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Rivaroxaban Versus Apixaban: A Comparison Without a Simple Solution

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Since the original Beers Criteria were developed in 1991 and subsequently expanded in 1997, the American Geriatric Society (AGS) Beers Criteria has become a very useful source of information to optimize patient safety and minimize patient harm in older adults (age older than 65 years).¹ Recently, the AGS published its 2023 updated AGS Beers Criteria for potentially inappropriate medication use in older adults.² This 2023 publication reviewed evidence published between 2017 and 2022 in order to update the previously published AGS 2019 Beers Criteria. The review we present below is focused solely on the recommendations within the 2019 and 2023 AGS publications pertaining to anticoagulation with the direct acting oral anticoagulants (DOACs).

We are concerned with the changes in the AGS recommendations for rivaroxaban, relative to apixaban, outlined in the 2023 publication.² As stated in the 2023 publication, “The recommendation for rivaroxaban has changed from ‘use with caution,’ to ‘avoid’ for long-term treatment of nonvalvular atrial fibrillation (NVAF) and venous thromboembolism (VTE), with the rationale being that observational studies and network meta-analyses find that this drug confers a higher risk of major and gastrointestinal (GI) bleeding in older adults than other DOACs, particularly apixaban but also dabigatran.”² The basis of this text is concerning to us as health care providers for older adults (age older than 65 years), who require oral anticoagulation.

Methods

We originally reviewed the original peer-reviewed, randomized controlled trials’ (RCTs) data collected from the rivaroxaban and apixaban registration trials,³⁻⁷ specifically

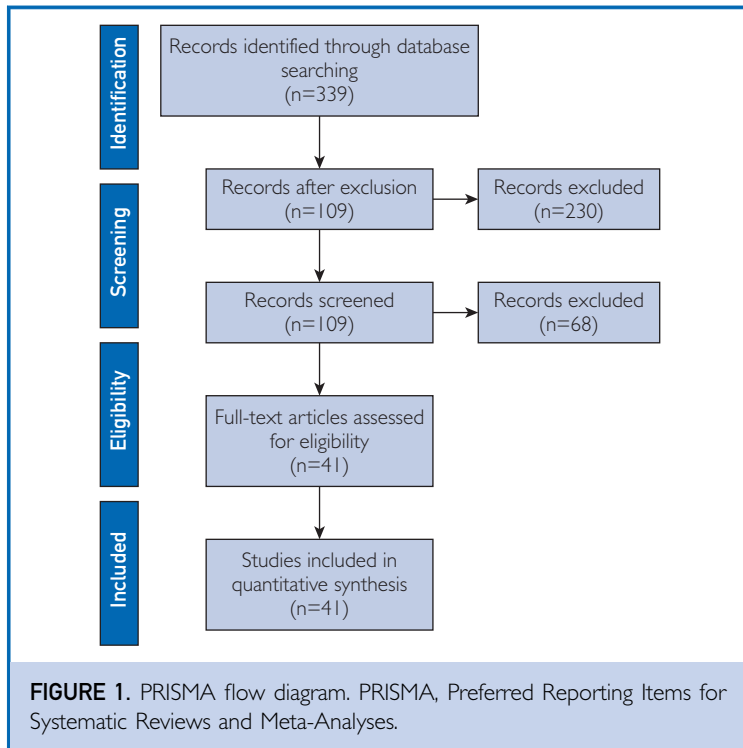
regarding the subgroup of older adults. The original Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF trial)^{3,4} analyses had already identified an increased rate of GI bleeding rate relative to warfarin, which is included in the US Food and Drug Administration (FDA) approved label. Subsequently, we conducted a literature search using the search term, *direct acting oral anticoagulants*, in PubMed from June 1, 2017, to May 31, 2023, and screened all full-text English studies comparing differences in outcomes within the class of direct acting oral anticoagulants. We included RCTs, cohort studies and meta-analysis. We excluded duplicated articles, review, case reports, case series, and studies that did not provide direct comparison of DOACs. Full texts of all eligible studies were retrieved. A total of 339 studies were initially identified of which 230 studies were excluded based on the exclusion criteria. On review of the remaining 109 studies, full texts were reviewed, and 41 studies were included for final review⁸⁻²⁴ (Figure 1). Not all studies reviewed are referenced further. No randomized studies were conducted comparing the direct oral anticoagulants with each other during this time frame. All studies were assessed for their quality of evidence using the American College of Physicians–based approach²⁵ and GRADE–based approach.²⁶ On the basis of either approach, all observational studies were of “low” quality, whereas all RCTs were of “high-quality” and with “low bias.”

