JACC
VOL. 86, NO. 6, 2025

PUBLISHED BY ELSEVIER

META-ANALYSIS

# Outcomes in Older Patients After Switching to a Newer Anticoagulant or Remaining on Warfarin

## The COMBINE-AF Substudy

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## ABSTRACT

**BACKGROUND** Whether frail, elderly patients with atrial fibrillation (AF) on a vitamin K antagonist (VKA) should switch to a direct-acting oral anticoagulant (DOAC) was studied in the FRAIL-AF trial and remains controversial.

**OBJECTIVES** The purpose of this study was to evaluate, in the COMBINE-AF data set, the impact on clinical outcomes of switching frail, elderly AF patients from VKA to DOAC.

**METHODS** COMBINE-AF consists of individual patient-level data from 71,683 patients with AF in 4 randomized clinical trials comparing DOAC vs warfarin. Frailty was evaluated using a frailty index derived from a modified Rockwood's Accumulation Model including 18 age-related conditions. Patients with a frailty index score above the median were considered frail. Prespecified outcomes were stroke or systemic embolic events, bleeding events, death, and a net clinical outcome combining these events.

**RESULTS** We identified 5,913 patients who were frail, elderly (age ≥75 years), and VKA-experienced and 52,721 patients who did not meet all 3 of these criteria. Patients were randomized to a standard-dose (SD) DOAC or warfarin. After 27 months median follow-up, there was no heterogeneity in treatment effect with SD-DOAC vs warfarin among those who met all 3 criteria vs those who did not for the endpoints of stroke or systemic embolic events (HR: 0.83 vs 0.81; $P_{int} = 0.75$) or for death (HR: 0.95 vs 0.91; $P_{int} = 0.54$). Major bleeding was similar with SD-DOAC vs warfarin in frail, elderly, VKA-experienced patients (HR: 1.06 [95% CI: 0.90-1.25]), while it was significantly reduced with SD-DOAC in patients without all 3 criteria (HR: 0.82 [95% CI: 0.76-0.89]; $P_{int} = 0.007$). Likewise, the net clinical outcome was similar in the frail, elderly, VKA-experienced patients with SD-DOAC vs warfarin (HR: 1.01 [95% CI: 0.91-1.13]), while significantly reduced with SD-DOAC patients without all 3 criteria (HR: 0.89 [95% CI: 0.85-0.93]; $P_{int} = 0.028$). Fatal and intracranial bleeding were significantly reduced with SD-DOAC in both subgroups to a similar degree (both $P_{int} > 0.05$), while gastrointestinal bleeding with SD-DOAC was increased to a greater degree in frail, elderly, VKA-experienced patients (HR: 1.83 [95% CI: 1.42-2.36]) compared with those without all 3 criteria (HR: 1.23 [95% CI: 1.09-1.39]; $P_{int} = 0.006$).

**CONCLUSIONS** Frail, elderly, VKA-experienced patients with AF switched to SD-DOAC experienced significant reductions in stroke or systemic embolism, fatal and intracranial bleeding, and death. Gastrointestinal bleeding was increased with SD-DOAC, while major bleeding and the primary net clinical outcome were similar. Based on these findings, SD-DOAC is a reasonable choice for frail, elderly, VKA-experienced patients to reduce stroke and systemic embolism, death, and the most serious types of bleeding. (JACC. 2025;86:426-439) © 2025 by the American College of Cardiology Foundation.

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ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2025.05.060

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and its incidence increases with age, affecting about 20% of patients age >80 years.[1,2] Older patients, especially those with a higher comorbidity burden, are at a higher risk of stroke or systemic embolic events (SEE), as well as more serious bleeding complications, like major and intracranial hemorrhage (ICH).[3] Frailty, a common condition in geriatric patients, is characterized by a decline in physical and cognitive reserve. In patients with AF, frailty increases the risks of both bleeding and ischemic events[4-6] and, among other clinical complexity domains, is independently associated with a high rate of nonprescription of anticoagulation and high rates of oral anticoagulation discontinuation.[7] As a result, frail, elderly patients with AF represent a particularly challenging group to manage, and underuse of anticoagulants is as high as 50%,[4,8] with discontinuation rates almost 3-fold higher than nonfrail patients.[5]

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Previous observational studies have showed that, even in extremely-high-risk, very elderly patients with AF, while warfarin is associated with a higher risk of the composite endpoint of stroke, ICH, major bleeding, and mortality compared with no anticoagulation, direct oral anticoagulants (DOACs) were associated with a lower risk of this composite endpoint.[9] The impact of switching from warfarin to DOAC in a particular population—frail, elderly, and vitamin K antagonist (VKA)-experienced—was recently assessed in the FRAIL-AF (Safety of Switching From Vitamin K Antagonist to Non-Vitamin K Antagonist Oral Anticoagulant in Frail Elderly With Atrial Fibrillation) trial.[10] To revisit this hypothesis is the objective of this paper.

In COMBINE-AF (A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulation Use in Atrial Fibrillation), a patient-level meta-analysis of the 4 large randomized clinical trials comparing DOACs with warfarin, DOACs significantly reduced stroke/SEE, ICH, and all-cause mortality compared with warfarin.[11] An even greater reduction of stroke/SEE was observed in patients age ≥75 years compared with younger patients.[6,12] Major bleeding in elderly patients was similar with DOAC and warfarin, while ICH was significantly reduced by 50% with DOACs.[6,13]

Frail individuals with AF are at particularly high risk for ischemic and bleeding events, and death.[4,14] However, prospectively defined, formal assessment of frailty was not undertaken in the large AF trials comparing DOACs vs warfarin. Instead, multiple subgroup analyses used surrogates for frailty including the presence of multiple comorbidities,[3] high risk of falling,[15] polypharmacy,[16,17] or a combination of high-risk features.[18] Each of these analyses in frail populations demonstrated similar or more favorable outcomes with DOACs compared with warfarin than were observed in the analyses of the overall trial populations. In contrast, the open-label FRAIL-AF trial randomized 1,330 patients who were age ≥75 years, frail, and treated with VKA to either switch from VKA to a DOAC (rivaroxaban 54%, apixaban 19%, edoxaban 18%, or dabigatran 9%) or to continue VKA. The trial was stopped prematurely for futility as there was a significant increase in major or clinically relevant nonmajor (CRNM) bleeding, mainly gastrointestinal bleeding, in patients switched to DOAC (HR: 1.69; 95% CI: 1.23-2.32).[10] These findings are cited to support a new Class IIb recommendation in the 2024 European Society of Cardiology AF Guideline that states maintaining VKA treatment rather than switching to a DOAC may be considered in patients aged ≥75 years on clinically stable therapeutic VKA with polypharmacy to prevent excess bleeding risk.[19] No differences in ischemic events or mortality were observed. Several limitations of this trial have been raised as potential

**ABBREVIATIONS AND ACRONYMS**

**AF** = atrial fibrillation

**CRNM** = clinically relevant nonmajor

**DOAC** = direct oral anticoagulation

**ICH** = intracranial hemorrhage

**VKA** = vitamin K antagonist

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Manuscript received March 14, 2025; revised manuscript received May 20, 2025, accepted May 23, 2025.

explanations for these unexpected findings.[20-22] To provide further data in a larger randomized population with longer follow-up, we used the COMBINE-AF database to identify patients who were "FRAIL-AF trial like" (ie, frail, elderly, VKA-experienced patients) and compared the efficacy and safety of switching to SD-DOAC vs remaining on a VKA (warfarin).

