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Review Paper

Major Bleeding Events Associated with Rivaroxaban Use in Patients Aged 75 Years and Older with Nonvalvular Atrial Fibrillation: A Review of the Literature

Diana Alzate Lopez^{*1}, Juan Hoyos Gomez², Daniela Olivera Barros³, Angela martinez Cortina⁴, Julian Amaya Perez⁵, Luis Tapia Contreras⁶, Luis Martinez Miranda⁷

¹General Physician, Universidad del Sinú, Cartagena

²General Physician, Universidad de Cartagena

^{3,7}General Physician, Corporación Universitaria Rafael Nuñez, Cartagena

⁴General Physician, Universidad del Sucre, Sincelejo

^{5,6}Resident Physician in Internal Medicine, Universidad del Norte, Barranquilla.

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ABSTRACT

Atrial fibrillation (AF) is highly prevalent among older adults and is associated with a substantial risk of thromboembolic events, making oral anticoagulation a fundamental component of stroke prevention. Rivaroxaban, a direct oral factor Xa inhibitor, is widely used in patients with nonvalvular atrial fibrillation (NVAf); however, advanced age is associated with an increased susceptibility to bleeding due to age related changes in renal function, vascular integrity, comorbidity burden, polypharmacy, and the frequent coexistence of antiplatelet therapy. Patients aged 75 years and older therefore represent a clinically relevant population in which the balance between thromboembolic protection and bleeding risk requires particular consideration. This review aims to analyze the available evidence regarding major bleeding events associated with rivaroxaban use in patients aged 75 years and older with NVAf, with particular emphasis on the incidence, clinical characteristics, and determinants of major bleeding, including gastrointestinal and intracranial hemorrhage. Evidence from randomized clinical trials, observational studies, real world cohorts, and systematic reviews indicates that older patients receiving rivaroxaban have a higher absolute risk of major bleeding than younger patients, although randomized trial data suggest that the relative bleeding risk compared with warfarin is not substantially modified by age. Real world evidence, however, suggests that very elderly patients may experience higher rates of major and

***Corresponding Author:** Diana Alzate Lopez

Address: General Physician, Universidad del Sinú, Cartagena.

Email ✉: juancho251997@hotmail.com

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gastrointestinal bleeding, particularly in the presence of renal impairment, hypertension, hepatic dysfunction, previous bleeding, low body weight, or concomitant antiplatelet therapy. These findings highlight the importance of individualized anticoagulant selection, appropriate dose adjustment according to renal function, systematic assessment of modifiable bleeding risk factors, and careful monitoring in older adults. Rivaroxaban remains an effective anticoagulant for stroke prevention in elderly patients with NVAf, but its use in individuals aged 75 years and older requires a careful assessment of the individual benefit-risk profile, particularly among the very elderly and those with multiple bleeding risk factors.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and its prevalence increases substantially with advancing age. Older adults with AF have a particularly high risk of ischemic stroke and systemic thromboembolism, making oral anticoagulation a fundamental component of stroke prevention. Direct oral anticoagulants (DOACs), including rivaroxaban, have become widely used alternatives to vitamin K antagonists because of their predictable pharmacokinetic profile, rapid onset of action, and reduced need for routine coagulation monitoring. However, advanced age is also associated with a greater susceptibility to anticoagulant-related bleeding due to the frequent coexistence of renal impairment, hypertension, anemia, frailty, polypharmacy, and other comorbid conditions. [1,3]

Rivaroxaban is a direct oral factor Xa inhibitor indicated for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAf). In the ROCKET-AF trial, rivaroxaban maintained its efficacy for prevention of stroke and systemic embolism in patients aged 75 years and older, although the absolute incidence of major bleeding was higher in this age group than in younger patients. Importantly, the relative effect of rivaroxaban compared with warfarin on major bleeding did not demonstrate a significant

interaction with age, suggesting that advanced age increases the baseline bleeding risk but does not necessarily eliminate the relative safety advantage of rivaroxaban compared with vitamin K antagonist therapy. [4]

Nevertheless, evidence from observational studies and real-world populations has highlighted the importance of gastrointestinal and other extracranial bleeding in elderly patients receiving rivaroxaban. The risk of bleeding may be further increased by impaired renal function, low body weight, previous bleeding, concomitant antiplatelet therapy, and other factors that are particularly prevalent among patients aged 75 years and older. [5,6] Consequently, the assessment of bleeding risk in this population cannot be based on chronological age alone but should incorporate the patient's overall clinical profile and potentially modifiable risk factors.

