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Lessons from the trials

ENGAGE AF: Effective anticoagulation with factor Xa in next generation treatment of atrial fibrillation

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INTRODUCTION

Recent trials have presented compelling evidence for the safety and efficacy of the new oral anticoagulants (NOACs) versus warfarin for stroke prevention in patients with atrial fibrillation (AF).[1,2,3] The ENGAGE AF-TIMI 48 trial,[4] the biggest of these trials, aims to evaluate the use of the direct factor Xa inhibitor, edoxaban.

ENGAGE TRIAL

The ENGAGE AF-TIMI 48 trial was a randomised, double-blind, double-dummy trial published in November 2013 in the New England Journal of Medicine. It compares two once-daily regimens of edoxaban with warfarin in 21,105 patients with moderate-to-high risk of stroke in AF. The study was conducted at 1393 centres across 46 countries and patients were enrolled between November 2008 and November 2010 with a median follow-up of 2.8 years.

Patients were randomly allocated in a 1:1:1 ratio to receive either dose-adjusted warfarin or edoxaban at a high or low dose (60 mg OD or 30 mg OD). The dose of edoxaban was halved, either at randomisation or at any point throughout the study, if creatinine clearance was below 50 ml/min, if body weight was 60 kg or less or if there was concomitant use of a potent P-glycoprotein inhibitor such as verapamil or quinidine. Each patient received a set of two drugs for the study, either warfarin plus placebo to match edoxaban, or edoxaban plus placebo to match warfarin. For patients in the edoxaban arm, blinding was maintained with sham INR values. Time in therapeutic range was calculated by means of linear interpolation, with INR values rounded to the nearest 0.1.

The primary efficacy endpoint was defined as time to first adjudicated stroke (ischaemic or haemorrhagic) or systemic embolic event. The principal safety endpoint was adjudicated major bleeding during treatment, as defined by the International Society on Thrombosis and Haemostasis. An independent committee was allocated responsibility to adjudicate all deaths, cerebrovascular and systemic embolic events, myocardial infarctions and bleeding events.

The baseline characteristics of the 3 study groups were well-balanced and complete information on the primary endpoint was attained for 99.5% of the total 56,346 patient-years of potential follow-up. The authors calculations estimated that the study had more than 87% power to reject the null hypothesis that edoxaban was inferior to warfarin.

RESULTS

The primary end-point of stroke or systemic embolic event occurred at a rate of 1.5% per year in the warfarin group, 1.18% per year with high-dose edoxaban (HR vs warfarin 0.79; 97.5% CI 0.63–0.99 $p < 0.001$ for non-inferiority, $p = 0.02$ for superiority) and 1.61% with low-dose edoxaban (HR vs warfarin 1.07, 97.5% CI 0.87–1.31 $p = 0.005$ for non-inferiority, $p = 0.44$ for superiority). The superiority

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of high-dose edoxaban over warfarin disappeared on intention-to-treat analysis, but both edoxaban doses remained non-inferior.

Edoxaban showed a clear benefit over warfarin in haemorrhagic stroke; annualised rate 0.47% with warfarin, 0.26% with high dose edoxaban (HR 0.54, $p < 0.001$) and 0.16% low dose edoxaban (HR 0.33, $p < 0.001$). The rate of ischaemic stroke for both warfarin and high-dose edoxaban was 1.25% per year, with an annualised rate of 1.77% with low-dose edoxaban.

Major bleeding events occurred at a rate of 3.43% per year with warfarin, 2.75% with high-dose edoxaban (hazard ratio, 0.80; 95% CI 0.71 to 0.91; $p < 0.001$) and 1.61% with low-dose edoxaban (hazard ratio, 0.47; 95% CI 0.41–0.55; $p < 0.001$). Annualised rates of life-threatening bleeding, intracranial bleeding and major bleeding plus clinically relevant non-major bleeding were lower at both doses of edoxaban versus warfarin ($p < 0.001$ for the comparison of warfarin with each dose of edoxaban). However, the rate of major GI bleeding was higher with high-dose edoxaban versus warfarin (1.51 vs 1.23, HR 1.23, 95% CI 1.02–1.5, $p = 0.03$) but lowest with low-dose edoxaban (0.82%, HR 0.67, 95% CI 0.53–0.83, $p < 0.001$).