## METHODS

The COMBINE-AF database includes individual patient-level data from the 71,683 patients enrolled in the 4 pivotal trials of DOACs vs warfarin in patients with AF. The design and main results have been published.[11,12] Patients who met dose-reduction criteria for apixaban, edoxaban, and rivaroxaban as described in the corresponding trial protocol (ie, apixaban 2.5 mg, edoxaban 30 mg, rivaroxaban 15 mg) were included in this analysis. Patients (n = 13,049) on lower-dose regimens of DOACs (dabigatran 110 mg or edoxaban 30/15 mg) were excluded from the current analysis because these doses are not universally approved for use in patients with AF. Anonymized data from the COMBINE-AF database are available to members of the COMBINE-AF Executive Committee but are unable to be shared outside of their institutions. Each individual trial protocol was approved by the local Institutional Review Board, and all study participants provided written informed consent. Creation of the COMBINE-AF database was approved by the Duke University Institutional Review Board.

**STUDY POPULATION AND DEFINITIONS.** We assessed frailty as a state of accumulated health deficits, as previously described by Rockwood and Searle.[23-25] This approach proposes that frailty is the consequence of age-related health deficit accumulation, and can be measured using a frailty index (FI), which, for any individual, is the number of deficits present divided by the number of deficits that were counted.[23] The same method has been used in previous trials evaluating AF and stroke.[26,27] We developed the COMBINE-AF FI consisting of 18 age-related chronic conditions to build a comprehensive frailty index (FI-18), with 1 point for each condition (Supplemental Table 1). Participants were categorized as frail if they had 6 or more frailty features (ie, FI-18 ≥6 or FI ≥0.33), as the median FI-18 score was 5 for the entire population, and an FI score of ≥0.33 is above the 0.20 cutoff proposed to define frailty (Supplemental Figure 1).[28]

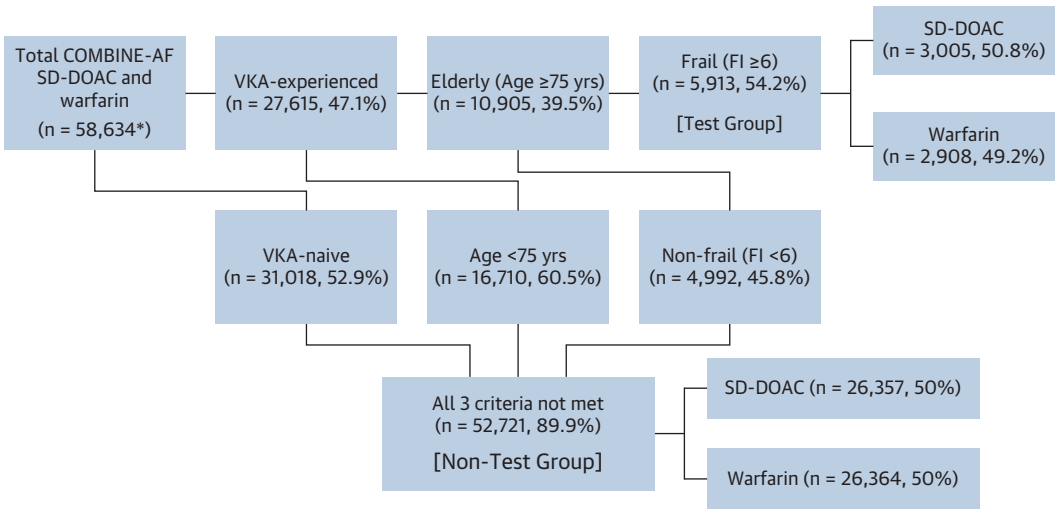
VKA experienced was defined as being on VKA treatment for more than 30 consecutive days in ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), 60 days in ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48), 6 weeks in ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) and 62 lifetime days in RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy). Patients who were frail, age ≥75 years, and VKA experienced were the population of interest (test group) for this analysis. We performed a comparison with the remaining patients (nontest group) included in COMBINE-AF randomized to SD-DOAC or warfarin who did not met all 3 of the aforementioned criteria.

**OUTCOMES.** All outcomes were adjudicated using similar definitions by an independent group of investigators who were unaware of treatment assignment. The primary efficacy outcome was a composite of stroke or SEE. Secondary efficacy outcomes included all-cause death, cardiovascular death, hemorrhagic stroke, ischemic stroke, and SEE. The primary safety outcome was major bleeding as defined by the International Society on Thrombosis and Haemostasis criteria.[29] Secondary safety outcomes included fatal bleeding, any bleeding, ICH, and gastrointestinal bleeding. Two net clinical outcomes (NCOs) were also evaluated: a primary NCO consisting of stroke/SEE, major bleeding, and death, and a secondary NCO of stroke/SEE, ICH, and death.

**STATISTICAL ANALYSIS.** We conducted a nonprespecified subgroup analysis of a patient-level metanalysis comparing treatment effects of SD-DOAC vs warfarin in patients who were frail, elderly (age ≥75 years), and VKA-experienced with those who did not meet all these 3 criteria. Outcomes were censored at 32 months because of differential durations of follow-up across trials.

For the primary analyses, Kaplan-Meier curves were generated for key outcomes, and univariable stratified Cox proportional hazard models stratified by trial were fitted, including the treatment strategy as an independent variable. A standard approach to a subgroup analysis was then used. First, we assessed for a statistically significant interaction ($P_{int}$) of the HRs between the 2 complementary subgroups (test vs nontest group) for each outcome. All event rates were reported as annualized rates. All $P$ values were 2-sided, and values <0.05 were considered statistically significant without correction for multiplicity. For endpoints where the $P$ interaction was <0.05, we

**FIGURE 1 Flow Diagram From COMBINE-AF**




The test group consisted of 5,913 patients (3,005 standard-dose direct oral anticoagulant [SD-DOAC], 2,908 warfarin) who were vitamin K antagonist (VKA)-experienced, elderly (age ≥75 years), and frail. The nontest group consisted of 52,721 patients (26,357 SD-DOAC, 26,364 warfarin) who did not meet all 3 of these criteria. SD-DOAC includes the dabigatran 150 mg arm from RE-LY, the rivaroxaban arm from ROCKET AF, the apixaban arm from ARISTOTLE, and the standard-dose edoxaban arm (60 mg, dose reduced to 30 mg) from ENGAGE AF-TIMI 48. *Patients (n = 13,049) on lower-dose regimen of DOACs (dabigatran 110 mg or edoxaban 30/15 mg) were excluded from the current analysis because these doses are not universally approved for use in patients with AF. FI = frailty index.

report the individual HRs and individual *P* values for both subgroups and interpret them separately. Adjustments for multiplicity were not undertaken because this was a post hoc analysis.

To evaluate the robustness of our findings, we analyzed results in 3 key patient subgroups based on baseline characteristics (stratified by age, renal function, and sex) and performed 2 sensitivity analyses. The sensitivity analyses included the following: 1) modeling the same distribution of DOAC utilization as was administered in the FRAIL-AF trial ("same DOAC-Mix population") using bootstrapping based on 1,000 samples; 2) given that apixaban and edoxaban have been extensively studied and are the 2 DOACs most widely used in older, more comorbid, and frail patients,[3,14,30-34] we conducted a second sensitivity analysis restricted to the ARISTOTLE (apixaban vs warfarin) and ENGAGE AF-TIMI 48 (edoxaban vs warfarin) trials.

Statistical computations were performed with SAS version 9.4 (SAS Institute).

## RESULTS

**PATIENT CHARACTERISTICS.** Individual data from 58,634 patients randomized to SD-DOAC or warfarin followed for a median 26.7 months (Q1-Q3: 18.5-32.0 months) were available for this analysis (n = 29,362 randomized to SD-DOAC, n = 29,272 randomized to warfarin). There were 27,615 (47.1%) VKA-experienced patients of whom 10,905 (39.5%) were age ≥75 years. Finally, among those who were both elderly and VKA experienced, 5,913 patients (54.2%) were classified as frail and represented the test group; 3,005 were randomized to SD-DOAC, and 2,908 to warfarin (**Figure 1**). Baseline characteristics comparing the test and nontest subgroups demonstrated major differences as expected (**Table 1**). Within the subgroup of patients who were frail, elderly, and VKA-experienced, baseline characteristics for patients randomized to SD-DOAC and warfarin were similar: mean age 79.8 years vs 79.7 years, 41.2% vs 41.6% women, and median $CHA_2DS_2$-VASc score was 5 in both the test and nontest subgroups.

