Invited Editorial Focus

# Direct Oral Anticoagulants in the Very Elderly

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One of the most important advantages of direct oral anticoagulants (DOACs) over warfarin is that DOACs can be given in fixed doses without routine coagulation monitoring, which simplifies patient management, leading to their recommendation in many guidelines globally.[1,2] Apixaban and rivaroxaban, which inhibit factor Xa, are the DOACs that are used most often, and real-world data comparing these agents have been published.[3] Guidelines recommend reduced doses of DOACs in a subset of patients with risk factors for drug accumulation, including older age, lower body weight, impaired renal function, or concomitant use of interacting drugs.[4]

Age is an important driver of stroke risk in patients with atrial fibrillation (AF).[5] Very elderly patients have the highest prevalence of comorbid conditions that predispose them to drug accumulation and are also amongst those at the highest risk of bleeding complications.[6] Consequently, clinicians are often reluctant to prescribe anticoagulants or to use the recommended doses of DOACs in the very elderly. Community-based registries consistently demonstrate that up to one-half of very elderly patients with AF who have guideline indications for oral anticoagulation remain untreated,[7,8] and many of those treated with a DOAC receive lower than recommended doses.[9–11] Also, such elderly AF patients represent a clinically complex phenotype, which is associated with a higher risk of stroke and bleeding, as well as a greater risk of anticoagulant discontinuation.[12]

In this issue of the journal, Foulon-Pinto and colleagues report the results of a study that explored the pharmacology of DOACs in very elderly patients with AF by measuring peak and trough blood levels of apixaban and rivaroxaban and their effects on thrombin generation in 215 hospitalized patients 80 years of age or older (mean: 87 years, 71% female).[13] Patients were eligible to participate if they had been treated with apixaban or rivaroxaban for at least 4 days. Blood samples collected 1 to 4 hours after the last DOAC dose were defined as peak levels and those taken 10 to 12 or 20 to 24 hours after the last dose of apixaban or rivaroxaban, respectively, were defined as trough levels. Patients also underwent DNA testing to detect common polymorphisms in the genes involved in the metabolism or transport of apixaban and rivaroxaban (CYP2J2, CYP3A4/5, and ATP-binding cassette subfamily B member 1 [ABCB1] encoding P-glycoprotein).

Most patients (apixaban 85/111 [76.6%]; rivaroxaban 86/104 [82.7%]) enrolled in the study by Foulon-Pinto et al were receiving reduced DOAC doses.[13] Surprisingly, despite being under the care of health care providers at a major academic institution, one-third of those treated with reduced doses (62/171 [36.3%]) did not meet guideline criteria for dose reduction ("off-label" dosing), and an additional 10 patients (4.9%) were receiving a higher dose than recommended by the guidelines. Analyses restricted to results from patients receiving reduced DOAC doses revealed that despite the dose reduction, at peak, drug levels were above the 95th centile of those previously reported in the pivotal trials comparing the DOACs with warfarin for stroke prevention in AF in 32 and 31% of patients treated with apixaban and rivaroxaban, respectively, whereas at the trough, only 10 and 22%, respectively, of the levels were below the 5th centile. These interesting findings suggest that the frequent off-label dose reduction in this elderly population did not result in systemic underexposure to apixaban or rivaroxaban because most of the out-of-range drug levels were higher than those reported in the pivotal trials.

Dosing was an important determinant of the trough and peak levels in patients treated with apixaban, but not in those treated with rivaroxaban, presumably because the reduced dose of apixaban is 50% lower than the full dose, whereas the reduced dose of rivaroxaban is only 25% lower than the full dose.[11] Clinical factors, most notably amiodarone use with or without co-administration of specific

