Circulation

ORIGINAL RESEARCH ARTICLE

# Direct Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation: Patient-Level Network Meta-Analyses of Randomized Clinical Trials With Interaction Testing by Age and Sex

# Background

- Direct oral anticoagulants (DOACs) are preferred over warfarin for stroke prevention in atrial fibrillation.
- Previously published trial-level meta-analyses used aggregate data from the 4 pivotal trials and demonstrated that DOAC use is associated with significant reductions in stroke, intracranial hemorrhage, and death compared with warfarin, with no statistically different risk of major bleeding.
- Study-level metaanalyses, however, are subject to important limitations.
- Metaanalyses using individual patient data offer substantial advantages over study-level data.

# AIM of the study

- To assess the overall safety and efficacy of DOACs versus warfarin, including 2 different DOAC treatment strategies (standard dose and lower dose).

# Methods

- Network meta-analysis.
- Data from the COMBINE AF (A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation) database which contains individual patient data from the 4 pivotal trials of DOACs versus warfarin in patients with AF.
- The primary efficacy outcome was a composite outcome of any stroke (ischemic, hemorrhagic, or other) or systemic embolism (ie, stroke or systemic embolism).
- Secondary efficacy outcomes included all-cause death, cardiovascular death, ischemic stroke, systemic embolism, hemorrhagic stroke, any stroke, and a composite efficacy outcome consisting of ischemic stroke, systemic embolism, or cardiovascular death.
- The primary safety outcome was major bleeding as defined by the International Society on Thrombosis and Haemostasis.
- Secondary safety outcomes included fatal bleeding, major or clinically relevant nonmajor bleeding, any bleeding (including fatal, major, clinically relevant nonmajor, or minor bleeding), intracranial bleeding, and gastrointestinal bleeding (adjudicated major bleeding events determined to be from gastrointestinal bleeding events only).

# Results (I)

- A total of 71 683 patients were included in these analyses ( n=29,362 randomized to standard-dose DOAC, n=13,049 randomized to lower-dose DOAC, and n=29,272 randomized to warfarin).
- No clinically meaningful differences were observed across randomized treatment groups.
- In the study population, the median age was 72 years, 37.3% were female, 34.5% had a CHADS2 score of 2, and 48.8% had a CHADS2 score ≥3 .
- More than two-thirds of patients (68.2%) had used a vitamin K antagonist (VKA) before randomization and 33.8% were on aspirin at baseline.
- A total of 19.6% of patients had creatinine clearance ≤50 at baseline.

# Results (II- efficacy)

- Compared with warfarin, patients randomized to **standard dose DOAC** had a lower hazard of stroke or systemic embolism (HR, 0.81 [95% CI, 0.74–0.89]) and a lower hazard of all-cause death, cardiovascular death, systemic embolism, hemorrhagic stroke, any stroke, and the composite efficacy outcome (ischemic stroke, systemic embolism, or cardiovascular death).
- Compared with warfarin, patients randomized to **lower dose DOAC** had no statistically different hazard of stroke or systemic embolism (HR, 1.06 [95% CI, 0.95–1.19]), but had a lower hazard of all-cause death, cardiovascular death, and hemorrhagic stroke and a significantly higher hazard of ischemic stroke compared with warfarin (HR, 1.35 [95% CI, 1.19–1.54]).

# Results (III- safety)

- Compared with warfarin, patients randomized to **standard-dose DOAC** had no statistically different hazard of major bleeding (HR, 0.86 [95% CI, 0.74–1.01]), but a lower hazard of fatal bleeding and intracranial bleeding .
- Compared with warfarin, patients randomized to **lower-dose DOAC** had a lower hazard of major bleeding (HR, 0.63 [95% CI, 0.45–0.88]) and a lower hazard of fatal bleeding, major or clinically relevant nonmajor bleeding, any bleeding, and intracranial bleeding.

