Should frail elderly AF patients on VKA switch to a DOAC?

A randomized comparison from COMBINE-AF, a patient-level metanalysis of 4 large RCTS of DOAC vs Warfarin

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BACKGROUND

FRAIL-AF was an open-label RCT in 1330 elderly, frail pts with AF on VKA who were randomized to either continued VKA or switching to DOAC. After 1 year of follow-up, switching to DOAC (54% rivaroxaban) led to increased bleeding without a benefit in thromboembolic events.

Our objetive is to revisit this hypothesis using the larger and longer study period of the COMBINE-AF database, an individual patient-level metanalysis of the 4 pivoval RCTs of DOAC vs Warfarin.

METHODS

We conducted a patient-level metanalysis in frail, elderly VKA-experienced pts with AF enrolled in the 4 large RCTs of DOAC vs. Warfarin (COMBINE-AF). To assess frailty, we utilized a modified Rockwood's accumulation model that included 18 age-related chronic conditions to build a comprehensive frailty index (FI-18). Each of the 18 conditions counted as 1 point. Pts with FI-18 ≥6 were classified as frail.

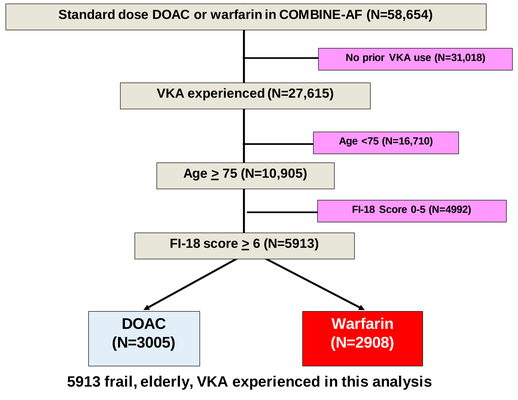
Additionally, multiple sensitivity analysis were performed, including:

1. Replicating the relative proportion of DOACs used in the FRAIL-AF trial
2. Restricting DOACs to apixaban or edoxaban only
3. Restricting to patients age ≥80
4. Employing 5 other frailty surrogates: CHADS-VASc score, high-risk factors for adverse outcomes, polypharmacy, Charlson Comorbidity Index, and high risk of falls.

Prespecified outcomes were: stroke (ischemic, hemorrhagic), systemic embolic events (SEE), major bleeding (ICH, GI, other), death, and a net clinical outcome combing these events.

RESULTS

Figure 1 – Consort Diagram



5913 frail, elderly, VKA experienced in this analysis

DISCLOSURES

RP Giugliano: Research grant support to his institution from Anthos, Daiichi-Sankyo; Honoraria for CME programs/lectures from Daiichi Sankyo, Medical Education Resources, Menarini, SAJA, Servier; Consulting fees from Artivion, Daiichi Sankyo, Inaria, PhaseBio Pharmaceuticals, Samsung, Sanofi

Table 1 – Baseline Characteristics

Characteristics	DOAC N=3005	Warfarin N=2908
Age, mean (SD)	80 (4) yrs	80 (4) yrs
Women	41%	42%
CHA_2DS_2-VASc score, median [IQR]	5 [4-6]	5 [4-6]
Congestive heart failure	52%	50%
Hypertension	92%	93%
Diabetes	37%	38%
Stroke or TIA	32%	33%
Vascular disease	56%	55%
History GI bleeding	7.5%	7.5%
FI-18 score (# frailty factors) [IQR]	7 [6-8]	7 [6-8]
Gencer* High risk factors, median [IQR]	4 [3-5]	4 [3-5]
# Co-medications, median	4 [3-5]	4 [3-5]
Charlson Comorbidity Score, median [IQR]	2 [0-2]	2 [0-2]
High fall risk	13%	14%
DOAC used	A=28%, D=20% E=33%, R=18%	N/A

