Patient-Centered Evaluation of DOACs versus Warfarin in Atrial Fibrillation:

A Weighted Composite and Win Statistics Analyses of the COMBINE-AF Dataset

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Beyond Traditional Outcomes

- Current Landscape: Pivotal trials comparing DOACs vs. Warfarin in AF [1-4] have established standard efficacy and safety profiles.
- Unmet Need: Traditional analyses do not routinely incorporate patient preferences regarding the trade-off between stroke prevention and bleeding avoidance.

Objective:

- To provide a more holistic evidence base for shared decision-making by applying patient-centered approaches:

  - Weighted Composite Endpoint (WCE)
  - Win Statistics

(1-4) RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48

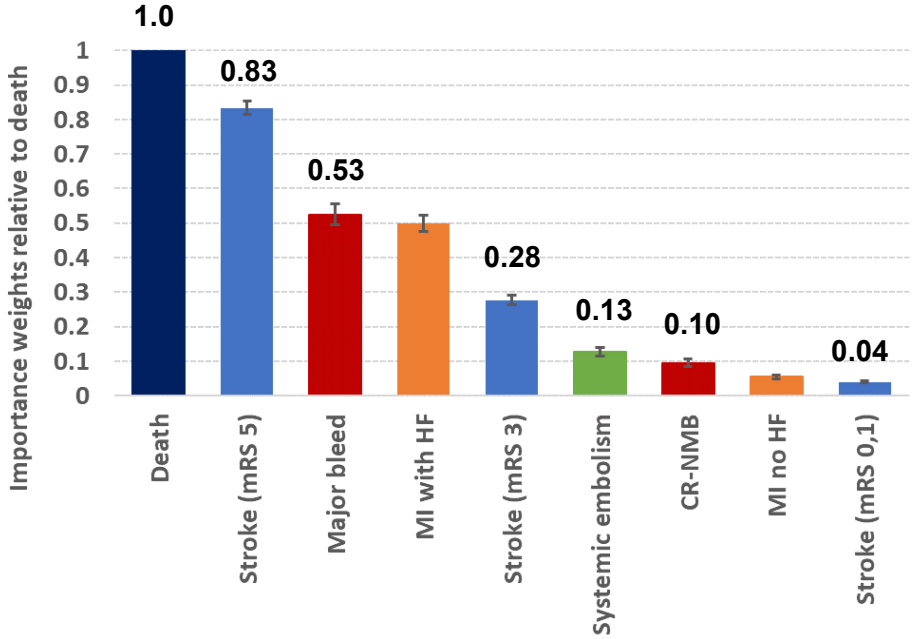
COMBINE-AF

- Data Source: Individual patient data from 58,634 participants across 4 pivotal trials (RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48).

- Comparison: Standard-dose DOACs vs. Warfarin.

Patient Preference Weights

- Seven clinical outcomes were weighted based on patient preferences (n=1,028) using object-case best–worst scaling.(1)
- All values were scaled relative to Death (1.0).
- These values were applied as:
  - Numerical weights for Weighted Composite Endpoint (WCE)
  - Hierarchical order for Win Statistics



Note: MI was excluded due to incompatibility with preference weights (distinguishing MI w/ vs w/o HF).

(1) PEARL-AF study: S. Reed et al. ***JACC: Advances*** 2024

Weighted Composite Endpoint (WCE) and Win Statistics

Weighted Composite Endpoint (WCE)

- **Method:** Survival-based approach incorporating weights of all initial and recurrent events.
  (Note: Unlike time-to-first-event, if a patient bleeds and later dies, the weights of both events are counted.)
- **Metric:** Calculates the expected number of "death-equivalent" events per 100 patients at 2 years.
  (e.g., Since weights are scaled to death [1.0], two Major Bleeds [0.53 x 2] are approximately equivalent to one Death.)
- **Primary Outcome:** The 2-year difference in "death-equivalent" events per 100 patients.

Win Statistics

- **Method:** Pairwise comparisons using outcomes hierarchically ordered based on patient preference weights.
- **Primary Outcome:** Win Ratio (Stratified).

Prespecified Subgroup Analysis = “FRAIL-AF”-like Population

- **The Clinical Dilemma (FRAIL-AF Trial)[1]**
  Switching to DOACs increased bleeding risk in frail, older, VKA-experienced patients.
  Early termination left the trial underpowered to assess ischemic events, creating a critical evidence gap.

