Recommendation on the Nomenclature for Oral Anticoagulants

On behalf of the Control of Anticoagulation Subcommittee of 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 (VKA), such as warfarin. VKAs reduce the synthesis of functional vitamin K-dependent factors (II, VII, IX, X as well as protein C and protein S) by interfering in the vitamin K redox cycle. The newer oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban and betrixaban) each directly inhibit an activated clotting factor, either IIa or Xa. Their pharmacokinetic and pharmacodynamic properties are more predictable than the VKAs and therefore do not require routine monitoring of anticoagulant effect.[1]

Various terms have been used to describe the "new" class of oral anticoagulants, although they are not so new or novel anymore. Acronyms 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, 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 using the term "non-VKA oral antagonists" (NOACs) to take advantage of the commonly used abbreviation without using the terms novel or 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 getting the critical therapy that was intended.[3]

There is a clear need to reach consensus for 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 (see appendix) to the leaders (primarily board members) of 16 thrombosis, hemostasis, anticoagulation and vascular medicine societies from North America and Europe (150 total recipients) in September 2014. 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: a) the need for consensus around oral anticoagulation nomenclature, b) concerns about the safety of using the term "NOAC" and c) their preferred term to describe this new class of oral anticoagulants. Based on these survey results, the following guidance statements were formulated.

The vast majority (89.6%) of the respondents felt there was a need to reach consensus on terminology. There was less agreement regarding the safety issue of the term "NOAC"; 54.7% felt there should be limited use of this term. When asked for the single best term (DOAC [direct oral anticoagulant], NOAC [non-VKA oral anticoagulant], NOAC [novel oral anticoagulant], ODI [oral direct inhibitors], SODA [specific oral direct anticoagulant], TSOAC [target specific oral anticoagulant] and Other) for this class of medications, the top three responses were: DOAC (direct oral

anticoagulants) 29.9%, NOAC (non-VKA oral anticoagulants) 28.6% and TSOAC (target specific oral anticoagulants) 23.4%. When asked to select all acceptable terms, the top three responses were: DOAC 58.4%, TSOAC 49.4% and NOAC 39.0%.

Concerns with the term "NOAC"

Anticoagulants are known to reduce 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 misinterprested as "No AntiCoagulation" which may lead to inadvertently omitting important anticoagulant therapy to 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 since 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 the "N" should represent *N*on-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 for using 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, while 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.

Guidance statements for consensus around oral anticoagulation nomenclature and harm with 'NOAC'

1. We suggest that consensus be reached for a single term to be used when describing the direct oral IIa and Xa inhibitors.
2. We recommend that a single term be used consistently for all oral direct anticoagulants which have inherently different mechanisms and clinical properties than vitamin K antagonists.
3. We suggest that the abbreviation 'NOAC' *not* be used to describe any class of oral anticoagulant.

Evidence for use of 'DOAC'

Unlike VKAs, the direct oral anticoagulants target one specific factor (currently either factor Xa or factor IIa). Specifically, dabigatran inhibits thrombin (Factor IIa), while rivaroxaban, apixaban, edoxaban and betrixaban all inhibit Factor Xa. Using the term 'direct' adequately distinguishes this class of medications from the VKAs and allows each of these medications to be discussed based on their similar (but not exact) clinical profiles. In our survey, DOAC received the highest votes, 45 (58.4%) as an acceptable term for this class of medications. When asked to pick the single best term, however, no single choice dominated. 23 (29.9%) respondents selected 'DOAC' while 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 '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 described the mechanism of action, such as direct thrombin inhibitor and direct Factor Xa 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. They can be distinguished by their mechanism of action in the few situations where it is clinically relevant.

Guidance statement for 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, betrixaban).
2. We suggest that a drug's specific mechanism of action (e.g. direct Factor Xa inhibitor or direct thrombin inhibitor) 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: XXX.

