News from the American Heart Association Scientific Sessions 2013

Highlights of the American Heart Association (AHA) Scientific Sessions 2013, held in Dallas, Texas, USA, last November included success with a fourth new oral anticoagulant in patients with atrial fibrillation, and some benefit with spironolactone for heart failure patients with preserved left ventricular function, a group for whom no treatment is currently available. More highlights from the meeting are online at www.bycardio.co.uk

ENGAGE AF-TIMI 48: success for edoxaban in AF

The new factor Xa inhibitor, edoxaban (Daiichi-Sankyo), was as effective in preventing strokes and safer than warfarin in patients with atrial fibrillation (AF) in the ENGAGE AF-TIMI 48 trial.

The ENGAGE AF-TIMI 48 (Effective AnticoaGulation with Factor XA Next Generation in Atrial Fibrillation – Thrombolysis In Myocardial Infarction 48) trial included more than 21,000 AF patients from 46 countries who were randomised to edoxaban at one of two doses (60 mg or 30 mg per day) or warfarin.

Results (**table 1**) showed that both edoxaban doses were associated with significantly less major bleeding than warfarin. The rate of ischaemic stroke was similar with high-dose edoxaban and warfarin but was higher with the low-dose edoxaban regimen. Haemorrhagic strokes and cardiovascular mortality were both significantly lower with both doses of edoxaban than with warfarin.

Dr Robert Giugliano (Brigham and Women's Hospital, Boston, USA) who was lead investigator of the study, said: "Once-daily edoxaban may be an important alternative to warfarin".

Designated discussant of the trial, Dr Elaine Hylek (Boston University Medical Center, Boston, USA), highlighted the reduction in haemorrhagic stroke that has been seen with all the new oral anticoagulants in comparison with warfarin. She commented: "The current trial provides very important confirmation for another oral factor Xa inhibitor, that indeed we are seeing a dramatic reduction in intracerebral haemorrhage."

Compared to previous studies of other new oral anticoagulants, the ENGAGE AF-TIMI 48 trial design stipulated a more rigorous dosage reduction for patients with certain features that enhance blood levels of the drug. This recommended dosage reduction was 50% for patients with renal dysfunction, low body weight, or those who were also taking P-glycoprotein-inhibiting drugs such as verapamil or quinidine. These dosage reductions applied to about a quarter of patients in the trial. "The dosage reduction worked in that it maintained similar efficacy as seen in those patients who did not need to be dose-reduced, and patients with dosage modifications did better on the trial's measures of safety." Dr Guigliano said.

Another impressive feature of the trial was that the benefit of edoxaban was compared with fairly well managed warfarin treatment, with warfarin patients being in the therapeutic INR range for 68.4% of the time, Dr Guigliano pointed out.

Edoxaban is now the fourth new oral anticoagulant to have shown benefit in this indication, joining dabigatran, rivaroxaban and apixaban. Answering questions on how clinicians will choose which agent to use, commentators at an AHA media briefing on the ENGAGE AF-TIMI 48 trial said all four new agents seemed to have benefits over warfarin, particularly on safety, but were hard to compare with each other. They suggested that clinicians will make a judgment on patient characteristics that may favour one drug over the others, such as individual side effects of the drugs and dosing schedules.

Edoxaban is currently only available in Japan for patients undergoing orthopedic surgery.

ENGAGE AF-TIMI 48 was also published online in the *New England Journal of Medicine* on 28th November 2013 (doi: 10.1056/NEJMoa1310907).

Table 1. Hazard ratio (97.5% CI) for major end points for edoxaban *vs.* warfarin

End point	Edoxaban 60 mg	Edoxaban 30 mg
Stroke or systolic embolic events (primary end point)	0.79 (0.63–0.99)	1.07 (0.87–1.31)
Major bleeding	0.80 (0.71–0.91)	0.47 (0.41–0.55)
Haemorrhagic stroke	0.54 (0.38–0.77)	0.33 (0.22–0.50)

STREAM: thrombolysis still an option if no immediate PCI

One-year results from the STREAM trial show similar survival rates between immediate thrombolysis with tenecteplase and transfer to percutaneous coronary intervention (PCI) in ST-elevation myocardial infarction (STEMI) patients for whom PCI is not immediately available.

