EFFECTIVE ANTICOAGULATION WITH FACTOR XA NEXT GENERATION IN ATRIAL FIBRILLATION – (ENGAGE AF - TIMI 48 TRIAL): PRIMARY RESULTS

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PRESENTATION SUMMARY

The following is an executive summary of the abstract presentation by Prof Robert Giugliano on the ENGAGE AF – TIMI 48 trial primary results. It was presented on 19th November 2013 at the American Heart Association (AHA) annual congress, held in Dallas, Texas.

Primary Results of the ENGAGE AF - TIMI 48 Trial

Prof Giugliano initially provided an overview of the therapy area and noted that while warfarin is an effective therapy for atrial fibrillation (AF) patients, reducing stroke by 64% versus placebo, it is linked to increased bleeding and has a number of other drawbacks. There are currently three novel oral anticoagulants (NOACs) that are at least as effective as warfarin in AF, reducing haemorrhagic stroke by 51%. Edoxaban is a new drug that inhibits Factor Xa; it has oral bioavailability of 62%, a fast onset of action, and a half-life of 10–14 hours. Edoxaban is taken once daily. 50% of the absorbed drug is eliminated by renal clearance, and dose reduction is recommended in patients with moderate renal impairment, low body weight and concomitant use of potent p-glycoprotein inhibitors.

Prof Giugliano described the study design of the ENGAGE AF – TIMI 48 trial, which enrolled 21,105 patients with documented AF and a moderate-to-high risk of stroke, based on a $CHADS_2$ score of ≥2. A double-blind, double-dummy design was used, and patients were randomised to one of three dosage regimens: warfarin titrated to an internationalised normalisation ratio (INR) of 2–3, high-dose edoxaban (60 mg once-daily), or low-dose edoxaban (30 mg once-daily). The edoxaban dose was halved to 30 mg once-daily and 15 mg once-daily, respectively, in patients with reduced renal function, low body weight and concomitant use of potent p-glycoprotein inhibitors. The primary endpoint was a composite of stroke or systemic embolic event (SEE). This was analysed for non-inferiority to exclude a risk ratio <1.38 (97.5% confidence interval). He outlined that the primary analysis was carried out on the modified intent-to-treat (mITT) cohort during the on-treatment period. Testing for superiority was carried out on the full ITT population, and analysed all events between randomisation and the final visit. Safety was analysed during the on-treatment period with the principal safety outcome being major bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH). Prof Giugliano noted that this was the longest duration trial with a novel agent, with a median of 2.8 years follow-up.

Prof Giugliano presented the baseline characteristics of the trial population. He noted that there were no significant differences in parameters across the treatment groups, and highlighted that the median age was 72 years, 25% of participants had paroxysmal AF, and the mean $CHADS_2$ score was 2.8, with over half of patients having a score ≥3. A quarter of patients had dose-reduction at randomisation and 59% of patients had prior experience with a vitamin K antagonist.

Of the patients enrolled in the trial, 99.6% received the study drug and complete follow-up was available for 99.5% of the potential years of follow-up. Only one patient was lost to follow-up, 0.9% of patients withdrew consent, and less than 9% of patients discontinued drug use each year. The median proportion of time in the therapeutic range (TTR) for warfarin was 68.4%; this was >77% for a quarter of patients. The trial results are summarised in Table 1.

Edoxaban was considered to be better tolerated than warfarin, and there was no difference between treatments in serious adverse events or liver function abnormalities. At the end of the trial, all patients were transitioned onto a vitamin K antagonist (approximately two-thirds) or NOAC (approximately one-third). Patients transitioning onto vitamin K antagonists had frequent INR measurements. These patients were also treated with a low dose edoxaban for up to 2 weeks until the INR was ≤2.0 and patients could transition to a NOAC when the INR was below 2.0. There was no difference in stroke, SEE or major bleeding between the treatment groups during the first 30 days of transition post-trial.

By comparison to well-managed warfarin (TTR 68.4%), edoxaban once daily was non-inferior in terms of stroke or SEE in both dosing regimens, with a trend towards reduced stroke and SEE observed in the high-dose edoxaban regimen treatment arm. Both edoxaban dosing regimens significantly reduced major bleeding events, intracranial haemorrhage, haemorrhagic stroke, and cardiovascular death. In addition, both edoxaban regimens showed superior net clinical outcomes and there was no excess in stroke or bleeding during the treatment transition at the trial end.

Table 1. Summary of ENGAGE-AF trial results.

Outcome	High-dose edoxaban* HR (p-value vs warfarin)	Low-dose edoxaban* HR (p-value vs warfarin)
Primary		
Stroke/SSE, non-inferiority	0.79 (<0.0001)	1.07 (0.005)
Stroke/SSE, superiority	0.87 (0.08)	1.13 (0.10)
Secondary		
Haemorrhagic stroke	0.54 (<0.001)	0.33 (<0.001)
Ischaemic stroke	1.00 (0.97)	1.41 (<0.001)
Stroke, SEE, cardiovascular death	0.87 (0.005)	0.95 (0.32)
Death or intracerebral haemorrhage	0.87 (0.004)	0.82 (<0.001)
All-cause mortality	0.92 (0.08)	0.87 (0.006)
Cardiovascular death	0.86 (0.013)	0.85 (0.008)
Myocardial infarction	0.94 (0.60)	1.19 (0.13)
Safety**		
ISTH major bleeding	0.80 (<0.001)	0.47 (<0.001)
Fatal bleeding	0.55 (0.006)	0.35 (<0.001)
Intracranial haemorrhage	0.47 (<0.001)	0.30 (<0.001)
Gastrointestinal bleeding	1.23 (0.03)	0.67 (<0.001)
Net clinical outcomes		
Stroke, SEE, death, major bleeding	0.89 (0.003)	0.83 (<0.001)
Disabling stroke, life-threatening bleeding, death	0.88 (0.008)	0.83 (<0.001)
Stroke, SEE, life-threatening bleeding, death	0.88 (0.003)	0.89 (0.007)

ISTH: International Society for Thrombosis and Haemostasis; HR: hazard ratio; SEE: systemic embolic event.
*Dose reduction by 50% was carried out in selected patients.
**Safety cohort, all patients who received at least one dose by treatment actually received.