The clinical relevance of this issue has increased with the progressive aging of the population and the growing use of DOACs for stroke prevention in AF. Determining the incidence and characteristics of major bleeding associated with rivaroxaban in older adults is essential for appropriately balancing the prevention of thromboembolic events against the potential harms of anticoagulation. Therefore, this review evaluates the available evidence regarding major hemorrhagic events associated with rivaroxaban in patients aged 75 years and older with NVAf, with particular emphasis on the incidence and characteristics of major bleeding, gastrointestinal and intracranial hemorrhage, age related risk factors, renal function, and evidence derived from randomized clinical trials and real world studies. [1,4,6]

METHODOLOGY

This literature review was conducted to identify and synthesize the available evidence regarding major bleeding events associated with rivaroxaban



use in patients aged 75 years and older with nonvalvular atrial fibrillation. A structured search of the scientific literature was performed in PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library. The search strategy combined controlled vocabulary and free text terms related to the study population, intervention, and outcomes, including “atrial fibrillation,” “nonvalvular atrial fibrillation,” “rivaroxaban,” “elderly,” “older adults,” “major bleeding,” “hemorrhage,” “gastrointestinal bleeding,” and “intracranial hemorrhage,” using Boolean operators AND and OR. The search included publications available from database inception through October 2026, with particular emphasis on contemporary evidence and studies specifically reporting outcomes in patients aged 75 years and older.

Eligible studies included randomized controlled trials, prospective and retrospective observational studies, cohort studies, systematic reviews, and meta-analyses evaluating rivaroxaban in adults with NVAf and reporting major bleeding outcomes in patients aged 75 years or older. Studies were considered relevant when they provided information on the incidence, relative risk, predictors, or clinical characteristics of major hemorrhagic events, including gastrointestinal and intracranial bleeding. Studies involving mixed populations were considered when age-specific results for patients aged 75 years and older were available. Publications not addressing NVAf, studies evaluating rivaroxaban exclusively for indications other than AF, case reports, editorials, narrative commentaries without original or synthesized evidence, and studies without clinically relevant bleeding outcomes were excluded.

The information extracted from eligible studies included study design, sample size, patient age, anticoagulation regimen, rivaroxaban dose, duration of follow-up, comparator treatment when

applicable, definition and incidence of major bleeding, bleeding location, mortality associated with hemorrhagic events, and relevant risk factors. Particular attention was given to renal function, concomitant antiplatelet therapy, previous bleeding, low body weight, hypertension, and other characteristics potentially associated with increased hemorrhagic risk in older adults. Given the heterogeneity of the available literature, findings were synthesized qualitatively, emphasizing consistency and differences between randomized clinical trials and real world observational evidence.

DEVELOPMENT

Rivaroxaban is a direct oral factor Xa inhibitor that has become an established option for stroke and systemic embolism prevention in patients with nonvalvular atrial fibrillation (NVAf). Its use in older adults is particularly relevant because advancing age simultaneously increases the risk of thromboembolic events and the probability of anticoagulant associated bleeding. In the prespecified elderly analysis of the ROCKET-AF trial, 6,229 participants were aged 75 years or older, representing approximately 44% of the study population. Compared with younger participants, elderly patients had higher absolute rates of both stroke or systemic embolism and major bleeding. Major bleeding occurred at a rate of 4.63 events per 100 patient-years among patients aged 75 years or older compared with 2.74 events per 100 patient-years in younger patients. However, when rivaroxaban was directly compared with warfarin, the relative treatment effect was not significantly modified by age. Among patients aged 75 years or older, major bleeding occurred at 4.86 versus 4.40 events per 100 patient-years with rivaroxaban and warfarin, respectively, corresponding to a hazard ratio of 1.11 (95% CI, 0.92-1.34). These findings indicate that advanced age substantially increases the



baseline hemorrhagic risk, but does not by itself demonstrate that rivaroxaban has a disproportionately greater relative bleeding effect than warfarin in this population. [7,8]

The relationship between age and bleeding is clinically complex because older patients frequently accumulate several independent risk factors. Renal function is particularly important because rivaroxaban undergoes partial renal elimination and impaired renal clearance can increase systemic exposure. In the ROCKET-AF population, major bleeding was associated with several baseline characteristics, including older age, reduced renal function, anemia, previous gastrointestinal bleeding, and other comorbid conditions. These factors frequently coexist in patients aged 75 years and older, meaning that chronological age should not be considered an isolated determinant of bleeding risk. Instead, the overall clinical phenotype, including renal function, body weight, concomitant medication use, previous bleeding, and the presence of comorbid disease, should guide the assessment of anticoagulation safety. [8,9]