**EFFICACY OUTCOMES.** In patients who were frail, elderly, and VKA-experienced, the HR in patients randomized to SD-DOAC vs warfarin for the primary efficacy endpoint of stroke or SEE (HR: 0.83 [95% CI: 0.65-1.07]) was similar to the HR in the nontest group (HR: 0.81 [95% CI: 0.73-0.89]; $P_{int} = 0.75$). There was no significant heterogeneity in treatment effects between SD-DOAC and warfarin across other efficacy endpoints among patients in the test vs nontest group ($P_{int} > 0.35$ for each) (**Table 2**, **Figures 2A and 2D, Central Illustration**), including all-cause mortality.

**TABLE 1 Baseline Characteristics of the COMBINE-AF in Patients Who Were Frail, Elderly, and VKA-Experienced vs Those Who Were Not**

| | Frail, Elderly, and VKA-Experienced (N = 5,913) | | All 3 Criteria Not Met (N = 52,721) | |
|---|---|---|---|---|
| | SD-DOAC (n = 3,005) | Warfarin (n = 2,908) | SD-DOAC (n = 26,357) | Warfarin (n = 26,364) |
| Age, y | 79.8 ± 3.7 | 79.7 ± 3.7 | 69.4 ± 9.3 | 69.4 ± 9.2 |
| Female | 1,239 (41.2) | 1,211 (41.6) | 9,730 (36.9) | 9,655 (36.6) |
| Paroxysmal AF | 469 (15.6) | 467 (16.1) | 5,881 (22.3) | 6,028 (22.9) |
| CCI score | 2 (0-2) | 2 (0-2) | 1 (0-2) | 1 (0-2) |
| Frailty index 18 | 7 (6-8) | 7 (6-8) | 5 (4-6) | 5 (4-6) |
| Number of comedications | 4 (3-5) | 4 (3-5) | 3 (2-4) | 3 (2-4) |
| $CHA_2DS_2$-VASc score | 5 (4-6) | 5 (4-6) | 4 (3-5) | 4 (3-5) |
| Heart failure | 1,563 (52) | 1,462 (50.3) | 12,170 (46.2) | 12,165 (46.1) |
| Coronary artery disease | 1,495 (49.8) | 1,444 (49.7) | 7,225 (27.4) | 7,267 (27.6) |
| Hypertension | 2,778 (92.4) | 2,716 (93.4) | 23,006 (87.3) | 23,050 (87.4) |
| Diabetes | 1,111 (37) | 1,099 (37.8) | 8,012 (30.4) | 7,912 (30) |
| History GI bleeding | 179 (7.5) | 177 (7.5) | 697 (3.3) | 734 (3.5) |
| History non-GI bleeding | 349 (14.5) | 333 (14.1) | 1,412 (6.8) | 1,372 (6.6) |
| Prior stroke or TIA | 950 (31.6) | 958 (32.9) | 7,519 (28.5) | 7,519 (28.5) |
| Body mass index, $kg/m^2$ | 28.8 ± 5.3 | 28.8 ± 5.4 | 29.2 ± 5.9 | 29.2 ± 6 |
| Creatinine clearance, mL/min | 56.9 ± 18.8 | 56.8 ± 18.5 | 77.8 ± 31.2 | 77.7 ± 36.7 |
| Concurrent platelet inhibitor use | 775 (25.8) | 761 (26.2) | 9,101 (34.5) | 9,137 (34.7) |
| TTR (% for each patient) | Not applicable | 68.6 (56.6-78.4) | Not applicable | 64.7 (50.5-75.8) |
| Direct acting oral anticoagulant | | Not applicable | | Not applicable |
| Rivaroxaban | 554 (18.4) | | 6,577 (25) | |
| Apixaban | 849 (28.3) | | 8,271 (31.4) | |
| Edoxaban | 997 (33.2) | | 6,038 (22.9) | |
| Dabigatran | 605 (20.1) | | 5,471 (20.8) | |

Values are mean ± SD, n (%), or median (Q1-Q3). Frail considered frailty index (FI)-18 ≥6 or FI >0.33 (see Methods section for details). Elderly considered age ≥75 years. All *P* values comparing baselines characteristics with standard-dose direct oral anticoagulant (SD-DOAC) vs warfarin within the same group were nonsignificant ($P > 0.05$). Creatinine clearance calculated with Cockcroft Gault formula in mL/min. All baseline characteristics differed significantly ($P < 0.05$) between those who were frail, elderly, and vitamin K antagonist (VKA)-experienced vs those who were not.

AF = atrial fibrillation; CCI = Charlson Comorbidity Index; GI = gastrointestinal; TIA = transient ischemic attack; TTR = time in therapeutic range.

**TABLE 2 Efficacy Outcomes in COMBINE-AF of DOAC vs Warfarin**

| | Frail, Elderly, VKA Experienced Patients (N = 5,903) | | | | | All 3 Criteria Not Met (N = 52,721) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Warfarin (n = 2,908) | | SD-DOAC (n = 3,005) | | | Warfarin (n = 26,364) | | SD-DOAC (n = 26,357) | | | |
| | n | %/y | n | %/y | HR (95% CI) | n | %/y | n | %/y | HR (95% CI) | $P_{int}$ Value |
| Stroke or SEE | 137 | 2.39 | 119 | 1.99 | 0.83 (0.65-1.07) | 943 | 1.84 | 764 | 1.48 | 0.81 (0.73-0.89) | 0.75 |
| Stroke | 125 | 2.17 | 109 | 1.82 | 0.84 (0.65-1.08) | 881 | 1.72 | 720 | 1.39 | 0.81 (0.74-0.90) | 0.79 |
| Ischemic | 86 | 1.49 | 93 | 1.55 | 1.04 (0.78-1.40) | 599 | 1.16 | 565 | 1.09 | 0.94 (0.84-1.05) | 0.49 |
| Hemorrhagic | 34 | 0.58 | 13 | 0.21 | 0.37 (0.19-0.70) | 237 | 0.46 | 121 | 0.23 | 0.51 (0.41-0.63) | 0.36 |
| Disabling or fatal | 75 | 1.29 | 65 | 1.08 | 0.83 (0.59-1.16) | 536 | 1.04 | 437 | 0.84 | 0.81 (0.72-0.92) | 0.86 |
| SEE | 13 | 0.22 | 13 | 0.21 | 0.96 (0.45-2.08) | 72 | 0.14 | 48 | 0.09 | 0.66 (0.46-0.96) | 0.39 |
| All-cause death | 387 | 6.61 | 383 | 6.30 | 0.95 (0.83-1.10) | 2,073 | 3.98 | 1,893 | 3.62 | 0.91 (0.85-0.97) | 0.54 |
| CV death | 228 | 3.90 | 214 | 3.52 | 0.91 (0.75-1.09) | 1,318 | 2.53 | 1,173 | 2.25 | 0.89 (0.82-0.96) | 0.82 |
| Hospitalization | 1,202 | 27.23 | 1,229 | 26.96 | 0.99 (0.92-1.07) | 7,532 | 17.57 | 7,281 | 16.82 | 0.96 (0.93-0.99) | 0.46 |

CV = cardiovascular; n = number of events; NCO = net clinical outcome; SEE = systemic embolic events; other abbreviations as in Table 1.