High-dose edoxaban is shown to have a statistically significant lower rate of the combined endpoint of stroke or systemic embolic event versus the lower dose ($p < 0.001$). This was largely driven by the relative reduction in ischaemic stroke (236 vs 333 events, in favour of the higher dose) which more than offset the higher incidence of haemorrhagic stroke (49 vs 30 events, in favour of the lower dose).

DISCUSSION

The results seen in the ENGAGE trial resemble those seen in other recent, large trials on other NOACs, as discussed in an article in this journal published earlier this year by Kaba et al.[5]

The RE-LY trial showed that dabigatran, at a dose of 150 mg BD, reduces the incidence of ischaemic stroke or systemic emboli versus warfarin (RR 0.66, CI 0.53–0.82) with similar rates of major bleeding.[1] Dabigatran also demonstrated a lower rate of intracranial haemorrhage (annualised ratios of 0.38% per year with warfarin and 0.10% with 150 mg BD dabigatran). However, as with edoxaban, dabigatran was found to have a higher rate of GI bleeding than warfarin.

The ROCKET-AF trial assessed rivaroxaban as an alternative to warfarin.[2] The primary endpoint of stroke or non-central nervous system embolisation occurred less in the rivaroxaban arm (HR 0.79, CI 0.66–0.96) but, as with edoxaban, this difference disappeared on intention-to-treat analysis. Rivaroxaban remained non-inferior to warfarin. Rates of major and non-major bleeding were similar in warfarin and rivaroxaban arms, but there was a reduction in both intracranial and fatal bleeding with rivaroxaban use.

Apixaban was evaluated in the ARISTOTLE trial.[3] It showed an advantage over warfarin in prevention of ischaemic stroke or systemic embolism (HR 0.69; 95% CI 0.66–0.95) along with a lower rate of major bleeding (HR 0.69; 95% CI 0.6–0.8). It also showed a lower rate of intracranial haemorrhage (HR 0.42; CI 0.3–0.58).

Poor compliance with warfarin regimes was a problem in both the ROCKET-AF and RE-LY trials, with time in therapeutic INR range at 55% overall. The ARISTOTLE trial showed an improvement at 62% while the ENGAGE trial had a time in therapeutic range of 67.4%, with INRs between 1.8–3.2 for 83.1% of the treatment period.

The ENGAGE trial is a well-designed, well-powered and robust study, providing important information on edoxaban as an alternative to warfarin in the prevention of stroke in patients with AF. At both higher and lower doses, edoxaban was shown to be non-inferior to warfarin in the prevention of stroke or systemic embolic event. It also carried a lower risk of bleeding across all categories with the exception of GI bleeding.

The four trials discussed have been incorporated into a meta-analysis published in The Lancet in December 2013.[6] The findings clarify and confirm trends seen across the trials. Use of the NOACs reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0.81, 95% CI 0.73–0.91; $p < 0.0001$) with this effect predominantly due to a reduction in haemorrhagic stroke. The NOACs also showed a significant reduction in all-cause mortality (RR 0.9, 95% CI 0.85–0.95; $p = 0.0003$) and intracranial haemorrhage (RR 0.48, 95% CI 0.39–0.59; $p < 0.0001$), but showed an increase in gastrointestinal bleeding (RR 1.25, 95% CI 1.01–1.55; $p = 0.04$).

The ENGAGE trial contributes to the expanding evidence base for NOACs as viable alternatives to warfarin that do not burden patients with regular blood tests and carry less food-drug and drug-drug interactions. It is the largest of the recent trials and improves on the warfarin compliance rates seen in

other studies. The recent ESC guidelines update[7] and the ACCP 9 guidelines[8] both recommend NOACs over warfarin for stroke prevention in AF; the ENGAGE trial serves to enhance these recommendations.

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