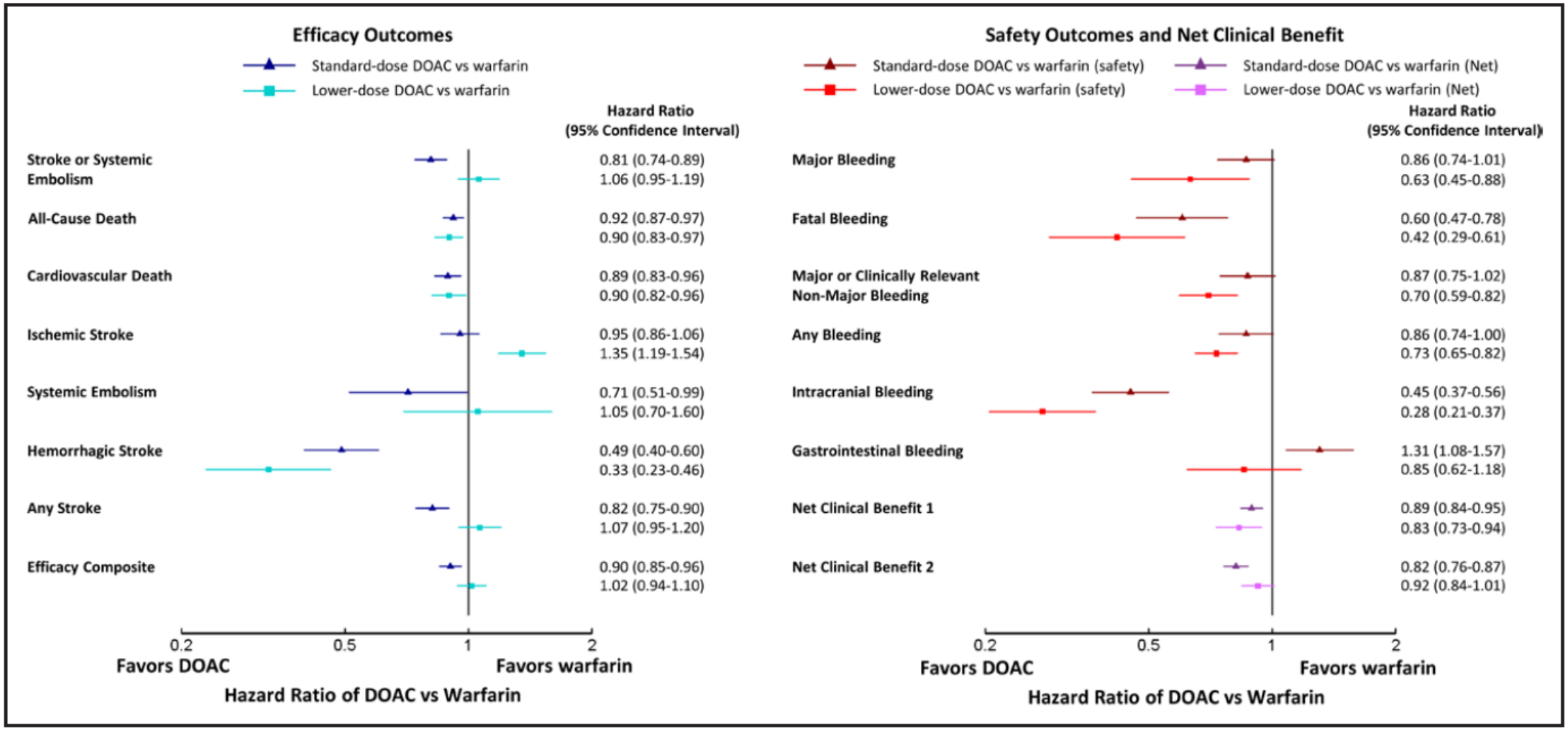


**Figure 1. Comparison of standard-dose and lower-dose direct oral anticoagulants vs warfarin for efficacy, safety, and net clinical benefit outcomes.**

Forest plots showing hazard ratios comparing standard-dose and lower-dose direct oral anticoagulants (DOACs) vs warfarin for efficacy outcomes (left) and safety and net clinical benefit outcomes (right).