Notably, SD-DOAC significantly reduced the risk of hemorrhagic stroke to a similar degree in test (HR: 0.37 [95% CI: 0.19-0.70]) and nontest (HR: 0.51 [95% CI: 0.41-0.63]) groups ($P_{int}$ = 0.36).

**SAFETY.** For the primary safety endpoint of major bleeding, significant heterogeneity in treatment effects with SD-DOAC vs warfarin was observed between the test vs nontest groups. Among patients who were frail, elderly, and VKA-experienced, there was no difference between SD-DOAC vs warfarin (HR: 1.06 [95% CI: 0.90-1.25]), whereas in the nontest group SD-DOAC significantly reduced major bleeding (HR: 0.82 [95% CI: 0.76-0.89]; $P_{int}$ = 0.007). Similar findings were observed for major or CRNM bleeding (test group: HR: 1.00 [95% CI: 0.90-1.12] vs nontest group: HR: 0.87 [95% CI: 0.83-0.91]; $P_{int}$ = 0.018). Meanwhile, SD-DOAC significantly increased gastrointestinal bleeding in both the test and nontest subgroups, with a greater increase in frail, elderly, and VKA-experienced patients (HR: 1.83 [95% CI: 1.42-2.36]) compared with the nontest group (HR: 1.23 [95% CI: 1.09-1.39]; $P_{int}$ = 0.006). No heterogeneity was observed for other safety outcomes. Importantly, SD-DOAC significantly reduced the incidence of fatal (HR: 0.46 [95% CI: 0.23-0.90] vs HR: 0.63 [95% CI: 0.48-0.83]) and intracranial bleeding (HR: 0.29 [95% CI: 0.17-0.48] vs HR: 0.48 [95% CI: 0.40-0.58]) to a similar degree in the test and nontest subgroups, $P_{int}$ = 0.38 and 0.06, respectively (**Table 3**, **Figures 2B and 2C**).

**NET CLINICAL OUTCOMES.** For the primary NCO, significant heterogeneity of treatment effect was observed between the test and nontest subgroups, with no difference between SD-DOAC and warfarin among patients who were frail, elderly, and VKA-experienced (HR: 1.01 [95% CI: 0.91-1.13]), but a significant reduction in the nontest subgroup (HR: 0.89 [95% CI: 0.85-0.93]; $P_{int}$ = 0.028). However, the secondary NCO was similarly reduced with SD-DOAC vs warfarin in both the test and nontest subgroups (**Table 3**).

**SUBGROUP ANALYSES BASED ON BASELINE PATIENT CHARACTERISTICS.** Results in 3 subgroups based on patient baseline characteristics within the frail, elderly, VKA-experienced group stratified by age (<80 years vs ≥80 years), renal function (creatinine clearance [CrCl] <50 mL/min vs ≥50 mL/min), and sex showed consistent results, with no significant heterogeneity of treatment effect (each $P_{int}$ > 0.10) (Supplemental Figure 2), with one exception. In frail, elderly, VKA-experienced patients with CrCl <50 mL/min, major bleeding tended to be lower with SD-DOAC (HR: 0.82 [95% CI: 0.63-1.06]), while in patients with CrCl ≥50 mL/min, major bleeding was significantly increased with SD-DOAC (HR: 1.27 [95% CI: 1.02-1.59]; $P_{int}$ = 0.01) compared with warfarin.

**SENSITIVITY ANALYSES.** Two sensitivity analyses were conducted within the frail, elderly, VKA-experienced group (**Table 4**, Supplemental Figure 3).

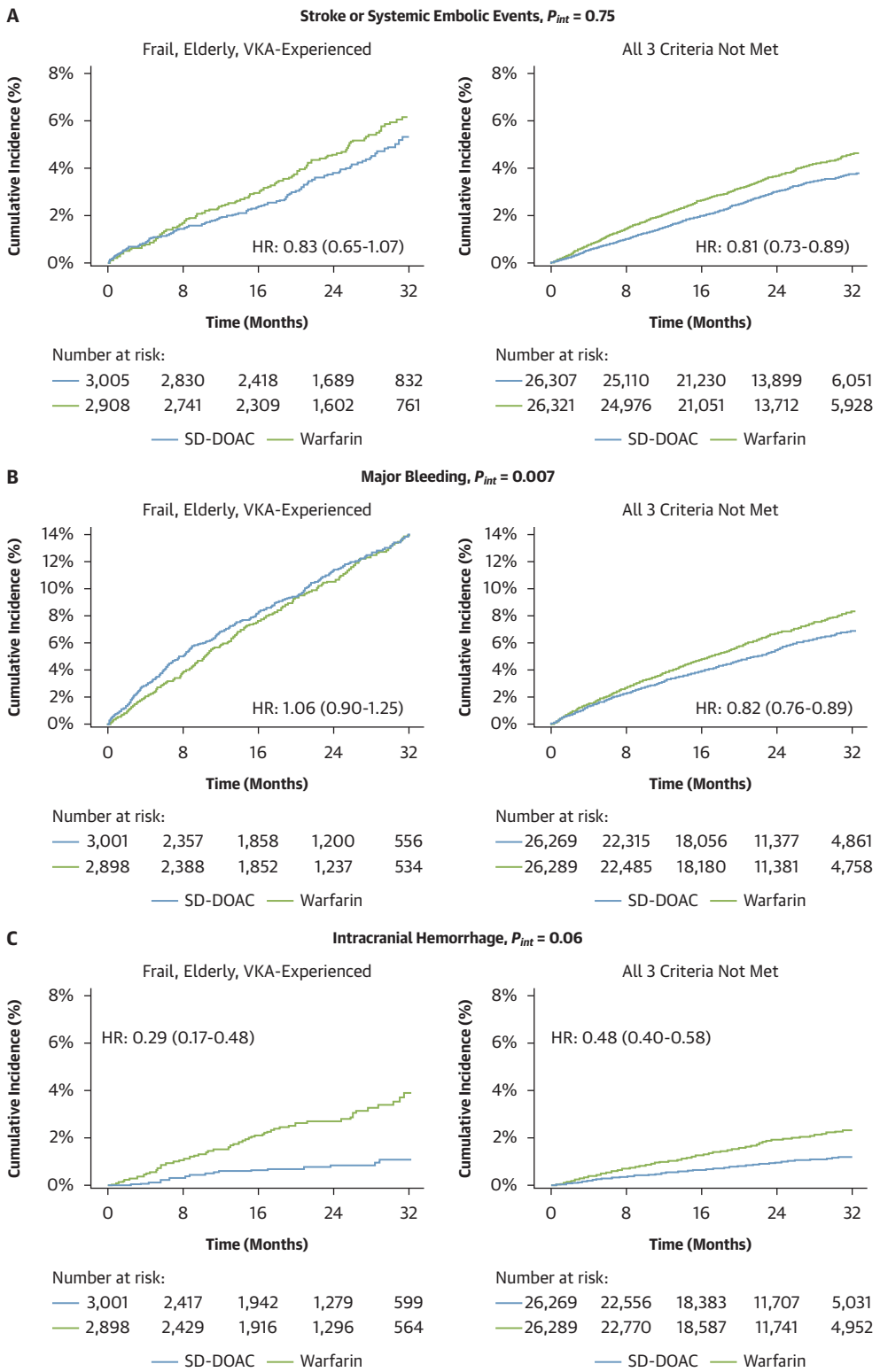
**Same DOAC mix as FRAIL-AF.** An analysis that replicated the same distribution of the 4 DOACs as was used in FRAIL-AF ("same DOAC mix") demonstrated no difference in stroke or SEE (HR: 0.92 [95% CI: 0.71-1.18]) between SD-DOAC and warfarin, but significantly lower risks of hemorrhagic stroke (HR: 0.35 [95% CI: 0.15-0.64]), fatal bleeding (HR: 0.55 [95% CI: 0.32-0.90]), and ICH (HR: 0.48 [95% CI: 0.32-0.73]) with SD-DOAC. However, higher risks of major (HR: 1.21 [95% CI: 1.00-1.44]), gastrointestinal (HR: 2.16 [95% CI: 1.68-2.72]), and major or CRNM bleeding (HR: 1.15 [95% CI: 1.04-1.26]) occurred with SD-DOAC vs warfarin when the DOAC mix matched that of the FRAIL-AF trial. Mortality and NCOs were similar between SD-DOAC and warfarin (Supplemental Figure 3A).

