For Atrial Fibrillation, DOACs Outperform Warfarin in Patients with Reduced Kidney Function

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At standard doses, direct oral anticoagulants (DOACs) were associated with a reduced risk of systemic embolism and intracranial hemorrhage (ICH) when compared with warfarin, with a greater derived benefit at lower creatinine clearance (CrCl-down to 25 mL/min). Lower doses of DOACs were associated with increased overall mortality without a significant decrease in ICH and incident bleeding when compared with standard dose DOACs and warfarin, across all CrCl down to 25 mL/min.[1] (J Am Board Fam Med 2024;00:000–000.)

Keywords: **Atrial Fibrillation, Drug Therapy, Renal Insufficiency, Warfarin**

Strength of Recommendation: A

Based on meta-analysis of high-quality RCTs.[1]

Illustrative Case

An 80-year-old male with chronic kidney disease (CKD) 3a (CrCl 52 mL/min) and nonvalvular atrial fibrillation (AF) has taken warfarin for 12 years without complication. After discussing with his doctor during his initial diagnosis of AF, he chose to start warfarin because he knew there was a reversal agent. He continues to be very active and bikes in the summer and volunteers as a ski instructor in the winter. He reports a few falls each year with these activities.

Should you consider switching his warfarin to a DOAC at this time? If so, what dose would you choose?

Clinical Context

AF is more common among patients with CKD with increasing incidence in more advanced CKD. In a prospective cohort study in Korea with 4.8 million participants, the annual incidence of AF was 1.17 per 1000 person-years in patients without CKD. Among those with CKD, AF incidence per 1000 person-years was 1.55 for Stage 1, 1.86 for Stage 2, 2.1 for Stage 3, and 4.33 for Stage 4.[2] CKD is associated with many conditions that increase the risk of AF, including hypertension, heart failure, vascular disease, diabetes, electrolyte derangements, and autonomic imbalance.[3]

The 2023 American College of Cardiology Guideline for the Diagnosis and Management of Atrial Fibrillation recommends patients with AF with CKD Stage 3 and at elevated risk of stroke are preferably treated with DOACs over warfarin to reduce the risk of stroke. The risk for stroke should be evaluated using a validated clinical score like CHA_2DS_2-VASc.[4]

Use of DOACs generally has been most studied in patients with AF and mild-to-moderate chronic kidney disease (CrCl >30 mL/min). A 2017 Cochrane review including 5 RCTs and 12,545 participants with AF and CKD concluded that DOACs are as likely as warfarin to prevent stroke and systemic embolism in CKD stage 3 and above. There was no conclusion for CrCl <30 mL/min since the sample size was too small (n = 391).[5]

This aim of this study is to examine the safety and efficacy of DOACs as compared with warfarin for a wide range of CrCl. It also investigates if reduced dosing of DOACs as compared with standard dosing impacts patient outcomes.

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Methods

This article was identified as a potential PURL through the standard systematic methodology.[6] An additional literature search was conducted by searching DynaMed, UpToDate, and PubMed with the terms "DOAC" and "renal function" to find additional literature to place this research into the context of current clinical practice.

Study Summary

This patient-level meta-analysis of data 71,683 patients extracted from the COMBINE AF database (A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation) evaluated the efficacy and safety outcomes for DOACS versus warfarin for patients with AF across different baseline CrCl.[1] This analysis included data from 4 randomized controlled trials. The ARISTOTLE trial compared apixaban 5 mg twice daily, or 2.5 mg twice daily for age ≥ 80 years, weight < 60 kg, creatinine ≥ 1.5 mg/dL, to warfarin 2 mg daily with adjustment for a goal INR of 2 to 3. The ENGAGE AF-TIMI 48 compared Edoxaban 60 mg daily or 30 mg daily for CrCl of 30 to 50 mL/min, weight < 60 kg or concomitant use of verapamil or quinidine to warfarin – dose adjusted to INR of 2 to 3. The RE-LY trial compared dabigatran 150 mg twice daily, or 110 mg twice daily, to warfarin adjusted to INR of 2 to 3. The ROCKET AF trial compared rivaroxaban 20 mg daily (CrCl ≥ 50 mL/min) or 15 mg daily (CrCl 30 to 49 mL/min) to warfarin adjusted to an INR of 2 to 3. This meta-analysis defined standard dose DOAC as the doses used in the ROCKET AF or ARISTOTLE trials and the 150 mg of dabigatran twice daily (RE-LY) or 60 mg or 30 mg (dose adjustment) of Edoxaban daily (ENGAGE AF-TIMI 48). Lower dosing was defined as 110 mg dabigatran twice daily (RE-LY), or 30 mg of Edoxaban once daily, 15 mg for patients meeting criteria for dose adjustment (ENGAGE AF-TIMI 48). The analysis generated hazard ratios (HR) among parallel subgroups taking standard dose DOACs, low dose DOACs, and warfarin across different baseline CrCl for major bleeding, intracranial hemorrhage (ICH), composite of stroke/systemic embolism, mortality, and composites of multiple outcomes. Patients with the lowest baseline CrCl (<30 mL/min) comprised only 510 out of the 71,683 extracted from COMBINE AF. Patients in this category tended to be of older age, have a diagnosis of heart failure or coronary artery disease, or have higher CHA2DS2VASc scores compared with patients in higher CrCl categories.

Across the subsets of CrCl, standard dose DOAC reduced the risk of stroke/systemic embolism and ICH as compared with warfarin (HR reduction 4.8%; 95% CI, 0.7%-12.6% and HR reduction 6.2%; 95% CI, 1.3%-8.1%, respectively) per 10 mL/min decline in CrCl below 87 mL/min. Standard dose DOACs and warfarin had similar risks of major bleeding and mortality. There was an increased risk of death with low dose DOAC compared with either warfarin or standard dose (HR 3.5%; 95% CI, 0.3%-6.9% CI and HR5.8%; 95% CI 2.4%-9.2%, respectively) per 10 mL/min decline in CrCl. There was no difference in the rate of stroke/systemic embolism, ICH, or major bleeding with low dose DOAC as compared with standard dose DOAC or warfarin. There was no difference in any of the composite outcomes between the groups.

What Is New

This meta-analysis shows that DOACs at standard-dose are more effective and safer compared with warfarin with worsening renal dysfunction down to a creatinine clearance of 25 mL/min. This meta-analysis also suggests that inappropriate dose reductions of DOACs in these patients carries a higher risk of stroke and death without decreasing the risk of bleeding.

Caveats

Limitations in this analysis include only using a baseline creatinine clearance at initiation of the study and not accounting for changes in creatinine clearance over time. In addition, there were few patients with creatinine clearance less than 25 mL/min included in this analysis, so the authors are unable to conclude that DOACs are preferrable to warfarin for patients with atrial fibrillation and creatinine clearance < 25 mL/min. Furthermore, only 510 out of the 71,683 patients included in this analysis had creatine clearance < 30 mL/min. Lastly, the only DOACs studied at the lower dose were Edoxaban and dabigatran.

Challenges to Implementation

Cost of DOACs may be significantly higher than warfarin depending on patient's insurance status

which makes it more difficult for patients who may benefit from a DOAC to afford this treatment. In addition, guidelines for DOACs in patients with CrCl <25 mL/min are based primarily on observational data and providers may not be as confident in the safety profile for DOAC use with CrCl <25 mL/min.[4] This may prevent providers prescribing DOACs for patients with CKD Stage 4 and 5.

To see this article online, please go to: http://jabfm.org/content/00/00/000.full.

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