Recommendation on the Nomenclature for Anticoagulants: Updated Communication from the ISTH SSC Subcommittee on the Control of Anticoagulation

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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 non-thrombotic 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 ISTH 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 target (e.g., oral Factor XIa inhibitor).

Keywords

Anticoagulant
Factor Xa inhibitors
Factor XIa
Factor XII
Atrial fibrillation
Venous thromboembolism

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, rivaroxaban). For the first 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 (VTE) and other thrombotic conditions and prevention of VTE 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 the suggestion that the 'NOAC' abbreviation can sometimes be misinterpreted to indicate 'no anticoagulation.' Nonetheless, NOAC is still the most used abbreviation in the world-wide 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 phase 2 and 3 clinical trials.[5] In some of these trials, the factor XI/XIa inhibitors are being compared head-to-head with DOACs, while 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, the factor XI/XIa inhibitors have different mechanisms of action and are expected to have a better benefit-risk profile than the 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.

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 (supplemental appendix).

Public comment was solicited through an online survey invitation sent to the approximately 1700 members of two different ISTH Scientific Standardization Committees subcommittees (Control of Anticoagulation, Factor XI and the Contact System) as well as promoted on social media and in ISTH e-mail 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 based on themes.

The expert panel re-convened 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.

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%) (supplemental 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.

Final Recommendation (Figure)

The final recommendation for how best to refer to emerging anticoagulant medications is:

1) 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.

Rationale for the Recommendation

Emerging pharmaceutical agents that target Factors XI/XIa and XII/XIIa have shown promise in pre-clinical 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) while 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 regulation of hemostasis.[7,8] As such, terms like “contact pathway inhibitors” or “intrinsic pathway inhibitors” are unhelpful descriptors of factor XI inhibitors.

Finally, while these emerging agents will likely have clinical utility in treatment and/or prevention of thrombosis, they also may have clinical utility for non-thrombotic 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. Yet it is important to acknowledge the limitation that not all clinicians and researchers were able to provide their input into this process. Furthermore, while 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.

Conclusion

The last 10-20 years have heralded an explosion in anticoagulant research. A class of drugs which 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.

References

1 Barnes GD, Ageno W, Ansell J, Kaatz S. Recommendation on the nomenclature for oral anticoagulants: Communication from the SSC of the ISTH: Reply. *Journal of Thrombosis and Haemostasis* 2015; **13**: 2132–3.

2 Wheelock KM, Ross JS, Murugiah K, Lin Z, Krumholz HM, Khera R. Clinician Trends in Prescribing Direct Oral Anticoagulants for US Medicare Beneficiaries. *JAMA network open* 2021; **4**: e2137288.

3 Husted S, de Caterina R, Andreotti F, Arnesen H, Bachmann F, Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Siegbahn A, Storey RF, Weitz JI, Disease ESCWG on TTF on A in H. Non-vitamin K antagonist oral anticoagulants (NOACs): No longer new or novel. *Thromb Haemost* 2014; **111**: 781–2.

4 Husted S, Lip GYH, De Caterina R. Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH: comment. *J Thromb Haemost* 2015; **13**: 2130–2.

5 Kluge KE, Seljeflot I, Arnesen H, Jensen T, Halvorsen S, Helseth R. Coagulation factors XI and XII as possible targets for anticoagulant therapy. *Thrombosis research* 2022; **214**: 53–62.

6 Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, Jones WS, Gorog DA, Durdil V, Viethen T, Neumann C, Mundl H, Patel MR, Auer J, Hubauer M, Pandzic S, Preishuber E, Primus-Grabscheit C, Reitgruber D, Schmalzer F, Adlbrecht C, et al. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. *The Lancet* 2022; **399**: 1383–90.

7 Hsu C, Hutt E, Bloomfield DM, Gailani D, Weitz JI. Factor XI Inhibition to Uncouple Thrombosis From Hemostasis. *Journal of the American College of Cardiology* 2021; **78**: 625–31.

8 Hoffman M, Monroe D. A Cell-based Model of Hemostasis. *Thromb Haemost* 2001; **85**: 958–65.

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

	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 • Fondaparinux • Danaparoid	• Argatroban • Bivalirudin		• Abelacimab • Fesomersen • Osocimab • Xisomab (AB023)	• Garadacimab
Oral	• Warfarin • Acenocoumarol • Phenprocoumon		• Dabigatran	• Apixaban • Edoxaban • Rivaroxaban	• Milvexian • Asundexian	

Draft ISTH Recommendation on Nomenclature of Emerging Anticoagulant Medications (February 2022)

Background:
When the oral direct thrombin and factor Xa inhibitors were first introduced to the market, there was significant variation in the names used to describe this new class of anticoagulants (new, novel, target specific, direct, direct-acting, etc). To reduce confusion, the International Society on Thrombosis and Haemostasis (ISTH) Scientific Standardization Committee (SSC) on Control of Anticoagulation undertook a project to establish a uniform nomenclature for those medications, eventually deciding on "direct oral anticoagulants (DOACs)" (DOI: 10.1111/jth.12969). While this nomenclature has been widely adopted in the hematology and thrombosis community worldwide, other communities (especially cardiology) continue to use other terms such as "non-vitamin K antagonist oral anticoagulant (NOAC)". As the ISTH SSC nomenclature recommendation was not published until 4+ years after these medications were first marketed, the ability to unify the scientific/medical community's use of a single term was limited.

