardiology community, as is reflected in both the survey respondents and the author list.

2.1 | Public comment survey results

A total of 137 surveys were completed by clinician-researchers ($n = 73$, 54.1%), clinicians ($n = 47$, 34.8%), researchers ($n = 6$, 4.4%), industry or society partners ($n = 5$, 3.7%), and others ($n = 6$, 4.4%). These respondents most commonly represented adult hematology (57/120, 47.5%), cardiovascular medicine (15/120, 12.5%), and internal medicine (15/120, 12.5%) and were mostly male ($n = 78$, 57.4%). Survey responses were collected from North America ($n = 66$, 48.2%), Europe ($n = 38$, 27.7%), South America ($n = 13$, 9.5%), Asia ($n = 12$, 8.8%), Oceania ($n = 6$, 4.4%), and the Middle East ($n = 2$, 1.5%). There was strong support for our draft recommendations, reflected by a high frequency of respondents who somewhat or completely agreed ($n = 108$, 78.7%) and completely agreed ($n = 77$, 56.2%) (Supplementary Appendix).

Two major themes emerged from the free text comments. The first was the belief that factor XI/XIa and factor XII/XIIa inhibitors are more similar than dissimilar to the existing factor Xa inhibitors. As such, splitting these agents into differently named groups might create confusion. The second was that if different terms were to be used for factor XI/XIa inhibitors, factor XII/XIIa inhibitors, and existing DOACs, then oral direct thrombin inhibitors and factor Xa inhibitors should also be separated and not grouped under a single class name.

2.2 | Final recommendation (Figure)

The final recommendation for how best to refer to emerging anticoagulant medications is as follows: Describe anticoagulant medications by their mode of administration and specific target (e.g., oral factor XIa inhibitor, parenteral factor XIIa inhibitor).

The expert panel recognized that the “DOAC” term is firmly entrenched in the thrombosis lexicon. As such, it is unlikely that the thrombosis community will embrace a change from DOACs to “oral factor Xa inhibitors” and “oral direct thrombin inhibitors.” However, given that emerging therapies (e.g., factor XIa inhibitors) may also be used to treat similar conditions (e.g., AF) but with different benefit-risk profiles, being specific about each medication’s target would be most clarifying. Furthermore, as different medications with the same target have different routes of administration, clarifying oral or parenteral will be helpful for determining how and when to use each medication.

The recommendation on the nomenclature for anticoagulant medications was approved by the ISTH SSC Subcommittee on Control of Anticoagulation.

2.3 | Rationale for the recommendation

Emerging pharmaceutical agents that target factors XI/XIa and XII/XIIa have shown promise in preclinical studies and early clinical trials for the prevention of thrombotic events and/or treatment of hereditary angioedema. However, it is plausible that these agents will

have unique indications and side effect profiles that do not significantly overlap with one another or with the current factor Xa and thrombin inhibitors. For example, garadacimab, a factor XII inhibitor, is being tested in patients with hereditary angioedema ([NCT04656418](#)), whereas phase 2 data in patients with AF showed that asundexian (an oral factor XIa inhibitor) was associated with a lower risk of bleeding than apixaban [6].

There are abundant linkages between the extrinsic and intrinsic pathways of coagulation and growing evidence that factor XI is important for thrombosis development but less important for the regulation of hemostasis [7,8]. As such, terms such as “contact pathway inhibitors” or “intrinsic pathway inhibitors” are unhelpful descriptors of factor XI inhibitors.

Finally, although these emerging agents will likely have clinical utility in treatment and/or prevention of thrombosis, they also may have clinical utility for nonthrombotic conditions (e.g., hereditary angioedema) [5].

To that end, the expert panel recommends referring to these medications according to their mode of administration and specific target rather than grouping them together under a general name, including the currently used DOAC label (Table).

This recommendation was developed by a diverse group of clinicians and researchers with feedback from a contingent of the global thrombosis and hemostasis community. However, it is important to acknowledge the limitation that not all clinicians and researchers were able to provide their input into this process. Furthermore, although the proposed nomenclature scheme provides more flexibility and specificity than the prior “DOAC” term, it may not easily incorporate the nuances of all anticoagulant medications (e.g., agents that have indirect actions on coagulation such as fondaparinux). Nonetheless, we believe that the proposed nomenclature scheme provides more flexibility and specificity for clinicians and researchers.

3 | CONCLUSION

The last 10 to 20 years have heralded an explosion in anticoagulant research. A class of drugs that was once limited to vitamin K antagonists and heparins now includes more than 20 currently available and emerging agents, each with its own unique mechanism of action, route of administration, indications, toxicity profile, and pharmacology. As anticoagulants become more varied, our nomenclature must reflect important differences among this expanding class of agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE.

Recommendation from the SSC of the ISTH on the Nomenclature for Oral Anticoagulants
Describe anticoagulant medications by their route of administration and specific target (e.g.,
oral Factor XIa inhibitor, parenteral Factor XIIa inhibitor).

This recommendation was approved by the ISTH SSC Subcommittee on Control of
Anticoagulation

TABLE
Proposed nomenclature for anticoagulant medications currently available or under investigation

Route of administration	Vitamin K antagonists	Heparins and heparinoids	Thrombin inhibitors	Factor Xa inhibitors	Factor XI or XIa inhibitors	Factor XII or XIIa inhibitors
Parenteral		• Unfractionated heparin • Low molecular weight heparin	• Argatroban • Bivalirudin		• Abelacimab • Fesomersen • Osocimab • Xisomab (AB023)	• Garadacimab
Oral	• Warfarin • Acenocoumarol • Phenprocoumon	• Fondaparinux • Danaparoid	• Dabigatran	• Apixaban • Edoxaban • Rivaroxaban	• Milvexian • Asundexian	