The 30-day results – showing similar outcomes in the two treatment groups – were presented at the American College of Cardiology (ACC) meeting last March.

STREAM (Strategic Reperfusion Early After Myocardial Infarction) is the first trial to have

succeeded in showing that fibrinolysis given before transfer to a PCI hospital can be as effective as primary PCI, which has been attributed to the fact that thrombolysis patients were only given urgent PCI on arrival at the PCI hospital if the electrocardiogram showed they had not reperfused. This avoided the situation of performing PCI with fibrinolysis on board – which has been associated with adverse outcomes – in two-thirds of patients.

The STREAM trial included 1,892 STEMI patients who were not able to undergo PCI within the first hour of arriving at hospital. They were randomised to medical therapy with age-adjusted bolus tenecteplase, clopidogrel and enoxaparin, which was followed by later PCI only if symptoms persisted, or to PCI as soon as it could be performed. Both groups were treated within three hours of symptom onset.

One-year mortality rates were 2.1% in the thrombolysis group versus 1.5% in the PCI group, a non-significant difference.

"In this study, the thrombolytic strategy proved a reasonable approach to take as an initial treatment immediately after severe heart attack when PCI is not immediately available," said Dr Peter Sinnaeve, the study's lead author and assistant professor of cardiology (University of Leuven, Belgium).

TOPCAT: spironolactone shows a signal of benefit

Spironolactone did not show a benefit on the composite primary end point in the TOPCAT trial in patients with heart failure with preserved ejection fraction, but the drug was associated with significantly fewer heart-failure hospitalisations.

Presenting the study, Professor Marc Pfeffer (Harvard Medical School, Brigham and Women's Hospital, Boston, USA) said the reduction in hospitalisation was "an important finding".

Noting that at present there is no therapy for patients with heart failure with preserved ejection fraction, Professor Pfeffer said that he would now use spironolactone for this patient population. "We have a generic medication that we can show how to use safely and we do believe it relieves the burden these patients have," he commented.

Designated discussant Dr Margaret M Redfield (Mayo Clinic, Rochester, USA) agreed that the trial, "although not statistically significant, showed a signal of benefit". But she also cautioned that the occurrence of worsening renal function and hyperkalaemia would likely be more common in clinical practice given the careful creatinine and potassium monitoring that occurred in the trial.

Table 1. Clinical outcomes in the TOPCAT study

End points	Spironolactone (%) n=1.722	Placebo (%) n=1,723	HR (95% CI	P value
Primary end point (CV mortality, aborted cadiac arrest or HF hospitalisation)	18.6	20.4	0.89 (0.77–1.04)	0.138
CV mortality	9.3	10.2	0.90 (0.73–1.12)	0.354
Aborted cardiac arrest	<1.0	<1.0	0.60 (0.14–2.50)	0.482
HF hospitalisation	12.0	14.2	0.83 (0.69–0.99)	0.042

Key: CV = cardiovascular; HF = heart failure; HR = hazard ratio

Table 2. Rates of hyperkalaemia and hypokalaemia in the TOPCAT study

End points	Spironolactone, n=1,722 (%)	Placebo, n=1,723 (%)	P value
Hyperkalaemia ≥5.5 mmol/L	18.7	9.1	<0.001
Hypokalaemia, <3.5 mmol/L	16.2	22.9	<0.001

TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) included 3,445 heart-failure patients aged 50 or over with an LVEF ≥45% from six countries. They were randomised to spironolactone (titrated up to 30–45 mg/day) or placebo. The mean follow up was 3.3 years.

There were no significant differences in clinical adverse events (**table 1**), but there was more hyperkalaemia with spironolactone and more hypokalaemia on placebo (**table 2**). There were no hyperkalemia-related deaths