Results

1. The AGS is making a specific therapeutic recommendation, regarding 2 very effective

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drugs that are US FDA approved for use in all adult age groups. The 2023 AGS Beers Criteria are relying on “observational studies and network meta-analyses.”²

Several elements regarding the data derived from the original, prospective, randomized DOAC trials, include, the median age of patients enrolled in ROCKET AF trial was 73 years.^{3,4} Twenty-five percentage of more than 14,000 randomized ROCKET AF trial patients were 78 years or older, and the follow-up was greater than 1.5 years. The median age of the 18,000 patients enrolled in Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE),⁷ the apixaban registration trial, was 70 years, and they were followed up for more than 1.5 years. The 2023 AGS recommendations are made in the absence of any direct, head-to-head rivaroxaban vs apixaban prospective, randomized trials in older adults incorporating blinded analysis of clinical outcomes. Therefore, there was no high-quality evidence²—for the change in AGS recommendation.

2. The AGS recommendation indicates to “avoid [rivaroxaban] for long-term treatment of nonvalvular atrial fibrillation and VTE.”

The original randomized ROCKET AF trial^{3,4} and ARISTOTLE⁷ trial had median follow-ups of 1.6 and 1.8 years, respectively. In many of the recent observational studies we reviewed,⁸⁻²⁴ many had follow-up durations of only 3 to 6 months. All major outcomes in ROCKET AF trial^{3,4} and ARISTOTLE⁷ vs vitamin K antagonists were adjudicated by committee members who were blinded to treatment allocation.

A major weakness of shorter-term follow-up of patients with NVAf and/or deep vein thrombosis (DVT)/pulmonary embolism treated with anticoagulant therapies is the potential difference in the event rates over time relating to individual end points. Major bleeding (MB) end points are often early, that is, “frontloaded,” and demonstrate some flattening/tapering over longer-term follow-up.²⁷ In contrast, the risk of stroke and/or systemic embolism (SSE) appears to be a relatively stable, constant function over time (Figure 2).²⁷ Therefore, short-term studies may have overrepresentation of MB rates and hazard ratios compared with thrombotic end points such as SSE or DVT/VTE.

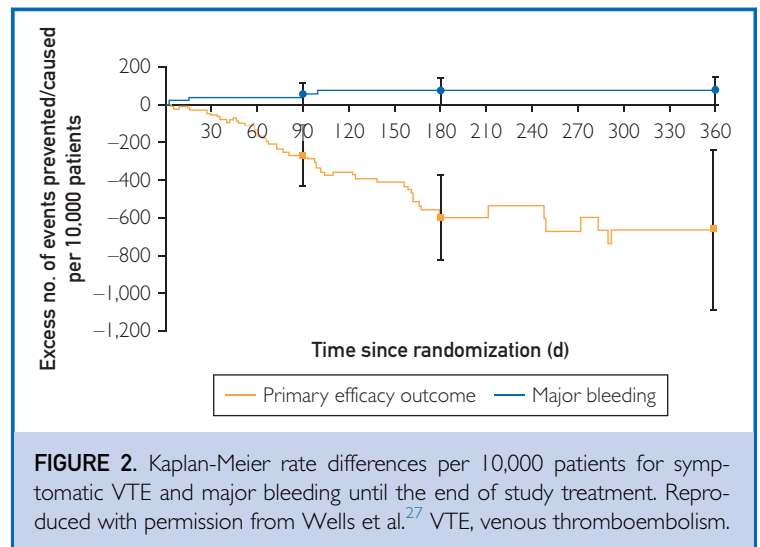
Among the observational trials that we reviewed, we identified 15 studies that had an average follow-up of less than 180 days. Eighteen studies had an average follow-up approaching 1 year. Only 8 studies had an average follow-up of more than 1 year. This broad range of follow-up among the observational studies has potential to introduce time bias on consistency of the measured end points.

Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients (ARISTOPHANES) Elderly study,¹⁸ a very large claims-based study (n=37,000) suggested a significant ($P<0.05$), favorable profile for apixaban vs rivaroxaban. This study was a subgroup analysis derived from the ARISTOPHANES study⁸ and focused only on NVAf patients aged 80 years or older. The patients were newly treated with a DOAC as per the pharmacy claims between 2013 and 2015.

Although the strength of this analysis was the large volume of patient data, the mean follow-up was substantially less than 1 year. Follow-up for the apixaban vs the rivaroxaban patients was only 210 and 248 days, respectively. Unfortunately, the median follow-up time among the matched cohorts was only 5 to 6 months. Using the metric of absolute rate difference per 100 patient-years (ARD/100 PY), this study¹⁸ suggested a significant ($P < 0.05$), favorable profile for apixaban vs rivaroxaban. Compared with apixaban, rivaroxaban had an excess SSE of 0.53/100 PY, an excess MB of ARD/100 PY of 4.24, and an excess GI bleed of ARD/100PY of 2.64.

Another real world, active-comparator, retrospective cohort study, was published by Fralick et al¹⁵ in 2020 focusing on patients with NVAf. This study used a nationwide commercial health care claims database from 2012 to 2019 in which 39,351 newly prescribed apixaban patients were propensity score matched with 39,351 patients with newly prescribed rivaroxaban. Their mean age was 69 years, and in contrast to ARISTOPHANES Elderly, the mean follow-up was 288 days for apixaban users and 291 days for rivaroxaban users. In addition, this study excluded patients using lower dosages of either medication (rivaroxaban < 20 mg daily or apixaban < 5 mg twice daily). All patients were followed up for up to 365 days, unless they reached the end of the study period, dis-enrolled, experienced a study outcome, or died. The authors noted the confounding patient behavior of treatment discontinuation and switching to the comparator medication. Rivaroxaban had an excess SSE compared with apixaban of only 0.14/100 PY, an excess MB of ARD/100 PY of 1.2, and an almost identical rate of intracranial hemorrhage (ICH) to apixaban. In contrast to ARISTOPHANES Elderly, this study suggested a much less dramatic, if any, difference of clinical outcomes favoring apixaban over rivaroxaban.

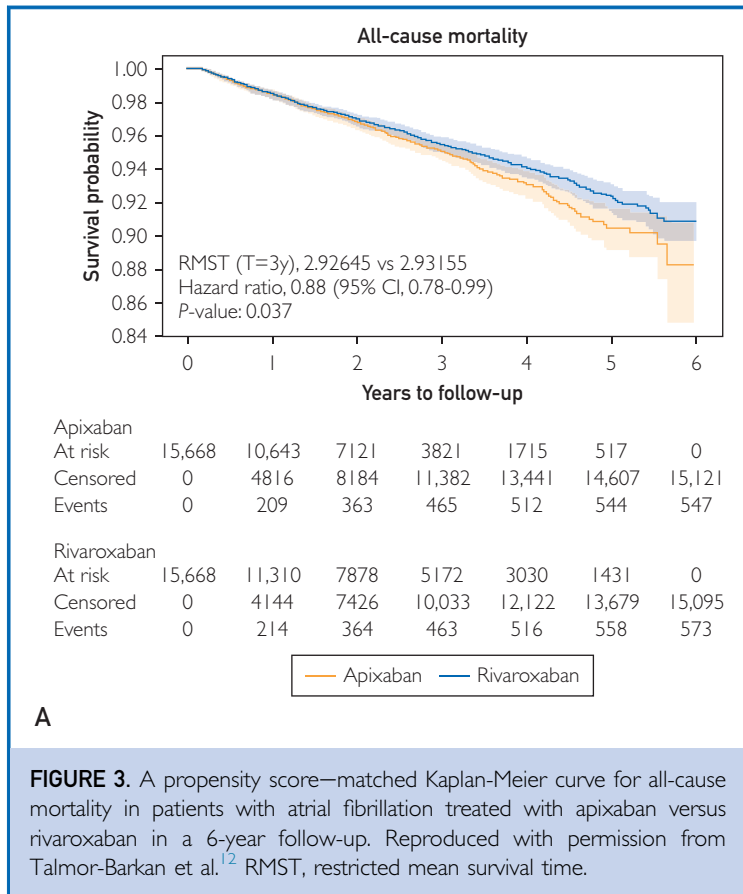
A large retrospective cohort study of patients with cancer-associated VTE and low risk of bleeding (OSCAR-US) compared 1093 patients on rivaroxaban and 1344 patients on apixaban with the outcome of developing recurrent VTE or any bleed resulting in hospitalization at 3 and 6 months.²⁸ The authors used inverse probability of treatment-



weighted Cox regression to calculate hazard ratios (HRs) and 95% CIs. Rivaroxaban was found to have similar hazard to apixaban for the composite outcome at 3 months (HR, 0.87; 95% CI, 0.60-1.27) and 6 months (HR, 1.00; 95% CI, 0.71-1.40) and for any other outcome at 3 or 6 months.²⁸

