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RECOMMENDATIONS AND GUIDELINES

Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH

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Scope and methodology

Oral anticoagulants are used to prevent and treat a wide range of thromboembolic diseases. Currently available oral anticoagulants include the vitamin K antagonists (VKAs), such as warfarin. VKAs reduce the synthesis of functional vitamin K-dependent factors (factor II, FVII, FIX, FX, as well as protein C and protein S) by interfering with the vitamin K redox cycle. The newer oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban) each directly inhibit an activated clotting factor, either FIIa or FXa. Their pharmacokinetic and pharmacodynamic properties are more predictable than those of the VKAs, so routine monitoring of the anticoagulant effect is not required [1].

Various terms have been used to describe the 'new' class of oral anticoagulants, although they are not so new or novel any more. Terms that are commonly encountered in the medical literature include: novel/new oral anticoagulants (NOACs), direct oral anticoagulants (DOACs), and target-specific oral anticoagulants (TSOACs). However, the use of multiple terms and abbreviations can lead to fragmentation of the medical literature, and confusion among providers and patients. The term NOAC has been used the longest, and, recently, some have argued for use of the term 'non-VKA oral antagonists' (NOACs), to take advantage of the commonly used abbreviation without using the terms novel and new [2]. However, identifying a class of drugs by what they are not is scientifically unappealing. Perhaps more importantly, there is at least one reported account where the term NOAC written in the medical record was interpreted as meaning 'No AntiCoagulation,' potentially resulting in the patient not receiving the critical therapy that was intended [3].

There is a clear need to reach a consensus on the nomenclature of oral anticoagulants, and several experts have called for consensus around the nomenclature for oral anticoagulants [2,4–7].

We aimed to develop guidance from the Control of Anticoagulation SSC of ISTH on the most appropriate abbreviation for the newer/novel/target-specific/direct-acting oral anticoagulants by seeking the opinions of thrombosis and anticoagulation thought leaders.

We administered a web-based survey (Data S1) to the leaders (primarily board members) of 16 thrombosis, hemostasis, anticoagulation and vascular medicine societies from seven different countries in North America and Europe (150 recipients in total) in September 2014. These societies were selected on the basis of their clinical interests in vascular medicine, thrombosis, or anticoagulation. All medical officers of each society whose contact information was available were invited to participate in the survey. Two reminders were sent to each participant, and those who participated were not compensated. Of the 150 recipients, 77 (51%) completed the survey. In this survey, we asked about their opinion regarding: (i) the need for consensus around oral anticoagulation nomenclature; (ii) concerns about the safety of using the term NOAC; and (iii) their preferred term to describe this new class of oral anticoagulants. On the basis of these survey results, the following guidance statements were formulated.

The vast majority (89.6%) of the respondents felt that there was a need to reach a consensus on terminology. There was less agreement regarding the safety issue of the term NOAC; 54.7% felt that there should be limited use of this term. When the respondents were asked about the single best term (DOAC [direct oral anticoagulant], NOAC [non-VKA oral anticoagulant], NOAC [novel oral

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anticoagulant], ODI [oral direct inhibitor], SODA [specific oral direct anticoagulant], TSOAC [target specific oral anticoagulant], and Other) for this class of medications, the top three responses were as follows: DOAC (direct oral anticoagulant), 29.9%; NOAC (non-VKA oral anticoagulant), 28.6%; and TSOAC (target-specific oral anticoagulant), 23.4%. When the respondents were asked to select all acceptable terms, the top three responses were as follows: DOAC, 58.4%; TSOAC, 49.4%; and NOAC, 39.0%.

Concerns with the term NOAC

Anticoagulants are known to reduce the morbidity and mortality associated with a number of thrombotic conditions. In each of these conditions, lack of anticoagulant therapy can have dramatic effects on patient outcomes. In some reports, use of the term NOAC has been misinterpreted as 'No AntiCoagulation', which may lead to the inadvertent omission of important anticoagulant therapy for a patient with a thrombotic disorder [3]. In our survey, only 41 (54.7%) respondents agreed that the term NOAC had safety implications that should limit its use. This is not surprising, because many physicians would not necessarily agree that many of the terms considered to be unsafe by the Institute for Safe Medical Practices are really unsafe [8]. Some have argued that the term NOAC should be used and evolve, and that the 'N' should represent Non-VKA antagonist instead of new/novel, because this terminology is well established in the medical literature [5]. However, many experts also feel that, ideally, a class of medications should be defined by a positive characteristic or general mode of action, rather than by a negative property that is lacking.