Gastrointestinal bleeding deserves particular attention in patients receiving rivaroxaban. An analysis of gastrointestinal bleeding from ROCKET-AF found that patients who experienced gastrointestinal bleeding were older than those without such events and more frequently had renal insufficiency, diabetes, hypertension, previous gastrointestinal bleeding, and concomitant aspirin or nonsteroidal anti-inflammatory drug exposure. Gastrointestinal bleeding occurred in the upper gastrointestinal tract, lower gastrointestinal tract, and rectum, demonstrating that the complication is not restricted to a single anatomical site. Importantly, the rate of major or non-major clinically relevant gastrointestinal bleeding was higher with rivaroxaban than with warfarin, at 3.61 versus 2.60 events per 100 patient-years, respectively (HR 1.42; 95% CI, 1.22-1.66).

Although these findings were derived from the overall ROCKET-AF population rather than exclusively from patients aged 75 years or older, they are particularly relevant when interpreting bleeding risk in the elderly, in whom gastrointestinal pathology and comorbidity are more prevalent. [10]

Intracranial hemorrhage represents a different aspect of the safety profile. Although the absolute risk of intracranial bleeding increases with age, randomized evidence has generally demonstrated a lower risk of intracranial hemorrhage with direct oral anticoagulants than with vitamin K antagonists. In ROCKET-AF, among patients aged 75 years or older, intracranial hemorrhage occurred in 0.66% of those receiving rivaroxaban compared with 0.83% of those receiving warfarin, although the difference did not reach statistical significance in this subgroup. The absence of a statistically significant difference should not be interpreted as evidence of equivalence, because subgroup analyses may lack sufficient statistical power. More broadly, contemporary AF guidelines recognize the lower risk of intracranial hemorrhage associated with DOACs as one of their major advantages over vitamin K antagonists. [7,11]

Evidence from real-world populations provides additional information because elderly patients encountered in routine practice may be older, frailer, and have a greater burden of comorbid disease than participants enrolled in randomized trials. In a real world Japanese cohort of patients receiving rivaroxaban for NVAf, individuals aged 75 years or older had a significantly higher rate of major bleeding than those younger than 75 years, with 2.22 versus 1.35 events per 100 patient-years, respectively (HR 1.63; 95% CI, 1.17-2.28). Among elderly patients, creatinine clearance below 50 mL/min, hepatic impairment, and hypertension were identified as specific predictors of major bleeding. Interestingly, intracranial



hemorrhage remained relatively uncommon, occurring at less than one event per 100 patient-years in both age groups. These findings reinforce the concept that the increased hemorrhagic burden observed in older patients is not explained by age alone but reflects the accumulation of physiological and clinical factors associated with aging. [12]

More recent evidence has strengthened concerns regarding bleeding in elderly patients treated with rivaroxaban. A 2024 systematic review and meta-analysis of randomized trials comparing bleeding outcomes in older and younger patients receiving the same rivaroxaban dose found a higher overall incidence of bleeding in older patients. The authors specifically identified atrial fibrillation, together with venous thromboembolic indications, as populations in which bleeding events were particularly relevant among older adults. Importantly, the study emphasized that age-related differences in bleeding cannot automatically be interpreted as evidence that every elderly patient should receive a reduced dose. Rather, these findings support individualized evaluation of factors that alter rivaroxaban exposure and bleeding susceptibility. [13]

Dose selection is therefore a central component of bleeding prevention in elderly patients. Current European guidance does not recommend reducing the rivaroxaban dose solely because a patient is 75 years old or older. For NVAf, the standard dose is 20 mg once daily, while a reduction to 15 mg once daily is recommended in patients with creatinine clearance between 15 and 49 mL/min. This distinction is clinically important because inappropriate underdosing may reduce thromboembolic protection without necessarily eliminating bleeding risk. Consequently, advanced age should prompt a careful assessment of renal function and other clinical variables rather than automatic dose reduction. [11,14]