**Apixaban and edoxaban only.** Restricting the analysis to 3,637 patients enrolled in the ARISTOTLE (apixaban vs warfarin) and ENGAGE AF-TIMI 48 (edoxaban vs warfarin) trials, the efficacy, mortality, and net outcome results were consistent with the results that included data with all 4 SD-DOACs vs warfarin (Supplemental Figure 3). However, neither major bleeding nor major or CRNM bleeding were increased, the excess in gastrointestinal bleeding was less marked, and the reduction in ICH even more pronounced when restricting the DOACs to apixaban and edoxaban (Supplemental Figure 3B).

## DISCUSSION

Given that AF is common among elderly patients, many of whom are frail and at a heightened risk for both thromboembolic and bleeding events, it is critical to select an antithrombotic therapy that maximized both efficacy and safety. In this analysis of frail, elderly, VKA-experienced patients who were randomized to receive SD-DOAC or warfarin in the COMBINE-AF study, we found no significant treatment-outcome interactions with SD-DOAC vs warfarin for the outcomes of stroke/SEE and mortality and thus concluded that the findings were consistent with those in the overall COMBINE-AF meta-analysis, in which stroke or SEE was reduced by 19% (HR: 0.81 [95% CI: 0.74-0.89]) and all-cause death was reduced by 8% (HR: 0.92 [95% CI:

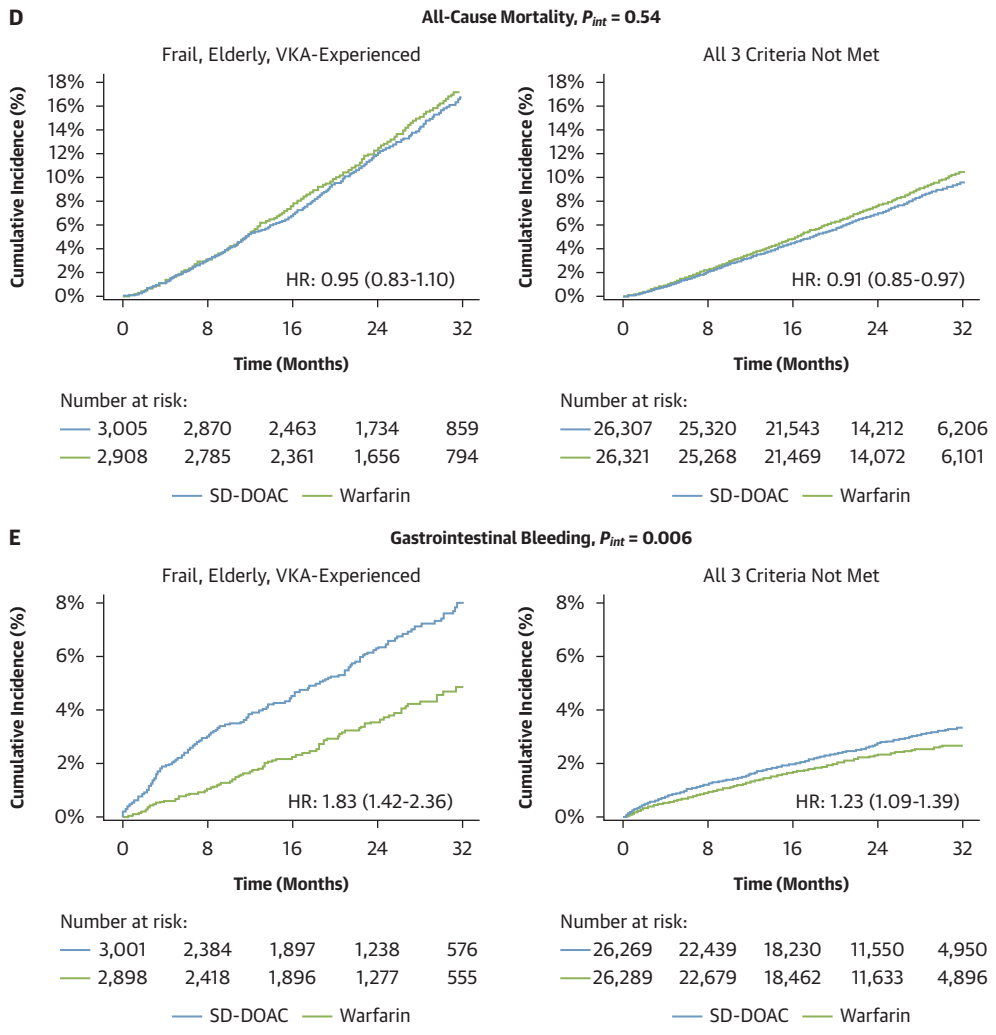
**FIGURE 2** KM Curve From COMBINE-AF: NOAC vs Warfarin for the Key Endpoints




Figures on the left refers to the frail, elderly, and VKA-experienced cohort. Figures on the right refers to those that did not meet all 3 criteria. Kaplan-Meier curves are shown comparing SD-DOAC vs warfarin for the following endpoints: (A) primary efficacy endpoint (stroke/SEE); (B) primary safety endpoint (major bleeding); (C) intracranial hemorrhage; (D) all-cause mortality; and (E) major gastrointestinal bleeding. COMBINE-AF = A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulation Use in Atrial Fibrillation; KM = Kaplan Meier; NOAC = Non-Vitamin K antagonist Oral Anticoagulants; other abbreviations as in Figure 1.