A recent meta-analysis of observational studies assessing 24,156 patients compared rivaroxaban with apixaban in the treatment of VTE using both fixed-effects and random effects modeling.²⁹ Although the authors found no differences in VTE recurrence with apixaban (RR, 0.77; 95% CI, 0.57-1.04), there was a significant reduction in MB favoring apixaban (RR, 0.68; 95% CI, 0.61-0.76). However, the studies had short durations of follow-up of only 3 to 6 months.²⁹

The study by Talmor-Barkan et al¹² published in 2022 derived data from patients with NVAf enrolled in the Israeli health care organization CLALIT, with follow-up started at first eligible DOAC prescription and ended at an outcome event including death, treatment discontinuation, disenrollment from the health care organization, end of follow-up (6 years after index event), or the end of the study (May 1, 2020), whichever occurred first. This analysis included 56,553 patients on different DOACs among which there were 35,101 on apixaban and 15,682 on rivaroxaban. In contrast to the ARISTOPHANES Elderly and the study by Fralick et al¹⁵,



mortality and ischemic stroke rates were lower with rivaroxaban vs apixaban (HR, 0.88 and 0.92, respectively; $P < 0.04$). No significant differences in the rates of myocardial infarction, SSE, and overall bleeding were noticed between the different DOACs groups. Using the metric of ARD/100 PY, this study suggested a more favorable profile for rivaroxaban vs apixaban. Compared with rivaroxaban, apixaban had an excess ischemic stroke rate of 0.7/100 PY, whereas rivaroxaban had an excess MB ARD/100 PY of 0.98, and a GI bleed ARD/100 PY of 0.16. The authors concluded, “We found significant differences in outcomes between the 3 studied DOACs. The results emphasize the need for RCTs that will compare rivaroxaban, apixaban, and dabigatran in order to better guide the selection among them.”¹² The 6-year follow-up allowed for generation of Kaplan-Meier survival curves of all-cause mortality (Figure 3),¹² suggesting

rivaroxaban had an equal or slightly better all-cause mortality rate than apixaban regardless of the increased GI bleed rate seen with rivaroxaban. In addition, Talmor-Barkan et al¹² identified that in the real world, greater than 24% of patients with NVAF treated with DOACs were using off-label doses, with most being underdosed. They summarized their results as follows: “The long follow-up data of 6 years may reveal differences in mortality risk in favor of rivaroxaban that were not found in previous studies in which the follow-up period was shorter. We found that the differences in mortality and ischemic stroke are age-related. A comparison between apixaban and rivaroxaban revealed decreased GI bleeding in the apixaban group and decreased ICH in the rivaroxaban group. We believe that the present study emphasizes the need for future RCTs that will compare apixaban, rivaroxaban and dabigatran in order to better guide the use of the different DOACs in clinical practice.”¹² As an example of how large a randomized trial is needed, in the setting of VTE to design a future RCT with a head-to-head comparison of 2 DOACs with 90% power and a 2-sided α of 0.05 would require approximately 45,000 patients, given low rates of both recurrent VTE and MB in the DOAC VTE registration trials.

3. The AGS’ 2023 therapeutic recommendation was based on, “with the rationale being that observational studies and network meta-analyses find that this drug [rivaroxaban] confers a higher risk of major and gastrointestinal bleeding in older adults...”