References

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APPENDIX 1

Survey Questions:

1. Do you believe that there is a need to reach consensus on terminology for oral anticoagulants?
2. Do you believe that there is a need to reach consensus on terminology for oral anticoagulants? (Comments)
3. Do you feel that the term NOAC (novel/new oral anticoagulant OR non-vitamin K oral anticoagulant) has safety implications that should limit its use?
4. Do you feel that the term NOAC (novel/new oral anticoagulant OR non-vitamin K oral anticoagulant) has safety implications that should limit its use? (Comments)
5. Please select ALL terms that you consider ACCEPTABLE
    a. DOAC (direct oral anticoagulant)
    b. NOAC (non-VKA oral anticoagulant)
    c. NOAC (novel oral anticoagulant)
    d. ODI (oral direct inhibitors)
    e. SODA (specific oral direct anticoagulant)
    f. TSOAC (target specific oral anticoagulant)
    g. Other
    h. Comments
6. Which SINGLE term would you favor using?
    a. DOAC (direct oral anticoagulant)
    b. NOAC (non-VKA oral anticoagulant)
    c. NOAC (novel oral anticoagulant)
    d. ODI (oral direct inhibitors)
    e. SODA (specific oral direct anticoagulant)
    f. TSOAC (target specific oral anticoagulant)
    g. Other
    h. Comments

7. Would your organization be interested in endorsing a consensus guidance statement?
8. Your clinical training:
    a. Physician
    b. Nursing
    c. Pharmacist
    d. Physician Assistant or Nurse Practitioner
    e. Other
9. Your clinical training:
    a. General Internal Medicine/Hospital Medicine
    b. Hematology
    c. Cardiology
    d. Vascular Medicine/Angiology
    e. Vascular Surgery
    f. Laboratory Medicine/Pathology
    g. Other
10. Please give any additional comments or suggestions

Appendix 2 – Comment Responses

Question 2 – Do you believe that there is a need to reach consensus on terminology for oral anticoagulants?

- See below
- We cannot have 5 or 10 different abbreviations floating around
- absence of consensus will create unnecessary confusion in the literature
- simplicity and harmonization
- terminology should be on mode of action
- they won't be novel forever, and someday the class(es) will have new members

- It would be helpful when educating patients to have a common term that we can use to describe the anticoagulants now available. Patients are very well informed these days with the internet.
- Consensus on a nomenclature system would be helpful, particularly with additional agents with differing mechanism(s) potentially being developed.

Question 3 – Do you feel that the term NOAC (novel/new oral anticoagulant OR non-vitamin K oral anticoagulant) has safety implications that should limit its use?

- And as pointed out, these drugs are no longer novel or new.
- I am familiar with and agree with ISMP statement recommending against its use
- I don't understand why this is considered.
- Important to stress that this is not a term that should ever be used in ordering a drug!
- No safety implications; the problem is that they are no longer novel or new.
- Novel / new implies better value / better efficacy to both patients and non-expert practitioners.
- They are new/novel and to be honest there are gaps in knowledge re: safety...
- They are not novel/new anymore.
- could be interpreted as No AC (anticoagulant) in patient charting
- i don't think it's unsafe but it is imprecise.
- no more new AC
- ISTH should remind members not to use abbreviations in the medical record that may be unfamiliar to others, including whatever is agreed upon with this survey.
- This term has been called out by the Institute of Safe Medical Practices as an abbreviation that should not be used.
- Abbreviations should not be used in the medical record, especially ones that are used predominantly within one specialty. For example, PE to us means pulmonary embolus, but for many other clinicians, it means physical exam.

