Which anticoagulant is safest for frail elderly patients with nonvalvular A-fib?

In a retrospective study comparing direct oral anticoagulants vs warfarin in this population, apixaban's adverse event rate was lower regardless of frailty status.

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PRACTICE CHANGER

Consider apixaban, which demonstrated a lower adverse event (AE) rate than warfarin regardless of frailty status, for anticoagulation treatment of older patients with nonvalvular atrial fibrillation (AF); by comparison, AE rates for dabigatran and rivaroxaban were lower vs warfarin only among nonfrail individuals.

STRENGTH OF RECOMMENDATION

C: Based on a retrospective observational cohort study.[1]

Kim DH, Pawar A, Gagne JJ, et al. Frailty and clinical outcomes of direct oral anticoagulants versus warfarin in older adults with atrial fibrillation: a cohort study. *Ann Intern Med*. 2021;174:1214-1223. doi: 10.7326/M20-7141

ILLUSTRATIVE CASE

A frail 76-year-old woman with a history of hypertension and hyperlipidemia presents for evaluation of palpitations. An in-office electrocardiogram reveals that the patient is in AF. Her CHA_2DS_2-VASc score is 4 and her HAS-BLED score is 2.[2,3] Using shared decision making, you decide to start medications for her AF. You plan to initiate a beta-blocker for rate control and must now decide on anticoagulation. Which oral anticoagulant would you prescribe for this patient's AF, given her frail status?

Frailty is defined as a state of vulnerability with a decreased ability to recover from an acute stressful event.[4] The prevalence of frailty varies by the measurements used and the population studied. A 2021 meta-analysis found that frailty prevalence ranges from 12% to 24% worldwide in patients older than 50 years[5] and may increase to > 30% among those ages 85 years and older.[6] Frailty increases rates of AEs such as falls[7] and fracture,[8] leading to disability,[9] decreased quality of life,[10] increased utilization of health care,[11] and increased mortality.[12] A number of validated approaches are available to screen for and measure frailty.[13-18]

Given the association with negative health outcomes and high health care utilization, frailty is an important clinical factor for physicians to consider when treating elderly patients. Frailty assessment may allow for more tailored treatment choices for patients, with a potential reduction in complications. Although CHA_2DS_2-VASc and HAS-BLED scores assist in the decision-making process of whether to start anticoagulation, these tools do not take frailty into consideration or guide anticoagulant choice.[2,3] The purpose of this study was to analyze how levels of frailty affect the association of 3 different direct oral anticoagulants (DOACs) vs warfarin with various AEs (death, stroke, or major bleeding).

STUDY SUMMARY

This DOAC rose above the others

This retrospective cohort study compared the safety of 3 DOACs—dabigatran, rivaroxaban, and apixaban—vs warfarin in Medicare ben-

Among older patients treated with anticoagulation for atrial fibrillation, apixaban had the lowest adverse event rate vs warfarin among frail patients, compared with dabigatran and rivaroxaban.

eficiaries with AF, using 1:1 propensity score (PS)–matched analysis. Eligible patients were ages 65 years or older, with a filled prescription for a DOAC or warfarin, no prior oral anticoagulant exposure in the previous 183 days, a diagnostic code of AF, and continuous enrollment in Medicare Parts A, B, and D only. Patients were excluded if they had missing demographic data, received hospice care, resided in a nursing facility at drug initiation, had another indication for anticoagulation, or had a contraindication to either a DOAC or warfarin.

Frailty was measured using a claims-based frailty index (CFI), which applies health care utilization data to estimate a frailty index, with cut points for nonfrailty, prefrailty, and frailty. The CFI score has 93 claims-based variables, including wheelchairs and durable medical equipment, open wounds, diseases such as chronic obstructive pulmonary disease and ischemic heart disease, and transportation services.[15-17] In this study, nonfrailty was defined as a CFI < 0.15, prefrailty as a CFI of 0.15 to 0.24, and frailty as a CFI ≥ 0.25.

The primary outcome—a composite endpoint of death, ischemic stroke, or major bleeding—was measured for each of the DOAC–warfarin cohorts in the overall population and stratified by frailty classification. Patients were followed until the occurrence of a study outcome, Medicare disenrollment, the end of the study period, discontinuation of the index drug (defined as > 5 days), change to a different anticoagulant, admission to a nursing facility, enrollment in hospice, initiation of dialysis, or kidney transplant. The authors conducted a PS-matched analysis to reduce any imbalances in clinical characteristics between the DOAC- and warfarin-treated groups, as well as a sensitivity analysis to assess the strength of the data findings using different assumptions.