*Continued on the next page*

**FIGURE 2 Continued**

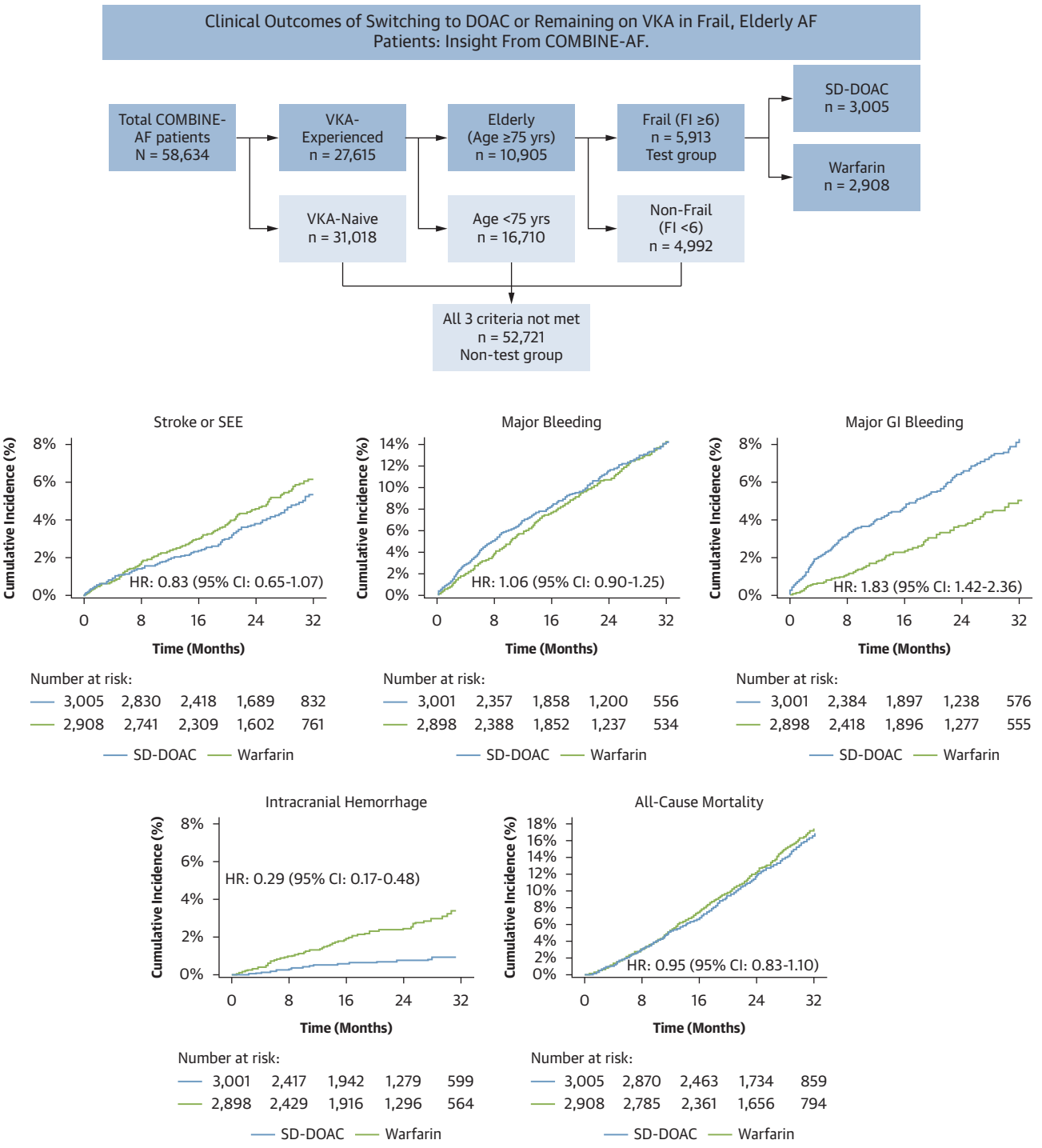



0.87-0.97]).[12] Importantly, switching to SD-DOAC in this vulnerable population significantly reduced the most severe types of bleeding, including intracranial hemorrhage, hemorrhagic stroke, and fatal bleeding, aligning with the key findings of the COMBINE-AF meta-analysis.[12] Counterbalancing these benefits, switching to SD-DOAC significantly increased gastrointestinal bleeding even further in frail, elderly, VKA-experienced patients, resulting in rates of extracranial, major, and CRNM bleeding that were less favorable than with warfarin. Overall, net outcomes were similar with SD-DOAC and warfarin in the frail, elderly, VKA-experienced patients, whereas the primary net outcome was significantly reduced with SD-DOACs in patients without all 3 criteria.

In the 1990s, 6 placebo-controlled randomized trials demonstrated that warfarin reduces stroke by 64% but substantially increased the risk of bleeding and ICH.[35,36] However, VKAs have a narrow therapeutic window, relatively long onset and offset of action, and multiple food and drug interactions. Because of these complexities, adherence to VKA is no more than 80% after the first year and decreases about 10% each year. Thus, patients who are well-controlled and remain on long-term on VKA treatment tend to be a selected subset.[37] Whether frail, elderly patients would benefit from switching to a SD-DOAC vs remaining on a VKA remained an open question despite over a decade since the introduction and rapid, widespread adoption of DOACs as the anticoagulant of choice for stroke prevention in AF.[38,39]

In the open-label FRAIL-AF trial[10] of 1,330 elderly frail patients on a long-term VKA,

## CENTRAL ILLUSTRATION SD-DOAC vs Warfarin in Older VKA-Experienced Patients




**Nicolau AM, et al. JACC. 2025;86(6):426–439.**

Standard-dose direct oral anticoagulant (SD-DOAC) is a reasonable choice for frail, elderly, vitamin K antagonist (VKA)-experienced patients to reduce stroke and systemic embolism, death, and the most serious types of bleeding. AF = atrial fibrillation; COMBINE-AF = A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulation Use in Atrial Fibrillation; FI = frailty index; GI = gastrointestinal; SEE = systemic embolic event; VKA = vitamin K antagonist.

**TABLE 3 Safety and Net Clinical Outcomes in COMBINE-AF of DOAC vs Warfarin Group**

| | Frail, Elderly, VKA Experienced Patients (n = 5,903) | | | | | All 3 Criteria Not Met (n = 52,721) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Warfarin (n = 2,908) | | SD-DOAC (n = 3,005) | | | Warfarin (n = 26,364) | | SD-DOAC (n = 26,357) | | | |
| | n | %/y | n | %/y | HR (95% CI) | n | %/y | n | %/y | HR (95% CI) | $P_{int}$ Value |
| Major bleeding | 269 | 5.58 | 282 | 5.89 | 1.06 (0.90-1.25) | 1,464 | 3.23 | 1,197 | 2.66 | 0.82 (0.76-0.89) | 0.007 |
| Fatal bleeding | 27 | 0.54 | 12 | 0.24 | 0.46 (0.23-0.90) | 133 | 0.29 | 83 | 0.18 | 0.63 (0.48-0.83) | 0.38 |
| Intracranial bleeding | 66 | 1.33 | 19 | 0.38 | 0.29 (0.17-0.48) | 343 | 0.74 | 165 | 0.36 | 0.48 (0.40-0.58) | 0.06 |
| Major or CRNM bleeding | 649 | 14.67 | 634 | 14.42 | 1.00 (0.90-1.12) | 3,744 | 8.77 | 3,271 | 7.63 | 0.87 (0.83-0.91) | 0.018 |
| GI bleeding | 91 | 1.85 | 164 | 3.37 | 1.83 (1.42-2.36) | 478 | 1.04 | 580 | 1.28 | 1.23 (1.09-1.39) | 0.006 |
| CRNM bleeding | 432 | 9.52 | 407 | 8.97 | 0.97 (0.85-1.11) | 2,501 | 5.76 | 2,259 | 5.19 | 0.90 (0.85-0.95) | 0.32 |
| Primary NCO[a] | 658 | 11.92 | 682 | 12.05 | 1.01 (0.91-1.13) | 3,732 | 7.47 | 3,349 | 6.65 | 0.89 (0.85-0.93) | 0.028 |
| Secondary NCO[b] | 481 | 8.39 | 457 | 7.64 | 0.91 (0.80-1.03) | 2,771 | 5.41 | 2,443 | 4.74 | 0.87 (0.83-0.92) | 0.55 |

HRs are defined as DOAC vs warfarin. [a]Primary NCO = stroke, systemic embolic events, major bleeding, death. [b]Secondary NCO = stroke, systemic embolic events, intracranial hemorrhage, death.
CRNM = clinically relevant nonmajor bleeding; other abbreviations as in Tables 1 and 2.

investigators reported that switching to a DOAC significantly increased the primary composite endpoint of major or CRNM bleeding after 344 days of median follow-up. These results were driven by excesses in major gastrointestinal bleeding (9 events vs 1 events) and CRNM gastrointestinal (8 vs 3), urogenital (20 vs 11), and skin (23 vs 10) bleeding events. Because the trial was designed to determine whether DOACs reduce major or CRNM bleeding, it was terminated early for futility. No differences between treatment groups were seen in thromboembolic events, fatal bleeding, or mortality, although there were few events, resulting in low power.[20]

Although a direct comparison between the results from these 2 studies was not our objective, the subgroup and sensitivity analyses conducted in this paper provide some insight into the divergent findings between the FRAIL-AF trial and our results. It is important to note that there are 2 conceptually different approaches to identifying frail individuals. We assessed frailty as a state of accumulated health deficits (clinical conditions) that result in poor health to construct an FI.[40] The FRAIL-AF trial used the Groningen Frailty Indicator (GFI), which is one of several tools used to identify frailty as a syndrome.[41] The GFI approach uses a questionnaire to evaluate 6 domains of health (mobility, vision and hearing,

