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COMMENTS

Comment on: 2023 updated AGS Beers Criteria for potentially inappropriate medication use in older adults

To the Editor:

We read with great interest the recently updated Beers Criteria for potentially inappropriate medication use in older adults authored by the American Geriatric Society (AGS) Expert Panel.[1] Of particular interest were significant changes pertaining to rivaroxaban, wherein the topline recommendation was changed from "use with caution" to "avoid use" for long-term treatment of non-valvular atrial fibrillation (NVAF) and venous thromboembolism (VTE) "in favor of safer anticoagulant alternatives." The expert panel stated this change was based on evidence from observational studies and network metanalyses showing rivaroxaban conveys a higher incidence of major and gastrointestinal bleeding in older adults compared to other direct oral anticoagulants (DOACs). While we commend the authors and share their mission of promoting stewardship around use of high-risk, yet essential, anticoagulant agents in this vulnerable population, there are several points around these changes we feel warrant comment and enhanced emphasis.

First, it is not possible to make conclusive inferences regarding differences between the DOACs, as no head-to-head, randomized controlled trials (RCTs) have been completed. Methodological considerations including differences in study populations, trial design and outcome definitions in landmark RCTs of warfarin versus DOACs for NVAF and VTE preclude cross-trial comparisons.[2] For example, a post-hoc analysis of the EINSTEIN trials with rivaroxaban showed that 31% of enrolled patients would not have been eligible for enrollment in the apixaban AMPLIFY RCT.[3] Further, retrospective observational studies and network metanalyses are inherently vulnerable to bias and confounding (e.g., use of over-the-counter aspirin, incorrect ICD-10 coding, selection bias, etc.), regardless of sophisticated statistical approaches such as propensity score matching or inverse probability of treatment weighting.[4,5] Results from the ongoing *CO*mparison of *B*leeding *R*isk between *R*ivaroxaban and *A*pixaban (COBRRA) trial, a pragmatic, multicenter, prospective randomized controlled superiority trial which will provide an unbiased comparison of bleeding outcomes between apixaban and rivaroxaban in adult patients with acute venous thromboembolism (ClinicalTrial.gov identifier: NCT03266783), are eagerly awaited. Other randomized trials are also underway (e.g., NCT04642430, NCT03129555, NCT03129490). Until such data are available, the "strong" recommendation (which, by definition, implies harms, adverse events and risks *clearly* outweigh benefits) to "avoid" rivaroxaban instead of "use with caution" seems somewhat disproportionate and unsubstantiated.

Second, we appreciate that the Beers expert panel provides important qualifying remarks throughout the guideline pertaining to intent, limitations and interpretation of the criteria. However, we believe that enhanced emphasis is warranted to ensure the clinicians applying these guidelines in practice do not focus solely on the topline recommendations, but rather carefully consider the guidance in its totality. Table 1 lists key statements excerpted from the guidelines that we feel should be highlighted and will promote optimized use of anticoagulants, including rivaroxaban, in older patients.

The Beers experts provide the important example of need for a once-daily anticoagulant to promote adherence as a special circumstance wherein rivaroxaban may be considered. We would also offer other situations, such as an older patient who has been maintained on rivaroxaban without complications and prefers to stay on rivaroxaban, or an older patient who needs therapeutic anticoagulation but is unable to afford or access apixaban. Additionally, the updated recommendations should not be extrapolated

TABLE 1 Key guideline excerpts pertaining to interpretation and application of the Beers Criteria.

- Rivaroxaban may be a reasonable option in select circumstances.
- The criteria are a blunt instrument, and it is not possible to delineate all specialized use cases and possible exceptions to the criteria.
- Prescribing for older adults is often a complex endeavor involving consideration of many factors, particularly the preferences and goals of the older person and their family.
- Medications listed in the Beer's Criteria are *potentially* inappropriate, not definitely inappropriate.
- Use of a medication with a recommendation to "avoid" is not an absolute contraindication, but rather a situation that calls for shared decision-making between the patient and their provider, with considerations for patient preferences, financial situation and goals of care.

See the Reply by Semla and Steinman in this issue.

to prophylactic-intensity dosing or ultra-low dose rivaroxaban used for coronary and/or peripheral arterial disease, as the evidence used to inform the guideline pertains only to therapeutic-intensity dosing for VTE and NVAF. It is possible that inappropriate interpretation and application of the Beers criteria may precipitate unnecessary, unwanted, and risky switches in DOAC therapy or even relegation to warfarin.