- **Addressing the Evidence Gap**
  Nicolau et al. (COMBINE-AF, JACC 2025): Traditional analysis showed DOACs reduced stroke/SE, death, and serious bleeding (e.g., intracranial hemorrhage), supporting DOACs as a reasonable choice.

- **Current Patient-Centered Analysis**
  We extend this by applying patient-derived weights to capture the cumulative burden of *all* events.

- **Population (N=5,913)**
  Same definition as Nicolau et al.: Frail (FI-18 ≥6), Older (≥75 years), VKA-experienced.

(1) Joosten LPT et al. ***Circulation*** 2024

Baseline Characteristics

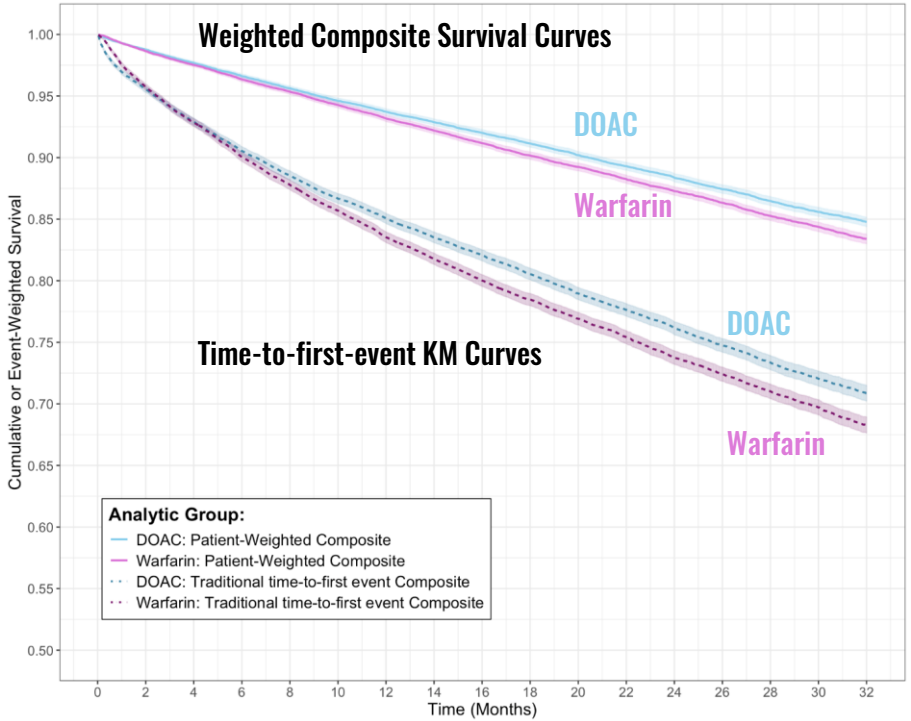
Characteristic	Overall Population (N = 58,634)	"FRAIL-AF"-like Population (N = 5,913)
Median Age, years	72 (IQR 65-77)	79 (IQR 77-82)
Female Sex	37%	41%
White	81%	90%
Body Mass Index (kg/m^2)	28.3	28.3
Median $CHADS_2$ Score	3	4

Overall Population -Weighted Composite Endpoint (WCE)

Favors DOACs

("death-equivalent" events at 2 years)

Difference: -1.10 "death-equivalent" events at 2 years (95% CI: -1.58 to -0.62)



Time-to-first-event Kaplan-Meier curves are shown for visual context only; due to different analytic frameworks, they are not directly comparable.