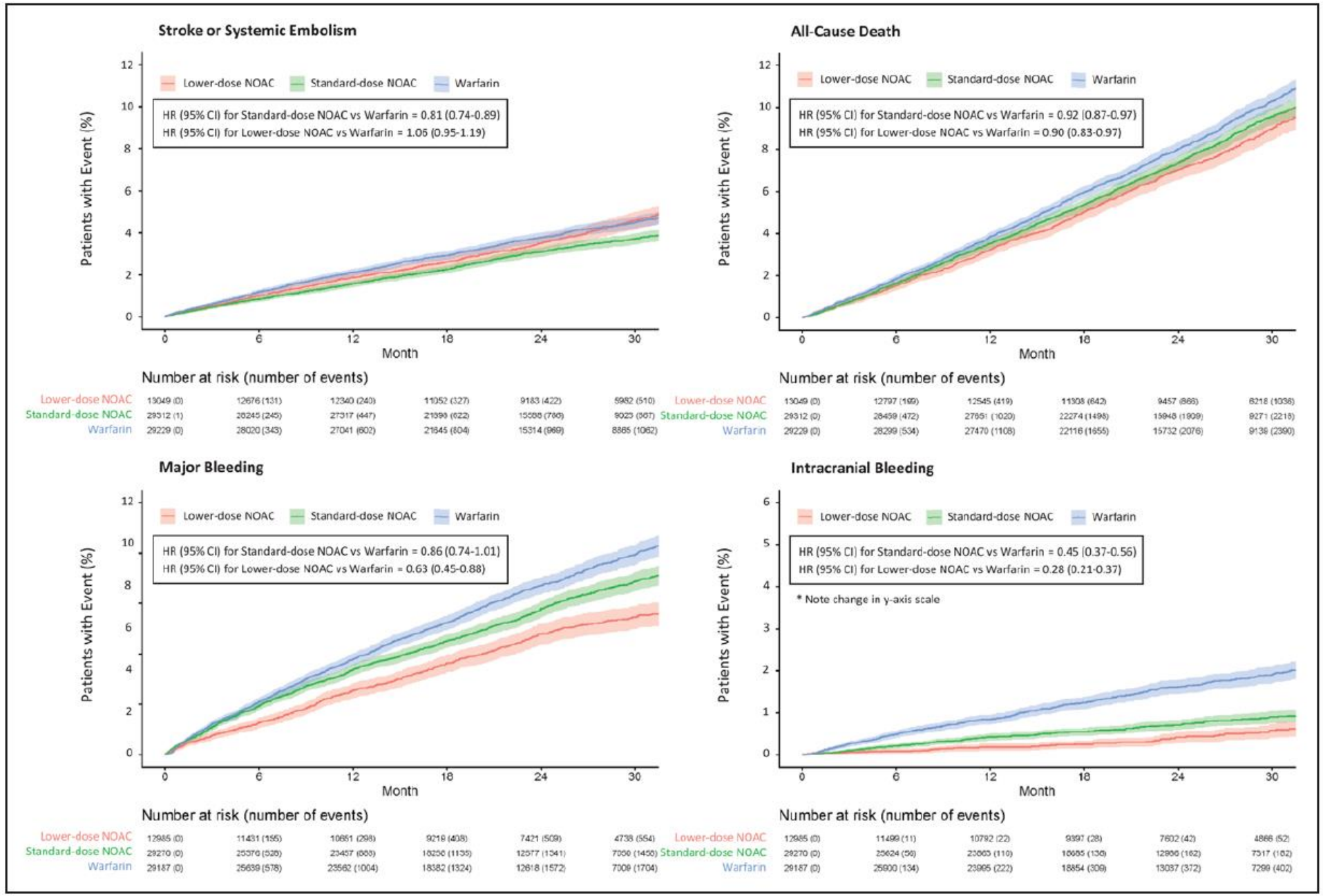


**Figure 2. Stroke or systemic embolism, all-cause death, major bleeding, and intracranial bleeding events.**
Kaplan-Meier curves for stroke or systemic embolism (top left), all-cause death (top right), major bleeding (bottom left), and intracranial bleeding (bottom right). HR indicates hazard ratio.

# Results (IV)

- For stroke or systemic embolism, potentially meaningful interactions suggesting a greater benefit of standard dose DOAC over warfarin were observed in patients with no history of previous VKA use and in patients with lower creatinine clearance.
- Potentially meaningful interactions suggesting a greater benefit of lower-dose DOAC over warfarin were observed in patients with no history of previous VKA use, with no history of previous gastrointestinal bleeding, and with older age.
- For major bleeding, potentially meaningful interactions suggesting a benefit of standard-dose DOAC over warfarin were observed in patients without diabetes, with no history of coronary artery disease, with no history of gastrointestinal bleeding, with younger age, and with lower weight .
- Potentially meaningful interactions suggesting a benefit of lower-dose DOAC over warfarin were observed in patients with no history of coronary artery disease, no history of heart failure, and younger age .

# Conclusions

- In this network meta-analysis using individual patient-level data from the pivotal randomized trials of DOACs versus warfarin in patients with AF, a standard-dose DOAC treatment strategy results in significant reductions in the risk of stroke or systemic embolism, intracranial bleeding, and all-cause death compared with warfarin.
- The benefit of standard-dose DOACs over warfarin for stroke or systemic embolism was consistent across the entire range of patient age and after stratification by sex.
- For major bleeding, statistically significant interaction was observed suggesting a greater benefit for standard-dose DOAC over warfarin in patients with lower body weight and younger age, regardless of sex.
- Results from these analyses provide the most robust evidence to date demonstrating the collective benefits of DOACs over warfarin in patients with AF and confirm that clinicians should have no hesitancy to start DOACs in eligible patients regardless of previous VKA use.