Unfortunately, in the United States, access to various DOACs is often challenging for patients despite an equivalent or better efficacy and safety profile than warfarin, with significantly more convenience that culminates in the entire class of anticoagulants being recommended as first-line therapy in NVAF and VTE guidelines. Formulary restrictions or exorbitant out-of-pocket costs for the uninsured are key barriers. Indeed, the Beers experts "urge policy makers, insurers and organizations in the pharmaceutical supply chain to ensure that out-of-pocket costs and access restrictions are not a barrier to safe and effective anticoagulation for all of us as we age."

Thus, as anticoagulation stewards, we feel it is imperative for clinicians to consider all the tools in their toolbox, including rivaroxaban if appropriate, when prescribing anticoagulants for prevention or treatment of thromboembolic disease. We ask that clinicians and health-system policy makers consider the importance of patient-clinician decision-making and avoid limiting access to DOACs based only on top-line Beers recommendations. We also ask the Beers criteria authors to reconsider the potential impact of their recommendations which may limit patient-clinician choices.

AUTHOR CONTRIBUTIONS

Allison E. Burnett and Geoff Barnes conceived of the manuscript and served as co-lead authors. All other authors provided critical revisions.

CONFLICT OF INTEREST STATEMENT

Arthur L. Allen: AstraZeneca, Pfizer. **Jack Ansell**: Acelis Home Monitoring, Covis Pharmaceuticals, Perosphere Technology Inc, Vaica Inc. **Geoffrey D. Barnes**: Abbot Vascular, Boston Scientific, Bristol-Myers Squibb, Janssen, Pfizer. **Allison E. Burnett**: N/A. **Marilyn Blumenstein**: N/A. **Jean M. Connors**: Abbott Laboratories, Anthos Pharmaceuticals, Bristol-Myers Squibb, Pfizer, Sanofi S.A. **William E. Dager**: N/A. **Scott Kaatz**: AstraZeneca, Bristol-Myers Squibb, Boston Scientific, Gilead, Inari, Janssen, Pfizer, Phase Bio, Osmosis Research, NIH. **Jori E. May**: N/A. **Ronni Nemeth**: N/A. **Carlee O'Connor**: N/A. **Bishoy Ragheb**: N/A. **Anita Rajasekhar**: N/A. **Lauri Sardo**: N/A. **Deborah M. Siegal**: Astra Zeneca, BMS-Pfizer, Roche, Servier. **Andrea Van Beek**: N/A.

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Reply to: Comment on: 2023 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults

To the Editor:

We thank Dr. Burnett and colleagues[1] for their interest in the 2023 AGS Beer Criteria® and for their recognition of the efforts by its panel.

The AGS Beers Criteria® seek to identify safety concerns for frequently prescribed medications to identify those best avoided or used with caution by older adults in most circumstances. The criteria are intended to support shared decision-making about pharmacologic therapy with adults 65 years and older.[2]

As head-to-head, randomized controlled trials comparing alternative treatments of interest in older adults are often scarce, as are sub analyses comparing older and younger adults, the AGS Beers Criteria® is, in many instances, reliant on other forms of evidence where analysis by age is available. Post-marketing safety findings, including the comparative safety of alternative treatments for a given condition, are often identified from observational studies and from meta-analyses and network meta-analyses of both observational and clinical trial data. Thus, while head-to-head randomized trials are valuable where available, papers using these other methodologies also provide an important evidence foundation for the AGS Beers Criteria®. We, too, look forward to the findings of the COBRRA trial and any other comparative clinical trials that provide additional evidence on anticoagulant safety and efficacy in older adults. In the meantime, based on available data and consistent with the evidence and our methods, the AGS Beers Criteria® panel voted that the "Quality of the Evidence" for the recommendation on rivaroxaban is "Moderate," while the "Strength of the Recommendation" is "Strong."[2]

We are largely in agreement with Burnett, et al.'s second point. The 2023 AGS Beers Criteria® panel had lengthy discussions on anticoagulants and the ramifications of our decisions.

As acknowledged in the 2023 AGS Beers Criteria® there are specific circumstances when rivaroxaban may be a good choice for older adults and the criteria are meant to support individualized clinical decision-making that is focused on the risks and benefits for a specific person.[2] In general, we encourage clinicians, health systems, and

This letter comments on the letter by Burnett et al. in this issue.

*AGS Beers Criteria® panel Co Chairs.