The authors created 3 DOAC–warfarin cohorts: dabigatran (n = 81,863) vs warfarin (n = 256,722), rivaroxaban (n = 185,011) vs warfarin (n = 228,028), and apixaban (n = 222,478) vs warfarin (n = 206,031). After PS matching, the mean age in all cohorts was 76 to 77 years, about 50% were female, and 91% were White. The mean HAS-BLED score was 2 and the mean CHA_2DS_2-VASc score was 4. The mean CFI was 0.19 to 0.20, defined as prefrail. Patients classified as frail were older, more likely to be female, and more likely to have greater comorbidities, higher scores on CHA_2DS_2-VASc and HAS-BLED, and higher health care utilization.

In the dabigatran–warfarin cohort (median follow-up, 72 days), the event rate of the composite endpoint per 1000 person-years (PY) was 63.5 for dabigatran and 65.6 for warfarin (hazard ratio [HR] = 0.98; 95% CI, 0.92 to 1.05; rate difference [RD] per 1000 PY = –2.2; 95% CI, –6.5 to 2.1). A lower rate of the composite endpoint was associated with dabigatran than warfarin for the nonfrail subgroup but not the prefrail or frail groups.

In the rivaroxaban–warfarin cohort (median follow-up, 82 days), the composite endpoint rate per 1000 PY was 77.8 for rivaroxaban and 83.7 for warfarin (HR = 0.98; 95% CI, 0.94 to 1.02; RD per 1000 PY = –5.9; 95% CI, –9.4 to –2.4). When stratifying by frailty category, both dabigatran and rivaroxaban were associated with a lower composite endpoint rate than warfarin for the nonfrail population *only* (HR = 0.81; 95% CI, 0.68 to 0.97, and HR = 0.88; 95% CI, 0.77 to 0.99, respectively).

In the apixaban–warfarin cohort (median follow-up, 84 days), the rate of the composite endpoint per 1000 PY was 60.1 for apixaban and 92.3 for warfarin (HR = 0.68; 95% CI, 0.65 to 0.72; RD per 1000 PY = –32.2; 95% CI, –36.1 to –28.3). The beneficial association for apixaban was present in all frailty categories, with an HR of 0.61 (95% CI, 0.52 to 0.71) for nonfrail patients, 0.66 (95% CI, 0.61 to 0.70) for prefrail patients, and 0.73 (95% CI, 0.67 to 0.80) for frail patients. Apixaban was the only DOAC with a relative reduction in the hazard of death, ischemic stroke, or major bleeding among *all* frailty groups.

WHAT'S NEW

Only apixaban had lower AE rates vs warfarin across frailty levels

Three DOACs (dabigatran, rivaroxaban, and apixaban) reduced the risk of death, ischemic stroke, or major bleeding compared with warfarin in older adults with AF, but only apixaban was associated with a relative reduction

of these adverse outcomes in patients of all frailty classifications.

CAVEATS

Important data but RCTs are needed

The power of this observational study is considerable. However, it remains a retrospective observational study. The authors attempted to account for these limitations and potential confounders by performing a PS-matched analysis and sensitivity analysis; however, these findings should be confirmed with randomized controlled trials.

Additionally, the study collected data on each of the DOAC–warfarin cohorts for < 90 days. Trials to address long-term outcomes are warranted.

Finally, there was no control group in comparison with anticoagulation. It is possible that choosing not to use an anticoagulant is the best choice for frail elderly patients.

CHALLENGES TO IMPLEMENTATION

Doctors need a practical frailty scale, patients need an affordable Rx

Frailty is not often considered a measurable trait. The approach used in the study to determine the CFI is not a practical clinical tool. Studies comparing a frailty calculation software application or an easily implementable survey may help bring this clinically impactful information to the hands of primary care physicians. The Clinical Frailty Scale—a brief, 7-point scale based on the physician's clinical impression of the patient—has been found to correlate with other established frailty measures[18] and might be an option for busy clinicians. However, the current study did not utilize this measurement, and the validity of its use by primary care physicians in the outpatient setting requires further study.

In addition, cost may be a barrier for patients younger than 65 years or for those older than 65 years who do not qualify for Medicare or do not have Medicare Part D. The average monthly cost of the DOACs ranges from $560 for dabigatran[19] to $600 for rivaroxaban[20] and $623 for apixaban.[21] As always, the choice of anticoagulant therapy is a clinical judgment and a joint decision of the patient and physician. JFP

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