Despite the frequent adoption of NOAC in the medical literature, and calls by some thrombosis and anticoagulation leaders to use non-vitamin K oral anticoagulant (NOAC), we feel that the potential safety implications and lack of pharmacologic specificity of this abbreviation should prevent its widespread use. Additionally, although some have encouraged the use of non-VKA OAC as the best term, we feel that this is both cumbersome and too easily abbreviated as NOAC by clinicians and in the literature, with the safety implications noted above.

Recommendation statements for consensus around oral anticoagulation nomenclature and harm with NOAC

1 We suggest that consensus be reached on a single term to be used for describing the direct oral FIIa and FXa inhibitors.
2 We recommend that a single term be used consistently for all oral direct anticoagulants that have inherently different mechanisms and clinical properties from those of vitamin K antagonists.
3 We suggest that the abbreviation NOAC should not be used to describe any class of oral anticoagulant.

Evidence for the use of DOAC

Unlike VKAs, the direct oral anticoagulants target one specific factor (currently either FXa or FIIa). Specifically, dabigatran inhibits thrombin (FIIa), whereas rivaroxaban, apixaban, edoxaban and betrixaban all inhibit FXa. Use of the term 'direct' adequately distinguishes this class of medications from the VKAs, and allows each of these medications to be discussed on the basis of their similar (but not exactly the same) clinical profiles. In our survey, DOAC received the most votes (45, 58.4%) as an acceptable term for this class of medications. When respondents were asked to pick the single best term, however, no single choice dominated. Twenty-three (29.9%) respondents selected DOAC, 22 (28.6%) selected NOAC (non-VKA oral anticoagulant), and 18 (23.4%) selected TSOAC. With low support for TSOAC in this survey of thrombosis and anticoagulation experts, this term was not felt to be the best single choice for routine use.

Given the potential safety limitations associated with the use of NOAC and the relative specificity of pharmacologic action, DOAC is a reasonable choice. DOAC is also used widely in the published literature, making it a very reasonable selection [6,9–11]. Many respondents commented that the best descriptive term is one that describes the mechanism of action, such as direct thrombin inhibitor and direct FXa inhibitor. However, given the many similarities between the oral agents of these two groups, it seems reasonable to describe them together for the majority of clinical scenarios. Nevertheless, they can be distinguished by their mechanism of action in situations where it is clinically relevant (e.g. selecting appropriate coagulation laboratory testing and for potential medication strategies).

Recommendation statement for the use of DOAC

1 We suggest using the term 'direct oral anticoagulant' (DOAC) to reference the class of oral anticoagulants that directly inhibit a single target and have similar clinical properties (e.g. dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban).
2 We suggest that a drug's specific mechanism of action (e.g. direct FXa inhibitor or direct thrombin inhibitor) should be used when it is clinically important to distinguish between the various DOAC medications.

Society endorsements

This guidance statement was written by the authors on behalf of the ISTH SSC Subcommittee on Control of Anticoagulation. The guidance statement is endorsed by the following societies: the American Thrombosis and Hemostasis Network (ATHN), the Anticoagulation Forum (AC Forum), the Canadian Pediatric Thrombosis and Hemostasis Network (CPTHN), the Dutch Society for Thrombosis and Hemostasis (NVTH), the French

Study Group in Hemostasis and Thrombosis, the Hemostasis and Thrombosis Research Society (HTRS), the National Blood Clot Alliance, the North American Specialized Coagulation Laboratory Association (NASCOLA), the North American Society on Thrombosis and Hemostasis (NASTH), the Society for Vascular Medicine (SVM), the Spanish Society of Thrombosis and Hemostasis (SETH), and Thrombosis Canada.

Addendum

G. D. Barnes conceived the project idea, collected and analyzed data, and wrote the initial and subsequent manuscript drafts. W. Ageno and J. Ansell provided critical study design critique, analyzed data, and edited initial and subsequent manuscript drafts. S. Kaatz conceived the project idea, analyzed data, and edited initial and subsequent manuscript drafts.

Disclosure of Conflict of Interests

S. Kaatz reports receiving personal fees from Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, Janssen, and CSL Behring, outside the submitted work. G. D. Barnes reports receiving grants from Bristol-Myers Squibb/Pfizer and personal fees from Portola, outside the submitted work. J. Ansell reports receiving personal fees from Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, and Janssen, outside the submitted work. W. Ageno reports receiving personal fees from Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, and GlaxoSmithKline, outside the submitted work.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Survey questions.

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