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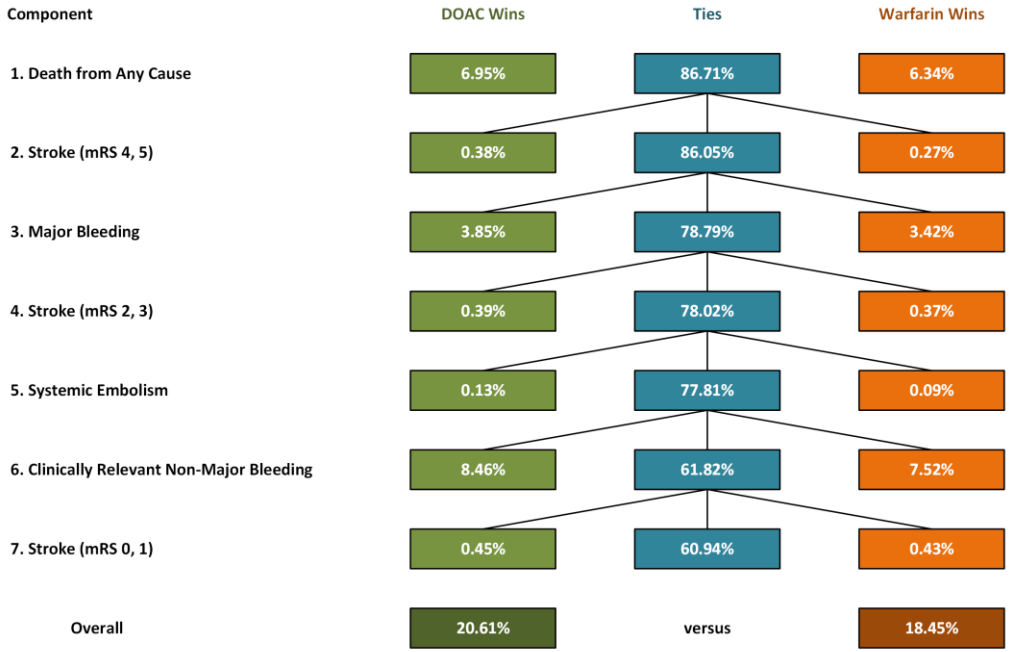
Overall Population - Win Statistics

DOAC (N=29,362) × Warfarin (N=29,272) = ~860 Million Pair

Favors DOACs



Win Ratio = 20.61%/ 18.45% = 1.11 (95% CI: 1.07 to 1.15)
Win Odds: 1.04 (95% CI: 1.03 to 1.06)
Net Benefit: +2.13% (95% CI: 1.45 to 2.81)

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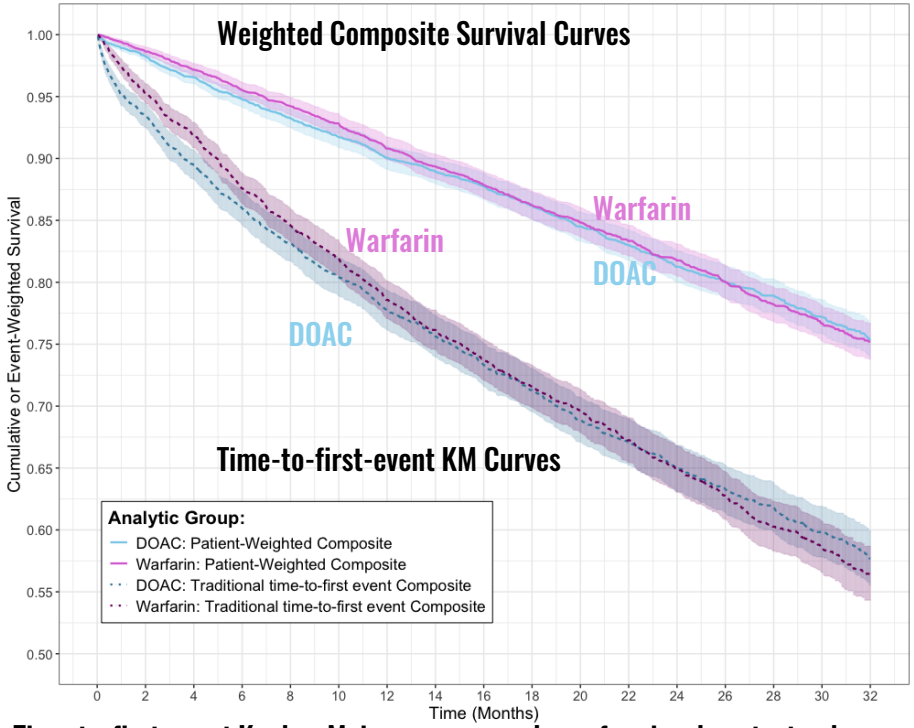
“FRAIL-AF”-like Population- Weighted Composite Endpoint (WCE)

No Significant Difference

(“death-equivalent” events at 2 years)

Difference: +0.51 “death-equivalent” events at 2 years (95% CI: -1.30 to 2.30)



Time-to-first-event Kaplan-Meier curves are shown for visual context only; due to different analytic frameworks, they are not directly comparable.