It is of concern that the basis of any therapeutic decision be dependent solely on a safety end point GI bleeding, without focusing on the balance between primary efficacy relative to the safety outcomes, that is, “net clinical benefit.” A perspective published by the US FDA entitled, “Weighing Benefits and Risks — The US FDA’s Review of Prasugrel”³⁰ highlighted the need for balance stating “the components of the primary end point represented irreversible tissue damage and concluded that the benefits of preventing such events is generally worth the risk of bleeding events that have no irreversible consequences.” In references to older adults, the

US FDA further stated, “However, older patients... particularly high risk patients... The US FDA made sure that prasugrel’s label clearly articulates the balance between efficacy and risk — a balance that physicians will need to assess carefully when choosing treatment for individual patients.”²⁸ Adverse effects need to be highlighted and their frequency minimized, but in the end, it is the balance that should dictate therapeutic decision making. Two published reports quantified benefit vs risk in NVAF²⁹ and long-term DVT/VTE prophylaxis.²⁷

Barnett et al³¹ analyzed the prospective, blinded, randomized ROCKET AF trial³ data and identified the rate differences for irreversible and reversible outcomes per 10,000 patient-years between rivaroxaban and warfarin. Regarding irreversible events (death, myocardial infarction, SSE, fatal, and/or critical organ bleeding), rivaroxaban had an advantage over warfarin with an ARD/100 PY of 1.3/100 PY.³¹ Regarding nonfatal or noncritical organ major bleeding, rivaroxaban had an excess in MB of 0.56 ARD/100 PY. The excess in MB identified in ROCKET AF trial is clearly identified in the package insert for Xarelto. In a post hoc net clinical benefit analysis from the ROCKET AF trial,³ dichotomized by age older vs younger than 75 years, Halperin et al⁴ focused on the irreversible events of all-cause mortality, life-threatening bleeding, and nonfatal nonhemorrhagic stroke. Analysis of the balance between irreversible events and nonfatal bleeding events suggested that rivaroxaban was more favorable than warfarin in older persons compared with those younger than 75 years.

By contrast, most observational studies published between 2017 and 2023 did not clearly delineate benefit vs risk analyses. A similar benefit-risk analysis was performed on the prospective, randomized EINSTEIN Extension trial patient data set²⁷ whose patients were followed up for a minimum of 1 year. They compared the absolute rate differences among the irreversible (primary efficacy outcome), as well as the nonfatal reversible end point of MB. Their analysis suggested that for patients with DVT/VTE, extending their prophylaxis with rivaroxaban vs placebo had a significantly favorable net clinical benefit. This rate difference was even more

significant in the older subgroup aged older than 75 years compared with younger patients. Another very important lesson emerged from their comparison of efficacy vs bleeding events that could only be appreciated as a consequence of their longer follow-up of at least 1 or more years (Figure 2). The figure shows that the time activity for MB was front-loaded in the first 3-4 months and subsequently was flat. By contrast, recurrent DVT/VTE appears to have an ongoing residual risk over time, at least over 6 months. Wells et al²⁷ concluded, “The reduction in recurrent VTE with rivaroxaban started early and continued to improve throughout the course of treatment. The increase in MB developed gradually and plateaued at approximately 100 days, suggesting that throughout the course of treatment, benefit would exceed risk.”

By contrast, a 2019 observational study by Dawwas et al⁹ analyzed the retrospective claims made data of over 36,000 patients with DVT/VTE comparing rivaroxaban with apixaban. Their ARD/100 PY for GI bleeding was 3.6, suggesting that apixaban was safer than rivaroxaban. However, their analysis reflected a median of only 102-105 days of follow-up. As stated earlier, short-term studies will be more likely to capture the early event of MB, but that only studies with longer-term follow-up will show a more valid benefit-risk analysis over time.

4. Quality of evidence: The 2023 AGS Beers Criteria are relying on “observational studies and network meta-analyses,” which the AGS elsewhere describes as “moderate-quality” or “low-quality.”²

Despite the lack of high-quality randomized trial data, AGS² states that its 2023 recommendations are of moderate-quality of evidence, with strength of recommendation being strong. According to the AGS, “Strength of recommendation ratings for each criterion are based on synthetic integration of the quality of evidence, the frequency and severity of potential adverse events and their relationship to potential benefits, and clinical judgment. **‘Strong’**; Harms, adverse events, and risks clearly outweigh the benefits. **‘Weak’**; Harms, adverse events, and risks may not outweigh

the benefits.”² The consensus that “risks clearly outweigh the benefits,” based on moderate or low-quality, retrospective, non-randomized studies, many of which had short duration, is in our opinion not supportable. Another point to consider is the fact that the relative/absolute differences between DOACs seen in the observational trial cited, often exceed those differences observed in the prospective blinded DOAC vs vitamin K antagonist randomized trials. This is counter-intuitive and suggests that the observational studies and network analyses, without any direct DOAC comparison arms, are confounded.