**TABLE 4 Comparison of Outcomes in the FRAIL-AF Trial With the Frail, Elderly, VKA-Experienced Population in COMBINE-AF**

| | FRAIL-AF (n = 1,330) | COMBINE-AF: All SD-DOAC (n = 5,913)[a] | COMBINE-AF: Same DOAC Mix as FRAIL-AF (n = 2,046) | COMBINE-AF: Apixaban and Edoxaban Only (n = 3,637) | COMBINE-AF: Age ≥80 y (n = 2,755) | COMBINE-AF: Age ≥85 y (n = 760) |
|---|---|---|---|---|---|---|
| Stroke/SEE[b] | 1.26 (0.60-2.61) | 0.83 (0.65-1.07) | 0.92 (0.71-1.18) | 0.92 (0.67-1.27) | 0.96 (0.68-1.35) | 0.90 (0.49-1.67) |
| All stroke | 1.30 (0.59-2.87) | 0.84 (0.65-1.08) | 0.91 (0.69-1.17) | 0.95 (0.68-1.32) | 0.89 (0.62-1.28) | 0.85 (0.44-1.64) |
| Ischemic stroke | NA | 1.04 (0.78-1.40) | 1.17 (0.85-1.56) | 1.14 (0.78-1.66) | 1.14 (0.75-1.73) | 1.24 (0.56-2.73) |
| Hemorrhagic stroke | NA | 0.37 (0.19-0.70) | 0.35 (0.15-0.64) | 0.48 (0.22-1.07) | 0.35 (0.15-0.83) | 0.38 (0.07-1.99) |
| Major bleeding | 1.52 (0.81-2.87) | 1.06 (0.90-1.25) | 1.21 (1.00-1.44) | 0.83 (0.67-1.04) | 0.99 (0.78-1.26) | 0.96 (0.61-1.49) |
| ICH | NA | 0.29 (0.17-0.48) | 0.48 (0.32-0.73) | 0.16 (0.07-0.36) | 0.37 (0.20-0.71) | 0.48 (0.15-1.57) |
| GI bleeding | NA | 1.83 (1.42-2.36) | 2.16 (1.68-2.72) | 1.36 (0.97-1.91) | 1.72 (1.19-2.47) | 1.99 (1.02-3.91) |
| Major or CRNM | 1.69 (1.23-2.32) | 1.00 (0.90-1.12) | 1.15 (1.04-1.26) | 0.84 (0.74-0.97) | 0.99 (0.85-1.16) | 1.03 (0.77-1.39) |
| CRNM | 1.77 (1.24-2.52) | 0.97 (0.85-1.11) | 1.13 (1.02-1.25) | 0.85 (0.72-1.00) | 0.97 (0.80-1.18) | 1.02 (0.70-1.49) |
| Mortality | 0.96 (0.64-1.45) | 0.95 (0.83-1.10) | 0.88 (0.75-1.01) | 0.94 (0.78-1.13) | 0.98 (0.81-1.19) | 0.87 (0.63-1.21) |
| Primary NCO | NA | 1.01 (0.91-1.13) | 1.03 (0.92-1.16) | 0.94 (0.82-1.08) | 1.02 (0.88-1.18) | 0.91 (0.69-1.18) |
| Secondary NCO | NA | 0.91 (0.80-1.03) | 0.90 (0.79-1.03) | 0.88 (0.75-1.04) | 0.97 (0.81-1.15) | 0.90 (0.66-1.22) |

Values are HR (95% CI). [a]n for COMBINE-AF: same DOAC mix as FRAIL-AF based on 1,000 samples with same mix of DOACs. [b]Stroke/SEE for FRAIL-AF trial was a composite of ischemic stroke, transient ischemic attack, and peripheral arterial thromboembolism. Primary NCO: stroke/SEE, major bleeding, or death; secondary net clinical outcome: stroke/SEE, intracranial hemorrhage (ICH), or death.
NA = not available; other abbreviations as in Tables 1 and 2.

nutrition, comorbidity, physical fitness, and cognition and psychosocial). These 2 distinct conceptual approaches may identify different subpopulations of individuals as frail. However, in the absence of a consensus on how frailty should be defined and assessed,[42] both general approaches are widely used in frailty research[28] to identify "frail" individuals who have diminished physiologic reserve leading to an increased vulnerability to adverse health outcomes.[28,41] Supplemental Table 1 provides further comparisons between these 2 methods to identify frail individuals.

Compared with the FRAIL-AF trial population, our study population had a greater burden of risk factors for stroke (eg, higher $CHA_2DS_2$-VASc score, more frequent prior stroke or TIA) and bleeding (eg, more frequent history of major bleeding), with the exception of age (Supplemental Table 2). However, in the subgroup analysis restricted to patients age >80 years (median age 83 years), the efficacy and safety outcomes with SD DOACs vs warfarin were qualitatively similar to the main cohort (**Table 4**, Supplemental Figure 2A). Prior research[41] comparing different assessments of frailty further supports our observations that the frail population identified in COMBINE-AF was at higher risk than those enrolled in the FRAIL-AF trial. In the FRAIL-AF trial, the minimum GFI was 3, and the median was 4 (low risk on the GFI scale is 0-3, and moderate risk is 4-6). Whereas in the current analysis, the minimum FI score index was 0.33 and the median was 0.39 (moderate risk is considered 0.20-0.39). Of note, the median FI score of 0.39 in the current analysis correlates to a median GFI of 6, which is higher than the median GFI of 4 in the FRAIL-AF trial. It is possible that the lower-risk population in FRAIL-AF (eg, higher median eGFR, lower $CHA_2DS_2$-VASc score, less frequent history of major bleeding) compared with the test cohort from COMBINE-AF, explains some of the divergent results.[18,43-49] Of note, the time-in-therapeutic range in FRAIL-AF was not provided, while it was 69% (median) in our test cohort.

Furthermore, 2 sensitivity analyses exploring the potential influence of the DOAC selection may have on outcomes in this vulnerable population point to another factor that likely contributed to the divergent findings between these 2 studies. In the FRAIL-AF trial, rivaroxaban was used in more than one-half of the patients randomized to DOAC. In contrast, in COMBINE-AF, 18% were treated with rivaroxaban and the majority received either apixaban or edoxaban (the 2 DOACs with a more favorable safety profile in elderly and frail patients).[14,30-34] In the first sensitivity analysis modeling the same distribution of DOACs in COMBINE-AF as was used in the FRAIL-AF trial, the HRs for SD-DOACs vs warfarin for both major bleeding and for major or CRNM bleeding were significantly increased (ie, less favorable for SD-DOAC). A second sensitivity analysis restricting the DOACs to apixaban and edoxaban showed relatively more favorable bleeding outcomes with these 2 DOACs vs warfarin. Specifically, we observed significant *reductions* in major bleeding and of major or CRNM bleeding, and a less marked, statistically nonsignificant increase in gastrointestinal bleeding in the sensitivity analysis restricted to apixaban and edoxaban vs warfarin (**Table 3**, Supplemental Figure 3). Thus, frail, elderly VKA-experienced patients who switch to a DOAC may experience differences in bleeding outcomes dependent upon which DOAC is selected.