Emerging anticoagulants with different mechanisms (e.g., Factor XI/XIa inhibitors, Factor XII/XIIa inhibitors) are in clinical testing and may come to market soon. We assembled a multi-disciplinary and diverse panel of global experts to propose a nomenclature scheme for this next phase of antithrombotic agents. By developing a nomenclature scheme before these agents come to market and by seeking comment and feedback from diverse stakeholders, our goal is to establish a terminology that is clear and will be well-accepted by the medical community.

Our recommendations are as follows:

1) Describe anticoagulant medications by their specific target and mode of administration (e.g., oral Factor XIa inhibitor, parenteral Factor XIIa inhibitor).
2) Factor XI/XIa and Factor XII/XIIa medications should not be included in the group of "direct oral anticoagulants (DOACs)" given their heterogenous mode of administration, targets (e.g., Factor XI, Factor XIa), mechanisms of action, unique impact on thrombosis/hemostasis, and likely distinct clinical uses in comparison to the oral Factor Xa and direct thrombin inhibitors.

Rationale:
Emerging pharmaceutical agents that target Factors XI/XIa and XII/XIIa have shown promise in pre-clinical studies and early clinical trials for the prevention of thrombotic complications. However, it is plausible that these agents will have unique indications that do not significantly overlap with one another or with the current Factor Xa and IIa inhibitors.

Furthermore, evolving understanding of coagulation challenges the traditional waterfall cascade model. Rather, there is likely a complex interplay between various clotting factors and endogenous anticoagulant proteins that regulate thrombus formation. As such, terms such as

"contact pathway inhibitors" or "intrinsic pathway inhibitors" are not accurate descriptors of our evolving understanding of coagulation.

Finally, while these emerging agents will likely have clinical utility treating and/or preventing thrombosis, they also may have clinical utility for non-thrombotic conditions (e.g., hereditary angioedema).

To that end, we believe that it is best to refer to these medications according to their specific target and mode of administration rather than grouping them together under a general name, including the currently used DOAC label.

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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 non-thrombotic 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 ISTH 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 target (e.g., oral Factor XIa inhibitor).

Keywords

Anticoagulant
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Factor XIa
Factor XII
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Venous thromboembolism

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, rivaroxaban). For the first 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 (VTE) and other thrombotic conditions and prevention of VTE 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 the suggestion that the 'NOAC' abbreviation can sometimes be misinterpreted to indicate 'no anticoagulation.' Nonetheless, NOAC is still the most used abbreviation in the world-wide 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 phase 2 and 3 clinical trials.[5] In some of these trials, the factor XI/XIa inhibitors are being compared head-to-head with DOACs, while 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, the factor XI/XIa inhibitors have different mechanisms of action and are expected to have a better benefit-risk profile than the 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.

Methods

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The expert panel re-convened 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.

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%) (supplemental 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.

Final Recommendation (Figure)

The final recommendation for how best to refer to emerging anticoagulant medications is:

1) 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.

Rationale for the Recommendation

Emerging pharmaceutical agents that target Factors XI/XIa and XII/XIIa have shown promise in pre-clinical 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) while 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]

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Finally, while these emerging agents will likely have clinical utility in treatment and/or prevention of thrombosis, they also may have clinical utility for non-thrombotic 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. Yet it is important to acknowledge the limitation that not all clinicians and researchers were able to provide their input into this process. Furthermore, while 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.

Conclusion

The last 10-20 years have heralded an explosion in anticoagulant research. A class of drugs which 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.

References

1 Barnes GD, Ageno W, Ansell J, Kaatz S. Recommendation on the nomenclature for oral anticoagulants: Communication from the SSC of the ISTH: Reply. *Journal of Thrombosis and Haemostasis* 2015; **13**: 2132–3.

2 Wheelock KM, Ross JS, Murugiah K, Lin Z, Krumholz HM, Khera R. Clinician Trends in Prescribing Direct Oral Anticoagulants for US Medicare Beneficiaries. *JAMA network open* 2021; **4**: e2137288.

3 Husted S, de Caterina R, Andreotti F, Arnesen H, Bachmann F, Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Siegbahn A, Storey RF, Weitz JI, Disease ESCWG on TTF on A in H. Non-vitamin K antagonist oral anticoagulants (NOACs): No longer new or novel. *Thromb Haemost* 2014; **111**: 781–2.

4 Husted S, Lip GYH, De Caterina R. Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH: comment. *J Thromb Haemost* 2015; **13**: 2130–2.

5 Kluge KE, Seljeflot I, Arnesen H, Jensen T, Halvorsen S, Helseth R. Coagulation factors XI and XII as possible targets for anticoagulant therapy. *Thrombosis research* 2022; **214**: 53–62.

6 Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, Jones WS, Gorog DA, Durdil V, Viethen T, Neumann C, Mundl H, Patel MR, Auer J, Hubauer M, Pandzic S, Preishuber E, Primus-Grabscheit C, Reitgruber D, Schmalzer F, Adlbrecht C, et al. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. *The Lancet* 2022; **399**: 1383–90.

7 Hsu C, Hutt E, Bloomfield DM, Gailani D, Weitz JI. Factor XI Inhibition to Uncouple Thrombosis From Hemostasis. *Journal of the American College of Cardiology* 2021; **78**: 625–31.

8 Hoffman M, Monroe D. A Cell-based Model of Hemostasis. *Thromb Haemost* 2001; **85**: 958–65.

Figure

~~Proposed~~ 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

	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 • Fondaparinux • Danaparoid	• Argatroban • Bivalirudin		• Abelacimab • Fesomersen • Osocimab • Xisomab (AB023)	• Garadacimab
Oral	• Warfarin • Acenocoumarol • Phenprocoumon		• Dabigatran	• Apixaban • Edoxaban • Rivaroxaban	• Milvexian • Asundexian	