The relationship between rivaroxaban and bleeding risk becomes particularly relevant when comparing individual DOACs in elderly patients. Although the DOAC class as a whole is associated with a substantially lower risk of intracranial hemorrhage than warfarin, differences between individual agents have been reported for gastrointestinal bleeding. Evidence summarized in contemporary reviews of AF in patients aged 75 years and older suggests that rivaroxaban may be associated with a less favorable gastrointestinal bleeding profile than some other DOACs, particularly apixaban. This does not imply that rivaroxaban is contraindicated in elderly patients, but it does emphasize the importance of considering the predominant bleeding phenotype and the patient's gastrointestinal risk when selecting an anticoagulant. [15]

A contemporary network meta-analysis published in 2025 further evaluated anticoagulant efficacy and safety specifically in patients aged 75 years and older with AF. The analysis included 14 randomized controlled trials and more than 16,000 participants, providing additional evidence that the balance between thromboembolic protection and bleeding varies among anticoagulant strategies in this age group. Although network meta-analysis results should be interpreted cautiously because the included trials differ in populations, dosing strategies, comparators, and outcome definitions, the study reinforces the importance of evaluating anticoagulant safety specifically in elderly populations rather than extrapolating results exclusively from younger patients. [16]

Overall, the available evidence indicates that patients aged 75 years and older have a higher absolute risk of major bleeding while receiving rivaroxaban than younger patients, but this observation must be distinguished from the relative safety of rivaroxaban compared with alternative anticoagulants. The ROCKET-AF trial demonstrated that the relative risk of major



bleeding compared with warfarin was not significantly modified by age, whereas observational studies demonstrate that bleeding rates increase substantially in older patients in routine clinical practice. The apparent difference between these findings is not necessarily contradictory: randomized trials primarily address comparative treatment effects under controlled conditions, whereas real-world studies capture the cumulative effects of frailty, renal impairment, polypharmacy, comorbid disease, and other characteristics that may be underrepresented in clinical trials. [7,9,12]

From a clinical perspective, major bleeding risk in an elderly patient receiving rivaroxaban should therefore be understood as a multidimensional phenomenon. Age is an important marker of risk, but renal function, previous bleeding, hypertension, anemia, gastrointestinal disease, hepatic dysfunction, concomitant antiplatelet or nonsteroidal anti inflammatory drug therapy, and inappropriate dosing may have substantial additional influence. Current AF guidelines continue to support DOACs as preferred alternatives to vitamin K antagonists in eligible patients, while emphasizing appropriate dose selection and management of modifiable bleeding risk factors. [11,14] The objective should not be to avoid anticoagulation solely because of advanced age, since elderly patients also have a high risk of disabling or fatal thromboembolic events. Instead, anticoagulant therapy should be individualized according to the patient's thromboembolic risk, bleeding risk, renal function, comorbidities, concomitant medications, and overall clinical context. [11,14,16]

In summary, current evidence supports the use of rivaroxaban as an effective anticoagulant in appropriately selected elderly patients with NVAf, but confirms that individuals aged 75 years and older constitute a population with a substantially higher absolute risk of major

hemorrhage. The strongest and most consistent signal appears to concern extracranial, particularly gastrointestinal, bleeding, whereas intracranial hemorrhage remains less frequent and is generally lower with DOAC therapy than with warfarin. The clinical relevance of these findings lies not in avoiding rivaroxaban solely on the basis of age, but in identifying patients in whom the hemorrhagic risk can be reduced through appropriate renal assessment, correct dose selection, avoidance of unnecessary antiplatelet or nonsteroidal anti inflammatory therapy, and periodic reassessment of the benefit-risk balance. This individualized approach is particularly important as the population receiving anticoagulation becomes progressively older and more clinically complex. [10,16]

DEVELOPMENT

Rivaroxaban is a direct oral factor Xa inhibitor that has become an established option for stroke and systemic embolism prevention in patients with nonvalvular atrial fibrillation (NVAf). Its use in older adults is particularly relevant because advancing age simultaneously increases the risk of thromboembolic events and the probability of anticoagulant-associated bleeding. In the prespecified elderly analysis of the ROCKET-AF trial, 6,229 participants were aged 75 years or older, representing approximately 44% of the study population. Compared with younger participants, elderly patients had higher absolute rates of both stroke or systemic embolism and major bleeding. Major bleeding occurred at a rate of 4.63 events per 100 patient-years among patients aged 75 years or older compared with 2.74 events per 100 patient-years in younger patients. However, when rivaroxaban was directly compared with warfarin, the relative treatment effect was not significantly modified by age. Among patients aged 75 years or older, major bleeding occurred at 4.86 versus 4.40 events per



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