Conclusion

It is our belief, that the 2019 recommendation “use with caution” for rivaroxaban is supported by high-quality prospective randomized trials and post hoc analyses of randomized data.³⁻⁶ These trials with blinded clinical events committees found a clear-cut benefit regarding irreversible stroke and ICH but with a concomitant increase in nonfatal MB primarily accounted for by GI bleeding relative to vitamin K antagonists. However, the more recent 2023 AGS Beers Criteria recommendation,² “avoid for long-term use,” prompted us to review the many reports published between 2017 and 2023. It is our belief that the 2023 recommendation to avoid rivaroxaban in favor of apixaban for long-term use is not adequately substantiated by the non-randomized studies. Many of these studies have very short follow-up periods, and many do not clearly articulate the balance between efficacy and risk. Further, many of these studies cannot account for the confounding role of frequent prescribing of inappropriate reduced dosing of DOACs.³²

In contrast to the 2023 AGS recommendations, multiple other Society guidelines recommend the use of rivaroxaban for NVAF and/or VTE. They include but are not limited to the American Heart Association, American College of Cardiology, American Stroke Association, European Society of Cardiology, 2020 Canadian Cardiovascular Society, Heart Rhythm Society, American Academy of Family Physicians, American Academy of Neurology, American College of Chest Physicians, and the American Society of Hematology.

We are now in the age of large data and “population health.” We are also susceptible to the mindset of “this study will never be done; no one will sponsor it.” Our belief is that in the absence of high-quality randomized trials, it is important to appreciate the general trends observed in carefully analyzed observational studies. However, we cannot and should not default to observational studies to set therapeutic decisions. Rather, we should insist on testing any serious outcome conclusions seen in the observational studies by undertaking high-quality prospective, randomized trials before changing clinical practice. Multicenter collaboration led to the very successful Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries and Thrombolysis In Myocardial Infarction trials of multiples of 100,000 patients. Despite frustration that a study cannot be done or would not be supported, multiple prospective randomized studies were properly executed during the worse infectious pandemic of our time, coronavirus disease.^{33,34}

POTENTIAL COMPETING INTERESTS

Dr Cohen reports speakers bureau fees from Janssen Pharmaceuticals. Dr Spyropoulos reports grant/research payments from Janssen Pharmaceuticals, AstraZeneca and Boehringer Ingelheim, receives consulting fees from Janssen, AstraZeneca, Bristol Meyer Squibb, Sanofi, Bayer, and Pfizer. Dr Bonaca is the Executive Director of CPC, a non-profit academic research organization affiliated with the University of Colorado, that receives or has received research grant/consulting funding between February 2021 and present from Abbott Laboratories, Adamis Pharmaceuticals Corporation, Agios Pharmaceuticals, Inc., Alexion Pharma, Alnylam Pharmaceuticals, Inc., Amgen Inc., Angionetics, Inc., ARCA Biopharma, Inc., Array BioPharma, Inc., AstraZeneca and Affiliates, Atentiv LLC, Audentes Therapeutics, Inc., Bayer and Affiliates, Beth Israel Deaconess Medical Center, Better Therapeutics, Inc., BIDMC, Boston Clinical Research Institute, Bristol-Meyers Squibb Company, Cambrian Biopharma, Inc., Cardiol Therapeutics Inc., CellResearch Corp., Cook Medical Abbott Laboratories, Adamis Pharmaceuticals Corporation, Agios

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Abbreviations and Acronyms: **ARISTOPHANES.** Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients; **ARISTOTLE.** Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; **AGS.** American Geriatric Society; **ARD.** absolute rate difference; **DOAC.** direct acting oral anticoagulants; **DVT.** deep vein thrombosis; **FDA.** Food and Drug Administration; **GI.** gastrointestinal; **MB.** major bleeding; **NVAF.** nonvalvular atrial fibrillation; **PY.** patient-years; **RCT.** randomized controlled trial; **ROCKET AF trial.** Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; **SSE.** systemic embolism; **VTE.** venous thromboembolism