- AS YOU POINT OUT, ACRONYMS OF ANY TYPE CAN BE DANGEROUS WHEN USED IN CLINICAL PRACTICE. EACH DRUG IS DIFFERENT AND SHOULD USE THEIR NAMES!!!
- I strongly feel that the term NOAC is misleading for the reasons given in the introduction of this survey. An additional important aspect is that the "NOACs" consist of very different drugs which require different monitoring/testing. The new names should reflect this
- However, I believe that non-vitamin K oral anticoagulants is the appropriate term but a revised/more appropriate abbreviation such as non-VKA OAC should be suggested
- very soon they not going to be "new" and we may have a lot of other "non-vitamin K" options in the future

Question 4 – Please select ALL terms that you consider ACCEPTABLE

Other suggestions:

- DOAC-XA and DOAC-IIa or ODXa and ODTI
- FSOA (factor-specific oral anticoagulant)
- TSA
- TSA
- TSOA (target specific oral anticoagulant)
- Direct Xa or DTI, depending

Comments:

- ? NVKA
- Target Specific Anticoagulant is much easier than TSOAC
- all drugs have a target so TSOAC doesn't inform
- i think there are at least two classes here, DTIs and X inhibitors.
- If NOAC is rejected for being misinterpreted as No Anticoagulation, then note that DOAC could be misinterpreted as Do Anticoagulate. -ODI could be misinterpreted as "OD" (every other day, optical density, right eye, or overdose). Also the full term written out is not clear to some not in our

specialty because it doesn't say anticoagulant. -SODA could be misinterpreted as the beverage. -TSOAC too many numbers -So overall NOAC seems the best

- While DOAC and SODA carry explicit details needed (route, selectiveness, anticoagulant), their proximity to other terms in use (DOA, soda) preclude their use in clinical practice. ODI lacks mention of mechanism. NOAC has too many possible interpretations.
- Dropping the C in all the terms would make ~all of them consistent with the 3-letter abbreviation for VKA. This would also eliminate the confusion of NOAC with No AC. Acronyms are meant to be short. So if 3 letters work, there is no need to use 4 or 5 letters. Should avoid "inhibitor" because of confusion with other acquired factor inhibitors.
- as per above, the name should be specific for subgroups with totally different profiles. We also do not call antihypertensives just oral antihypertensives only because they are given as a pill.
- As suggested above, the non-vitamin K oral anticoagulants category is most appropriate based on the mechanism of action of these agents, however the abbreviation used should NOT be "NOAC" but it should a more appropriate term such as non- VKA OAC, etc
- These drugs are no longer novel, but the NOAC terminology is well established. I like the concept of changing the N to non- VKA
- DOAC could be misread as DO Anticoagulate ODI could be misread as every other day, optical density, overdose, or right eye SODA could be misread as the beverage TSOAC too many letters
- in fact to keep the same acronym profile "VKA" you can suggest "ODA" oral direct anticoagulant
- Why not use the term that actually describes the specific anticoagulant activity? I suggest using the terms "direct thrombin inhibitor" and "direct Xa inhibitor".

Question 5 – Which SINGLE term would you favor using?

Other responses:

- NOA
- None of the above
- OFTI (oral factor ten inhibitors)
- TSA
- XXXX
- Oral anti-Xa or oral anti-thrombin

Comments:

- Best describes the mechanism, route of anticoagulation
- DOAC is easier to pronounce than TSOAC, and sounds clear enough
- Flows off the tongue and well known
- I hate changing nomenclature.
- NOAC is already in the lexicon and is easy to remember; we should stick with it.
- TSOAC is "wordy" but specific and (I think) unique among acronyms.
- grouping together medications that have different targets (Xa vs Thrombin) does not make sense
- i don't prefer any of the others so i guess this wins.
- this acronym underline all the characteristics of these anticoagulants and it is "easy to remember" that it is only for oral route and so "common" to treat thrombosis. "eat SODA so do it!"
- Many are already familiar with NOAC and using NOA would cause the least amount of confusion in the switch. The N should stand for non-VKA.
- As suggested above, the non-vitamin K oral anticoagulants category is most appropriate based on the mechanism of action of these agents, however the abbreviation used should NOT be "NOAC" but it should a more appropriate term such as non-VKA OAC, etc
- This is the term I have used most often in writing, presenting and teaching. It has become comfortable and familiar.

- As per above, it does not make sense to use ONE term for different drugs with different mechanisms of action. What are we doing, if the next drug is e.g. an FIX inhibitor (hypothetically)?

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