The findings from this study suggest that switching to an SD-DOAC is a reasonable strategy for frail, elderly, VKA-experienced patients, particularly for reducing the risk of stroke, systemic embolism, death, and the most severe bleeding events, such as intracranial and fatal bleeding. These results offer important, new, and more detailed evidence relevant to the recommendation in the 2024 European Society of Cardiology guidelines for the management of AF,[19] which state, "Maintaining VKA treatment rather than switching to a DOAC may be considered in patients aged ≥75 years on clinically stable therapeutic VKA with polypharmacy to prevent excess bleeding risk." In addition, our findings that both major and major or clinically relevant nonmajor bleeding were significantly reduced in the analysis restricted to apixaban or edoxaban vs warfarin warrant further evaluation in future studies of frail individuals and consideration in future guidelines.

**STUDY STRENGTHS AND LIMITATIONS.** The strengths of the current analysis from COMBINE-AF, a patient-level meta-analysis of 4 randomized trials of DOACs vs warfarin, include the large size (4.5-fold larger population than FRAIL-AF) and longer-term follow-up (>2-fold longer than FRAIL-AF), more rigorous design (randomized, double-blind, active control in the 3 Factor Xa inhibitor trials, PROBE design in the RE-LY trial with dabigatran vs warfarin), with independent blinded endpoint adjudication by an expert committee. The >10-fold increase in patient-years of follow-up resulted in >8-fold more bleeding events, >9-fold more ischemic events, and >8-fold more deaths than in the FRAIL-AF trial, thus providing for more reliable estimates of the HRs (Supplemental Figure 4).

Important limitations of this analysis arise from the post hoc nature of this subgroup analysis. This includes, but is not limited to, the post hoc definition of frailty, which was based on a modification of Rockwood's deficit accumulation model—a well-validated tool to assess frailty as an accumulation of clinical conditions. This differs from the classical Fried frailty phenotype that describes a clinical syndrome of individuals with altered metabolism combined with abnormal stress response.[50] We could not use traditional geriatric assessment for frailty,[51,52] such as the Groningen Frailty Indicator used in FRAIL-AF, because these large global pivotal outcome trials were conducted more than a decade ago with the focus on evaluation of clinical efficacy and safety in a broad, rather than frail, population. It is important to note that frailty in the FRAIL-AF trial, included factors such as social isolation, inability to walk around in the home, and cognitive impairment, were not available in the COMBINE-AF data set and represent a different approach from the cumulative deficit model used in our analysis to identify frail patients.[23] As a result, this analysis utilized an alternative accepted approach to identify frail individuals, and comparisons of treatment outcomes between these 2 methods need to consider that these 2 approaches likely identify overlapping but non-equivalent frailty subgroups. In addition, this subgroup analysis was not prespecified, some events were infrequent resulting in lower power, and adjustments for multiplicity were not undertaken. Also, in this analysis, the prevalence of frailty among elderly, VKA-experienced patients was 54%, which is slightly higher than previously reported.[53-55] Nevertheless, the elderly, frail, VKA-experienced group in COMBINE-AF had similar to greater comorbidity and experienced higher rates of ischemic or hemorrhagic events than the population in the ANAFIE (All Nippon AF In the Elderly) Registry of >30,000 Japanese patients with AF and in the FRAIL-AF trial (Supplemental Table 2). Finally, the external validity of the findings of a clinical trial is a limitation of this study because patients included in these trials are more motivated in terms of health behaviors. Additional dedicated randomized trials in frail populations with cardiovascular disease are needed.

## CONCLUSIONS

In 5,913 frail, elderly, VKA-experienced AF patients from the 4 large randomized clinical trials of SD-DOAC vs warfarin, switching to an SD-DOAC resulted in stroke and mortality outcomes that were consistent with those seen in the overall cohorts of 58,634 patients randomized in the 4 pivotal trials of SD-DOAC vs warfarin. Rates of major bleeding, major or CRNM bleeding, and the primary net outcome were similar between switching to SD-DOAC and remaining on warfarin, whereas these outcomes were significantly reduced with SD-DOAC in patients without all 3 criteria. Gastrointestinal bleeding was increased to a greater degree with SD-DOACs in the frail, elderly, and VKA-experienced subgroup. Importantly, hemorrhagic stroke, ICH, and fatal bleeding were significantly reduced with switching to a SD-DOAC compared with remaining on VKA. Based on these findings, after shared decision making, SD-DOAC is a reasonable choice for frail, elderly, VKA-experienced patients to reduce stroke and systemic embolism, death, and the most serious types of bleeding (ICH and fatal bleeding).

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Giugliano has received research support from Anthos Therapeutics, Daiichi-Sankyo, and Novartis; has received honoraria for lectures from Daiichi-Sankyo, Medical Education Resources, Menarini, SAJA Pharmaceuticals, Shanghai Medical Technology, and SUMMEET; and has received consulting fees from Artivion, Celecor, Daiichi-Sankyo, Novartis, Perosphere, PhaseBio Pharmaceuticals, Samsung, Sanofi, SFJ Pharmaceuticals, and Thrombosis Research Institute. Dr Steffel has received consultant and/or speaker fees from Abbott, Bayer, Berlin-Chemie, Biosense Webster, Biotronik, Boehringer Ingelheim, Boston Scientific, Daiichi-Sankyo, Medscape, Medtronic, Menarini, Pfizer, Saja, Servier, and WebMD; and has ownership of Swiss EP and CorXL. Dr Eikelboom has received honoraria and/or research support from Anthos, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Idorsia, Janssen, Merck, and Pfizer. Dr Granger has received consulting fees from AbbVie, Abiomed, Alnylam Pharmaceuticals, Amgen, Anthos, Bayer Corporation, Boehringer Ingelheim, Boston Scientific Corporation, Bristol Myers Squibb, Cardionomic, CeleCor Therapeutics, Janssen Pharmaceutical, Merck, Novo Nordisk, Novartis, Pfizer, Philips, and Roche; has salary funded by Duke grants sponsored by Alnylam Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Janssen Pharmaceuticals, National Heart, Lung, and Blood Institute, Novartis, Pfizer, and Philips; and has equity in tenac.io. Dr Patel has received consulting fees from Bayer, Janssen, and Novartis; and has received research grants from the National Heart, Lung, and Blood Institute, Bayer, Novartis, and Philips. Dr Lopes has received research grants or contracts from Amgen, Bristol Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer, and Sanofi; has received funding for educational activities or lectures from Pfizer, Daiichi-Sankyo, and Novo Nordisk; and has received funding for consulting or other services from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, and Novo Nordisk. Dr Ruff has received research grants through Brigham and Women's Hospital from Anthos, AstraZeneca, Daiichi-Sankyo, Janssen, and Novartis; and has received honoraria for scientific advisory boards and consulting from Anthos, Bayer, Bristol Myers Squibb, Daiichi-Sankyo, Janssen, and Pfizer. Dr Braunwald has received research grants through his institution from AstraZeneca, Daiichi-Sankyo, Merck, and Novartis; and has consulted for Amgen, Bristol Myers Squibb, Boehringer Ingelheim, Cardurion, Edgewise, and Verve. Dr Wallentin has received institutional research grants

from Bristol Myers Squibb/Pfizer, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, and Roche Diagnostics; and is a patent holder on GDF-15 for prognostication in acute coronary syndrome. Mr Palazzolo, Dr Ruff, Dr Antman, Dr Braunwald, and Dr Giugliano are members of the TIMI Study Group, which has received institutional research grant support through Brigham and Women's Hospital from Abbott, Amgen, Anthos Therapeutics, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc, Daiichi-Sankyo, Eisai, Intarcia, MedImmune, Merck, Novartis, Pfizer, Quark Pharmaceuticals, Regeneron Pharmaceuticals, Inc, Roche, Siemens Healthcare Diagnostics, Inc, The Medicines Company, and Zora Biosciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**KEY WORDS** atrial fibrillation, directing acting oral anticoagulant, elderly, frail, vitamin K antagonist

**APPENDIX** For supplemental tables and figures as well as the COMBINE AF Analysis Proposal Form, please see the online version of this paper.