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REFERENCES

1. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2019;67(4):674-694. <https://doi.org/10.1111/jgs.15767>.
2. By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2023;71(7):2052-2081. <https://doi.org/10.1111/jgs.18372>.
3. Patel MR, Mahaffey KW, Garg J, et al. rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883-891. <https://doi.org/10.1056/NEJMoa1009638>.
4. Halperin JL, Hankey GJ, Wojdyla DM, et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the rivaroxaban once daily, oral, direct factor xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Circulation.* 2014;130(2):138-146. <https://doi.org/10.1161/CIRCULATIONAHA.113.005008>.
5. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, et al. Oral Rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010;363(26):2499-2510. <https://doi.org/10.1056/NEJMoa1007903>.
6. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med.* 2017;376(13):1211-1222. <https://doi.org/10.1056/NEJMoa1700518>.
7. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-992. <https://doi.org/10.1056/NEJMoa1107039>.
8. Lee S-R, Choi E-K, Kwon S, et al. Effectiveness and safety of contemporary oral anticoagulants among asians with nonvalvular atrial fibrillation. *Stroke.* 2019;50(8):2245-2249. <https://doi.org/10.1161/STROKEAHA.119.025536>.

9. Dawwas GK, Brown J, Dietrich E, Park H. Effectiveness and safety of apixaban versus rivaroxaban for prevention of recurrent venous thromboembolism and adverse bleeding events in patients with venous thromboembolism: a retrospective population-based cohort analysis. *Lancet Haematol*. 2019;6(1):e20-e28. [https://doi.org/10.1016/S2352-3026\(18\)30191-1](https://doi.org/10.1016/S2352-3026(18)30191-1).
10. Lau WCY, Torre CO, Man KKC, et al. Comparative effectiveness and safety between apixaban, dabigatran, edoxaban, and rivaroxaban among patients with atrial fibrillation: a multinational population-based cohort study. *Ann Intern Med*. 2022;175(11):1515-1524. <https://doi.org/10.7326/M22-0511>.
11. Jaksa A, Gibbs L, Kent S, et al. Using primary care data to assess comparative effectiveness and safety of apixaban and rivaroxaban in patients with nonvalvular atrial fibrillation in the UK: an observational cohort study. *BMJ Open*. 2022;12(10):e064662. <https://doi.org/10.1136/bmjopen-2022-064662>.
12. Talmor-Barkan Y, Yacovzada N-S, Rossman H, et al. Head-to-head efficacy and safety of rivaroxaban, apixaban, and dabigatran in an observational nationwide targeted trial. *Eur Heart J Cardiovasc Pharmacother*. 2022;9(1):26-37. <https://doi.org/10.1093/ehjcvp/pvac063>.
13. Ingason AB, Hreinsson JP, Ágústsson AS, et al. Rivaroxaban is associated with higher rates of gastrointestinal bleeding than other direct oral anticoagulants: a nationwide propensity score-weighted study. *Ann Intern Med*. 2021;174(11):1493-1502. <https://doi.org/10.7326/M21-1474>.
14. Grymonprez M, De Backer TL, Bertels X, Steurbaut S, Lahousse L. Long-term comparative effectiveness and safety of dabigatran, rivaroxaban, apixaban and edoxaban in patients with atrial fibrillation: a nationwide cohort study. *Front Pharmacol*. 2023;14:1125576.
15. Fralick M, Colacci M, Schneeweiss S, Huybrechts KF, Lin KJ, Gagne JJ. Effectiveness and safety of apixaban compared with rivaroxaban for patients with atrial fibrillation in routine practice: a cohort study. *Ann Intern Med*. 2020;172(7):463-473. <https://doi.org/10.7326/M19-2522>.
16. Durand M, Schnitzer ME, Pang M, et al. Effectiveness and safety among direct oral anticoagulants in nonvalvular atrial fibrillation: a multi-database cohort study with meta-analysis. *Br J Clin Pharmacol*. 2021;87(6):2589-2601. <https://doi.org/10.1111/bcp.14669>.
17. Dhamane AD, Ferri M, Keshishian A, et al. Effectiveness and safety of direct oral anticoagulants among patients with non-valvular atrial fibrillation and multimorbidity. *Adv Ther*. 2023;40(3):887-902. <https://doi.org/10.1007/s12325-022-02387-9>.
