



Randomising the Grey Zone: Evaluating the SINGLE-AF Trial in the Intermediate Risk Cohort with Atrial Fibrillation

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ATRIAL FIBRILLATION (AF) is among the most common sustained cardiac arrhythmias, and its association with an increased risk of ischaemic stroke has shaped decades of cardiac risk stratification. The congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischaemic attack/thromboembolism, vascular disease, age 65–74 years, and sex (CHA₂DS₂-VASc) score, which ranges from 0–9, stratifies patients by their expected risk of stroke, with higher scores indicating greater risk. Current American and European guidelines strongly recommend oral anticoagulation for men with a CHA₂DS₂-VASc score of 2 or more, and for women with a score of 3 or more.^{1,2} Between the lowest and highest ends of this scale sits an intermediate zone, defined as a CHA₂DS₂-VASc score of 1 in men and 2 in women. This intermediate risk cohort represents a substantial proportion of newly diagnosed patients with AF, and clinicians have long lacked a definitive answer as to whether the expected reduction in thromboembolism from anticoagulation outweighs the bleeding risk in this population.

CLINICAL BENEFIT OF ORAL ANTICOAGULANTS

The observational literature addressing anticoagulation use in patients at intermediate risk has been notably inconsistent. Analyses from the Danish and Swedish registry data suggested that the net clinical benefit of oral anticoagulation was uncertain among patients with a CHA₂DS₂-VASc score of 1.^{3,4} More recent registry-based analyses, including the

Norwegian AFNOR study and a separate Danish nationwide registry study, have reported divergent estimates of the thromboembolic risk conferred by a score of 1, further complicating clinical decision-making.^{5,6} The AFNOR study, which included 34,460 patients with AF with a score of 1, showed that the incidence rate of ischaemic stroke was 0.51 events per 100 person-years, and that oral anticoagulant use was associated with an increased risk of major bleeding (adjusted hazard ratio [HR]: 1.37)

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but a lowered risk of the combined outcome of ischaemic stroke, major bleeding, and mortality (adjusted HR: 0.57).⁵ A multicentre European observational study found positive outcomes with oral anticoagulation among patients at low stroke risk, underscoring the inherent limitations of confounded, nonrandomised comparisons in this population (direct oral anticoagulant [DOAC] versus no treatment; HR: 0.72 for lowered risk of stroke).⁷ Randomised trial data have been only indirectly informative. The pivotal DOAC trials, including ARISTOTLE, enrolled few patients at the lowest end of the risk spectrum, and were designed to compare DOACs with vitamin K antagonists in broader, higher risk populations rather than test anticoagulation against no treatment among intermediate risk patients specifically.⁸ In the absence of randomised clinical trial data, and relying on observational data, both the American College of Cardiology (ACC)/American Heart Association (AHA)/American College

of Clinical Pharmacy(ACP)/Heart Rhythm Society (HRS) and the European Society of Cardiology (ESC) offer a Class IIa recommendation for oral anticoagulants, a reasonable option for consideration rather than a firm mandate for intermediate risk patients with AF, explicitly acknowledging the need for randomised evidence to clarify this recommendation.^{1,2}

THE SINGLE-AF RANDOMISED CLINICAL TRIAL

Results from the SINGLE-AF randomised clinical trial were recently presented at the ESC Congress 2026, and were simultaneously published.⁹ The study by Kim et al.⁹ was an investigator-initiated, multicentre, open-label, randomised superiority trial with blinded adjudication of outcome events, conducted at 18 centres in South Korea, and designed to assess whether the risk of adverse clinical events would be lower with oral anticoagulation than with no anticoagulation among patients with AF who are at intermediate risk for stroke. Investigators enrolled patients with AF at an intermediate risk of stroke, defined as a CHA₂DS₂-VASc score of 1 in men or 2 in women, and who were



at least 19 years of age, between July 2020–June 2023. Those with clinically significant kidney or liver disease; those on an anticoagulant owing to the presence of a mechanical prosthetic valve, moderate-to-severe mitral stenosis, or deep-vein thrombosis; and those with clinically significant structural heart disease were excluded. A total of 1,803 eligible patients with AF underwent 1:1 randomisation to receive DOAC therapy (n=902), either with apixaban or rivaroxaban at the treating physician's discretion, or no-anticoagulant therapy (n=901). The investigators hypothesised that DOAC therapy would prove superior to no anticoagulation with respect to a composite primary endpoint of stroke, systemic embolism, major bleeding, or death from cardiovascular causes at 24 months after randomisation.

DOAC THERAPY COMPARED TO NO ANTICOAGULATION

The mean age of the patients was 60.4 years, with nearly 24% being women, and 72% having paroxysmal AF in both groups. At 24 months after randomisation, the primary endpoint occurred in four (0.5%) patients assigned to the DOAC therapy group, compared to 13 (1.5%) patients assigned to the no-anticoagulation group, a difference of –1.0 percentage points (95% CI: –2.0–0.1; p=0.03) and an HR of 0.31 (95% CI: 0.10–0.94). This benefit appeared

to be driven predominantly by a reduction in ischaemic events, as evidenced in post-hoc analyses, which showed that ischaemic stroke or systemic embolism occurred in one patient in the DOAC group and in 10 patients in the no-anticoagulant group (HR: 0.10). Major bleeding occurred infrequently and similarly in both groups (three in the DOAC and four in the no-anticoagulant group), and no deaths from cardiovascular causes occurred in either arm. Serious adverse events were also comparable between both groups (~9%). The authors concluded that among patients with AF at intermediate risk for stroke, DOAC therapy led to a lower risk of the primary composite endpoint than no anticoagulation, while explicitly cautioning that the absolute number of events was small and that confirmatory trials or pooled analyses would be needed to refine the precision and magnitude of the treatment effect.

UNANSWERED QUESTIONS REQUIRE FURTHER EVIDENCE

SINGLE-AF is, to date, the first dedicated randomised clinical trial designed to directly test anticoagulation versus no anticoagulation in a population defined strictly by their intermediate CHA₂DS₂-VASc score. Therefore, this study is an important and meaningful step towards resolving a question that cardiovascular society guidelines have long flagged as



unanswered for years. The reduction in the primary composite endpoint, without a corresponding increase in major bleeding, offers a signal that the modest thromboembolic risk in this patient population is amenable to modification with modern oral anticoagulants. However, the authors would argue that this study is just a step in the right direction, and that guidelines should only be modified to upgrade oral anticoagulation use in intermediate risk patients once more data from future studies corroborate these findings. The enthusiasm for an immediate change in clinical practice is tempered by the markedly lower than anticipated event rate, and the lack of generalisability from this study, which only included East Asian patients from a single country, a population in which bleeding risk profiles arguably differ from those of other cohorts. Nearly one-third of patients in the no-anticoagulation group received antiplatelet

therapy (acetylsalicylic acid/aspirin: 36.5%; clopidogrel: 33.9%), a practice not recommended by clinical guidelines.

The authors believe that results from the SINGLE-AF clinical trial are more hypothesis confirming than hypothesis settling, and only once data from more diverse populations and confirmatory trials are obtained should guidelines consider upgrading anticoagulation use to a Class I recommendation in intermediate risk patients. In the interim, shared decision-making remains pivotal, incorporating each patient's individual bleeding risk and values regarding medication burden, and with an understanding that decisions made in the grey zone rest on the best available evidence rather than on default generalised practice.

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