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CARDIOVASCULAR DISEASE IN THE ELDERLY (M CHEN, SECTION EDITOR)

Reduced Dose Direct Oral Anticoagulants in Older Adults with Atrial Fibrillation

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Background

- Atrial fibrillation is a major risk factor for stroke in older adults, with risk increasing with age
- International guidelines recommend use of dabigatran, apixaban, rivaroxaban or edoxaban as a class I indication for patients with NVAF
- While all four DOACs have approved lower dosing recommendations, clinicians may reduce doses for older adults based on factors such as age, bleeding risk, and frailty or fall risk
- To date, there exists little evidence for this practice, with some findings suggesting that inappropriately reduced DOAC doses may be associated with higher rates of stroke

Purpose of review

- This review assesses recent evidence for safety and efficacy of reduced dose DOAC regimens in older adults.

Results: dabigatran

- The 110 mg dose was non-inferior compared to warfarin (RR 0.91; 95% CI 0.74–1.11) for stroke/embolism, but had a lower rate of major bleeding (RR 0.80, 95% CI 0.69–0.93).
- In Europe,Canada, and Australia the 110 mg twice daily dose is recommended for older adults >80 years old, or for younger age with additional risk factors for bleeding
- Taken together, evidence suggests using the 110 mg dose in older adults age > 75 or 80, or those with a propensity for higher dabigatran levels (females, lower renal function) may be a rational approach.

Results: rivaroxaban

- Rivaroxaban was non-inferior to warfarin for prevention of stroke or systemic embolism regardless of whether it was dose-reduced
- In a study examining the clinical effectiveness and safety of reduced dose DOACs, rivaroxaban and warfarin were found to have event rates of ischemic stroke/systemic embolism of 3.5% and 3.7% respectively. The safety outcome (any bleeding event) of rivaroxaban vs. warfarin was similar (HR 1.06, 95% CI 0.87–1.29) with rivaroxaban 15 mg showing a trend towards lower thromboembolic rates
- To date, there are no studies directly comparing rivaroxaban 20 mg and 15 mg.

Results: apixaban

- Compared to warfarin, apixaban-treated patients had lower rates of ischemic or hemorrhagic stroke or systemic embolic (HR 0.79, 95% CI 0.66–0.96), lower rates of major bleeding (HR 0.69, 95% CI 0.60–0.80), and hemorrhagic stroke (HR 0.51, 95% CI 0.35–0.75)
- However, in the ARISTOTLE trial the dose-reduced apixaban was only administered to 4.7% of patients
- Uncertainty remains regarding the efficacy of dose-reduced apixaban due to infrequent use in randomized control trials

Results: edoxaban

- In the ENGAGE-AF trial 41% of patients ≥ 75 years of age received a dose reduction of edoxaban, most commonly due to the presence of moderate renal insufficiency (CrCl < 50 mL/min)
- The efficacy of low dose edoxaban compared with warfarin in preventing stroke was preserved, while there was a significant reduction in major bleeding

Table 1 FDA-approved dosing for DOACs for non-valvular atrial fibrillation

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Normal or mildly impaired renal function	150 mg twice daily (CrCl > 30 mL/min)	20 mg daily (CrCl > 50 mL/min)	5 mg twice daily	60 mg daily (CrCl 51–95 mL/min)
Moderately impaired renal function	75 mg twice daily (CrCl 15–30 mL/min)	15 mg daily (CrCl 15–50 mL/min)	2.5 mg twice daily if ≥ 2 of the following: age ≥ 80 years, weight ≤ 60 kg, SCr ≥ 1.5	30 mg daily (CrCl 15–50 mL/min)
End-stage renal disease (ESRD)	Not recommended	Not recommended (CrCl < 15 mL/min)	5 mg twice daily in ESRD on hemodialysis*	Not recommended (CrCl < 15 mL/min)**

CrCl creatinine clearance, *SCr* serum creatinine

*Only based on small, single-dose pharmacokinetic study of 8 patients [9]

**Labeled dose is not recommended in CrCL < 15 mL/min, but ENGAGE AF-TIMI 48 trial excluded patients with CrCL < 30 mL/min [5]

Conclusions

- Dose reduction based on labeled dosing of each DOAC is appropriate
- However, there is limited evidence for effectiveness and safety of inappropriately dose-reduced DOACs, a relatively common phenomenon
- The risk of stroke compared to bleeding should be carefully considered and discussed with each patient in the decision to dose-reduce a DOAC off-label