*Gencer, AHJ 2022;247:24-32

P >0.10 for each comparison

FIG 2 – Outcomes DOAC vs warfarin

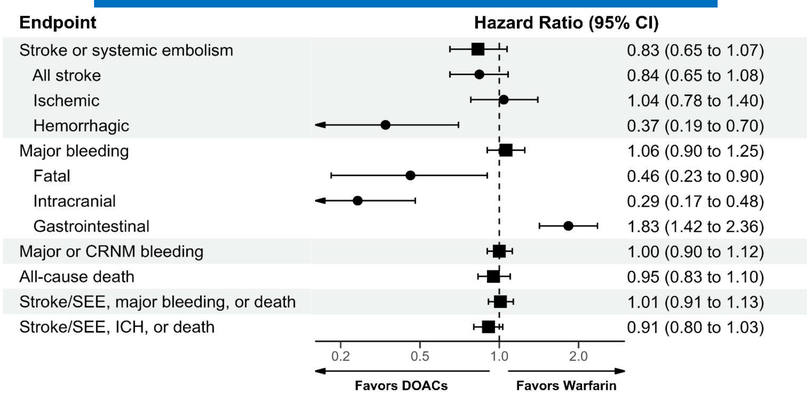


FIG 3 – KM curves DOAC vs warfarin

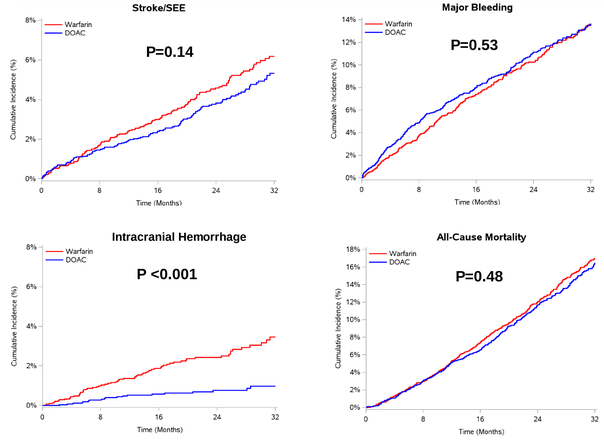
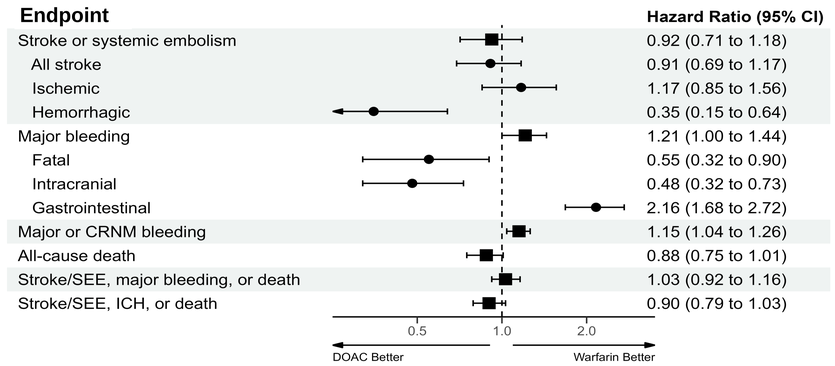
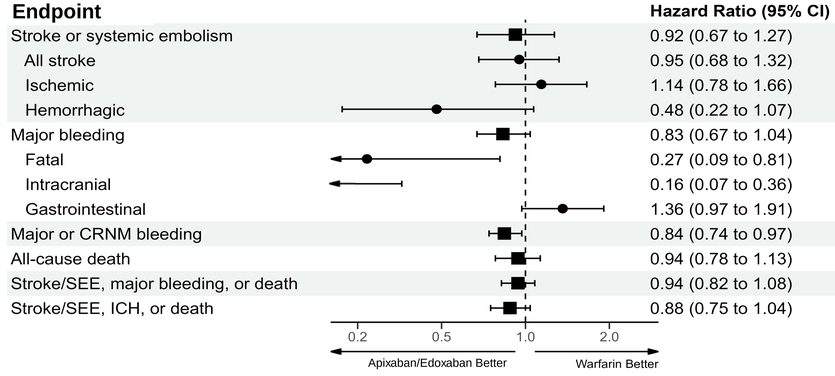


FIG 4 – Replicating the Same DOAC Mix* as in FRAIL–AF Trial



*Rivaroxban 54%, Apixaban 19%, Edoxaban 18%, Dabigatran 9%

FIG 5 – Outcomes with Apixaban and Edoxaban vs Warfarin



DISCUSSION

In contrast to the FRAIL-AF trial results, this larger and longer-term analysis of frail, elderly VKA-experienced patients from COMBINE-AF showed that patients randomized to DOAC had similar rates of ischemic stroke, major bleeding, death and net outcomes compared to warfarin. Hemorrhagic stroke and ICH were significantly reduced with DOACs, but major GI bleeding was significantly increased compared to warfarin.

Important differences from the FRAIL-AF trial include >4x number of patients with 2.7x longer follow-up yielding **7.9x** more major or CRNM bleeding events, with a more balanced use of individual DOACs, and independent blinded event adjudication.

CONCLUSION

In 5913 frail, elderly, VKA-experienced AF pts from the 4 large RCTs of DOAC vs warfarin followed for 2.7 years, results were consistent with those seen in the total cohorts. Our findings do not support the results reported in the FRAIL-AF trial.