18. Deitelzweig S, Keshishian A, Li X, et al. Comparisons between oral anticoagulants among older nonvalvular atrial fibrillation patients. *J Am Geriatr Soc*. 2019;67(8):1662-1671. <https://doi.org/10.1111/jgs.15956>.
19. Deitelzweig S, Keshishian A, Kang A, et al. Delaying clinical events among patients with non-valvular atrial fibrillation treated with oral anticoagulants: insights from the Aristophanes study. *Eur J Intern Med*. 2023;108:37-42. <https://doi.org/10.1016/j.ijim.2022.10.021>.
20. Amin A, Keshishian A, Trocio J, et al. A Real-World observational study of hospitalization and health care costs among nonvalvular atrial fibrillation patients prescribed oral anticoagulants in the U.S. Medicare population. *J Manag Care Spec Pharm*. 2020;26(5):639-651. <https://doi.org/10.18553/jmcp.2020.26.5.639>.
21. Abraham NS, Noseworthy PA, Yao X, Sangaralingham LR, Shah ND. Gastrointestinal safety of direct oral anticoagulants: a large population-based study. *Gastroenterology*. 2017;152(5):1014-1022.e1. <https://doi.org/10.1053/j.gastro.2016.12.018>.
22. Ray WA, Chung CP, Stein CM, et al. Association of rivaroxaban vs apixaban with major ischemic or hemorrhagic events in patients with atrial fibrillation. *JAMA*. 2021;326(23):2395-2404. <https://doi.org/10.1001/jama.2021.21222>.
23. Lip GYH, Keshishian AV, Kang AL, et al. Oral anticoagulants for nonvalvular atrial fibrillation in frail elderly patients: insights from the Aristophanes study. *J Intern Med*. 2021;289(1):42-52. <https://doi.org/10.1111/joim.13140>.
24. Yao X, Inselman JW, Ross JS, et al. Comparative effectiveness and safety of oral anticoagulants across kidney function in patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2020;13(10):e006515. <https://doi.org/10.1161/CIRCOUTCOMES.120.006515>.
25. Qaseem A, Snow V, Owens DK, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. *Ann Intern Med*. 2010;153(3):194-199. <https://doi.org/10.7326/0003-4819-153-3-201008030-00010>.
26. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401-406. <https://doi.org/10.1016/j.jclinepi.2010.07.015>.
27. Wells PS, Prins MH, Levitan B, et al. Long-term anticoagulation with rivaroxaban for preventing recurrent VTE: a benefit-risk analysis of EINSTEIN-Extension. *Chest*. 2016;150(5):1059-1068.
28. Caroti KS, Becattini C, Carrier M, et al. Rivaroxaban versus apixaban for treatment of cancer-associated venous thromboembolism in patients at lower risk of bleeding. *TH Open*. 2023;7(3):e206-e216. <https://doi.org/10.1055/s-0043-1770783>.
29. Fredman D, McNeil R, Eldar O, Leader A, Gafter-Gvili A, Avni T. Efficacy and safety of rivaroxaban versus apixaban for venous thromboembolism: a systematic review and meta-analysis of observational studies. *J Thromb Thrombolysis*. 2024;57(3):453-465. <https://doi.org/10.1007/s11239-023-02926-3>.
30. Unger EF. Weighing benefits and risks—the FDA's review of prasugrel. *N Engl J Med*. 2009;361(10):942-945. <https://doi.org/10.1056/NEJMp0907122>.
31. Barnett AS, Cyr DD, Goodman SG, et al. Net clinical benefit of rivaroxaban compared with warfarin in atrial fibrillation: results from ROCKET AF. *Int J Cardiol*. 2018;257:78-83. <https://doi.org/10.1016/j.ijcard.2017.06.110>.
32. Bikdeli B, Zahedi Tajrishi FZ, Sadeghipour P, et al. Efficacy and safety considerations with dose-reduced direct oral anticoagulants: a review. *JAMA Cardiol*. 2022;7(7):747-759. <https://doi.org/10.1001/jamacardio.2022.1292>.
33. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. *JAMA Intern Med*. 2021;181(12):1612-1620. <https://doi.org/10.1001/jamainternmed.2021.6203>.
34. REMAP-CAP Investigators, ACTIV-4a Investigators, ATTACC Investigators, et al. Therapeutic anticoagulation with heparin in critically ill patients with covid-19. *N Engl J Med*. 2021;385(9):777-789. <https://doi.org/10.1056/NEJMoa2103417>.