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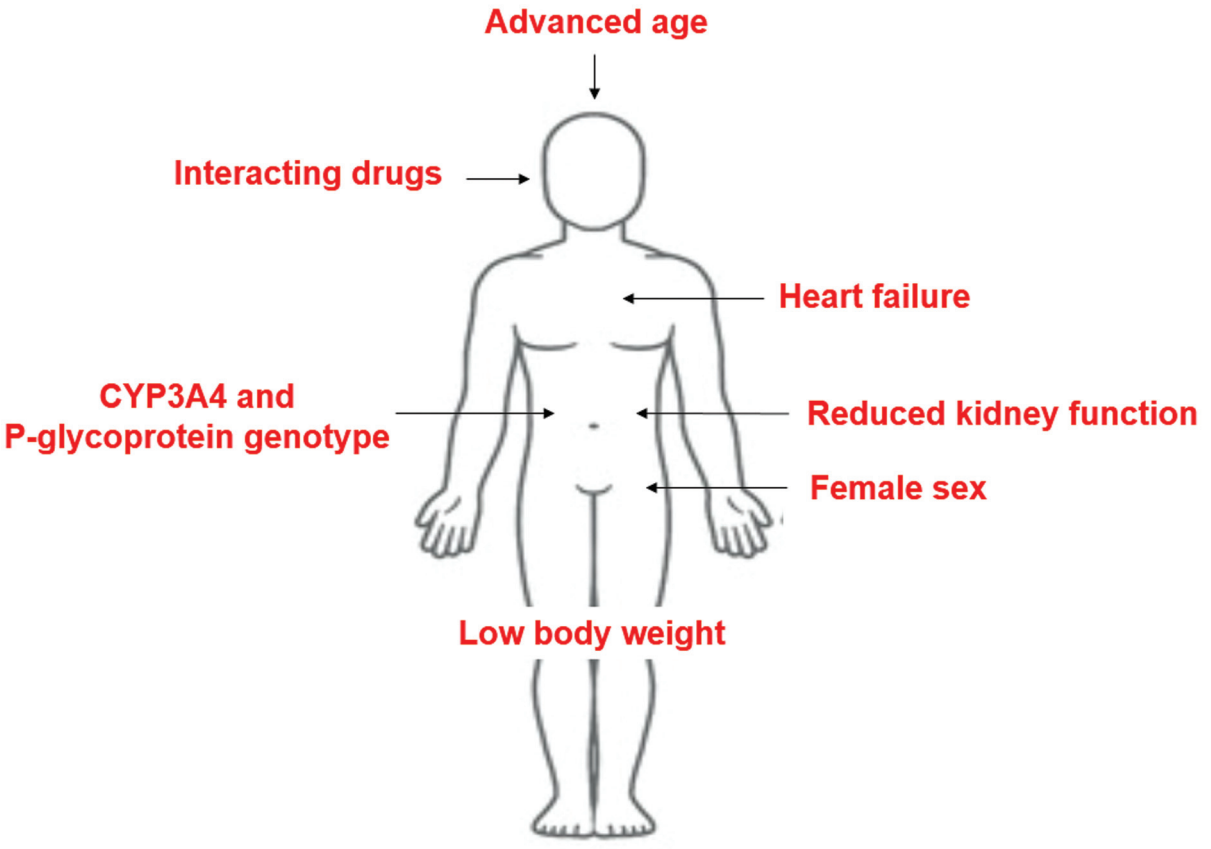


**Fig. 1** Independent determinants of drug levels of apixaban and rivaroxaban and thrombin generation inhibition in patients with atrial fibrillation.

CYP3A4/5 or ABCB1 modulators or loss or gain of function polymorphisms, are important independent determinants of the variability in both apixaban and rivaroxaban drug levels (►**Fig. 1**).

Drug levels were in turn correlated with measures of thrombin generation, but neither drug levels nor thrombin generation results were associated with clinical outcomes.[13] Six-month mortality rates ranged from 15 to 20% reflecting the advanced age of the study population. The incidence rates for major bleeding at 6 months with apixaban and rivaroxaban were 5 and 7%, respectively, and were higher than the incidence rates for thromboembolism of 4 and 1%, respectively.

The results of the study by Foulon-Pinto and colleagues must be interpreted with caution because there is no evidence that the reported pharmacokinetic or pharmacodynamic variables predict clinical outcomes.[13] Nonetheless, the findings provide valuable lessons for the management of very elderly patients with AF. First, although the pharmacokinetic and pharmacodynamic data do not inform the appropriateness of treating the very elderly with reduced DOAC doses in an off-label manner, the high variability in drug levels suggests that there is room for improvement in DOAC dosing in this population. Previous studies have shown that extremes of drug levels predict clinical outcomes,[14] and it is possible that a tailored dosing strategy that incorporates information about genotype and the concomitant use of one or more interacting drugs could reduce variability in drug levels, thereby improving clinical outcomes. However, demonstrating an improvement in clinical outcomes with a tailored strategy would require such a large number of patients that it is unlikely that such a study will be performed.[14] Second, the finding that reduced kidney function had minimal effects on the variability in drug levels is consistent with the known pharmacology of apixaban and rivaroxaban, both of which are cleared via predominantly extra-renal pathways. Although guidelines recommend regular monitoring of kidney function in patients treated with DOACs,[4] there is accumulating evidence that apixaban and rivaroxaban can be safely used in those with advanced kidney disease because of the low risk of clinically important drug accumulation. Third, the high rates of major bleeding relative to thromboembolic events at 6 months in very elderly patients with AF may prompt clinicians to question the net benefit of anticoagulant therapy in this high-risk population. However, advanced age is one of the most powerful risk factors for thromboembolism in patients with AF, and randomized trials with both warfarin[15] and very low-dose edoxaban[16] have demonstrated the efficacy of anticoagulation over no treatment for stroke prevention in the very elderly. The low incidence rates of thromboembolism with apixaban and rivaroxaban reported in this study are therefore most likely explained by the efficacy of these agents because both are expected to reduce the risk of stroke

 

by about two-thirds. Accordingly, despite the high incidence rates for major bleeding, the best strategy to reduce morbidity and mortality in the very elderly with AF is to prescribe DOACs using the dosage regimens recommended by the guidelines.

Conflict of Interest
None declared.

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