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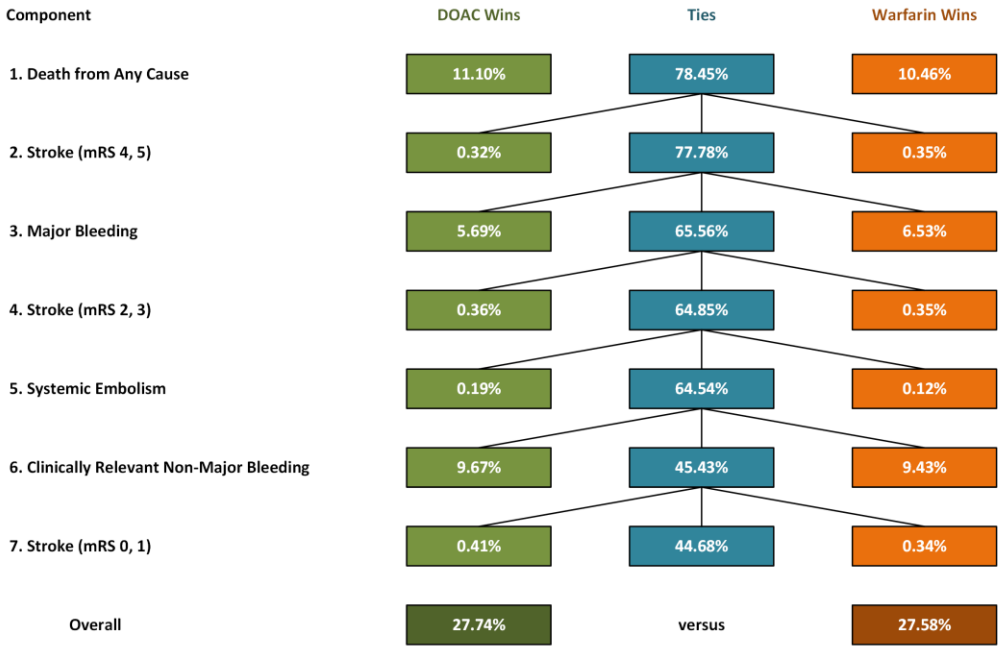
“FRAIL-AF”-like Population- Win Statistics

DOAC (N=3,005) × Warfarin (N=29,08) = ~8.7 million pair

No Significant Difference



Win Ratio = 27.74%/ 27.58% = 0.99 (95% CI: 0.90 to 1.08)
Win Odds: 0.99 (95% CI: 0.95 to 1.04)
Net Benefit: –0.37% (95% CI: –2.83 to 2.08)

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Limitations

- **Patient-Derived Weights:**
  - Weights derived from the PEARL-AF study (N=1,028) represent average preferences from a single U.S. cohort, potentially masking individual or cultural variations.
  - However, as the largest empirical preference study to date, these weights provide a robust and necessary starting point for quantifying patient values in clinical trials.

- **Imputation:**
  Missing mRS scores (26%) and uncollected CRNMB (RE-LY) required imputation, introducing potential uncertainty.

- **Subgroup Definition:**
  The "Frail, Older, VKA-experienced" subgroup was defined retrospectively using trial-specific criteria and may under-represent the most vulnerable populations.

Discussion & Conclusion

- In this patient-centered analysis of pivotal AF trials, DOACs were associated with a more favorable net clinical benefit than warfarin in the overall population.
- The Weighted Composite Endpoint (WCE) framework translated this advantage into a tangible, patient-valued metric—the prevention of approximately 1 "death-equivalent" event per 100 patients for 2 years.
- In frail, older, VKA-experienced patients, the overall net benefit was less clear. However, this finding contrasts with prior concerns about harm, supporting the view that a DOAC remains a reasonable choice for this complex population.
- These findings
  - underscore the value of patient-centered metrics for shared decision-making
  - serve as a robust methodological model to inform the design of future studies in other complex clinical conditions where trade-offs are central
  (e.g., left atrial appendage occlusion vs. anticoagulation, or statin therapy)