News from the American College of Cardiology Scientific Session 2013

Highlights of this year's American College of Cardiology (ACC) meeting held in San Francisco, USA, in March 2013, included positive results for eplerenone in myocardial infarction and also for ranolazine in diabetes, but concerns about intensive glycaemic control on heart failure risk. But perhaps the biggest story of the meeting was the last-minute removal of the PREVAIL trial from the programme because of an embargo break by the sponsor. Further reports from the meeting are available online including the first study to show a benefit of treating STEMI patients in community hospitals with fibrinolysis, as well as evidence supporting the use of PCI in hospitals without surgical back up. There were also good results with a new IV anti-platelet agent – cangrelor – in PCI but bad news for niacin in HPS-THRIVE and for high doses of vitamins in TACT.

PREVAIL not presented but eases safety concerns on Watchman

The PREVAIL trial of a new device which closes the left atrial appendage in the heart (Watchman®, Boston Scientific) attracted huge controversy at the ACC meeting when it was removed from the programme within an hour of its presentation because of an embargo break by the sponsor, Boston Scientific. But the slides and a press release were still made available to the media, and preliminary results appear to suggest some reassurance on safety concerns generated in a previous study.

The device, which is implanted via a trans-septal catheter-based delivery system, is already available in Europe for the prevention of stroke in atrial fibrillation (AF) patients, but it has not been approved by the USA Food and Drug Administration (FDA) because of safety concerns raised in the previous PROTECT-AF trial. These related to a high initial rate of pericardial effusions and procedure-related strokes. The PREVAIL trial was therefore conducted to give more information on safety and to confirm the efficacy results shown in PROTECT-AF.

The PREVAIL trial enrolled 407 patients who were randomised 2:1 to the device or warfarin. Device patients were given 45 days of warfarin therapy. The study had a Bayesian design, which means that the PROTECT results were also taken into account when assessing efficacy. Results showed that the device had a 95.1% implant success rate, up from the 91% rate in PROTECT.

The trial had three co-primary end points, one for safety and two for efficacy. The safety end point was met, as was one of the efficacy end points; the other efficacy end point was narrowly missed. The efficacy results are, however, very preliminary, with only 58 device patients and 30 controls having reached the 18-month follow-up time.

The main safety end point – acute (seven-day) occurrence of death, ischaemic stroke, systemic embolism and procedure, or device-related complications requiring major cardiovascular or endovascular intervention – occurred in six out of 269 patients (2.2%) who received the device. A second, broader, safety end point, including cardiac perforation, pericardial effusion with tamponade, ischaemic stroke, device embolisation, and other vascular complications, occurred in 4.4% of patients receiving the device in PREVAIL, compared with 8.7% in PROTECT.

Cardiac perforation requiring surgical repair occurred in 0.4% of PREVAIL patients receiving the device compared with 1.6% in PROTECT-AF. Pericardial effusion with cardiac tamponade requiring pericardiocentesis occurred in 1.5% of Watchman® patients in PREVAIL *vs.* 2.4% of those in PROTECT AF.

Speaking to the media, lead investigator Dr David Holmes (Mayo Clinic, Minnesota, USA) said: "Despite inclusion of higher-risk patients in PREVAIL than in PROTECT, there were fewer complications, and results show the device can be safely implanted by new operators. The Watchman® device therefore offers an alternative to oral anticoagulation therapy for thromboembolic prevention in patients with nonvalvular AF".

Independent commentator, Dr Gordon Tomaselli (Johns Hopkins University, Baltimore, USA), said he was reassured by the safety data in PREVAIL, and said he would use the device in patients at high risk of stroke who can't take anticoagulant drugs because of bleeding issues. He added that there were not enough data yet to recommend its use in patients who could take anticoagulants.

Intensive glycaemic control ups heart failure risk

Both intensive glycaemic control and poor glycaemic control were associated with an increased risk of heart failure in diabetes patients in a new case-control study.

The study was conducted in the diabetes population of the GoDARTS registry. Cases were patients with heart failure defined as either a hospital discharge code for chronic heart failure or systolic dysfunction requiring a loop diuretic. They were matched with controls for gender and age at diagnosis of diabetes. Cox-regression analysis was used to examine the link between

mean HbA1c and time to chronic heart failure, accounting for all possible confounders.

Of 8,890 patients with diabetes, 759 developed heart failure during the study. Those with poor glycaemic control (HbA1c >6.9%) were twice as likely to develop heart failure (odds ratio 2.26; p<0.01).

However, intensive glycaemic control (HbA1c <6%) also appeared to be associated with a similar increased risk for heart failure (OR 2.48; p<0.01). The incidence of coronary artery disease and myocardial infarction also increased when mean HbA1c was outside the range of 6–7%.

Presenting the results, Dr Helen Parry (University of Dundee) recommended that type 2 diabetes patients should aim for tight glycaemic control, keeping an HbA1c in the range of 6.0% to 6.9% if they want to reduce their risk of heart failure. But she added that achieving this level of control is not easy.

Dr Parry said the mechanism behind heart failure risk with intensive glycaemic control was probably multifactorial. She noted that heart failure has been associated with several classes of diabetes drugs, which are probably used more in this with intensive control, and that patients with low levels of HbA1c more often experience acute hypoglycaemic events.

REMINDER: eplerenone beneficial in MI?

The aldosterone blocker, eplerenone, started within the first day after an acute myocardial infarction (MI) in patients without heart failure or left ventricular dysfunction can improve outcomes, according to the results of the REMINDER trial. But the trial generated some controversy, in that the only component of the complex composite primary end point to be significantly reduced was the level of natriuretic peptides.

The primary end point of the study included cardiovascular mortality, rehospitalisation, prolonged heart failure hospitalisation, sustained ventricular tachycardia or ventricular fibrillation, left ventricular ejection fraction (LVEF) ≤40% after one month, or levels of natriuretic peptides. REMINDER (Impact of Eplerenone on Cardiovascular Outcomes in Patients Post Myocardial Infarction) included 1,012 STEMI patients, who received eplerenone 25–50 mg/day or placebo. Treatment started within the first 24 hours of symptom onset and preferably before myocardial reperfusion.

At a mean of 10.5 months follow-up, the composite primary end point occurred in 29.6% of the placebo group versus 18.4% in the eplerenone group (p<0.0001). Most of the benefit was attributable to the natriuretic peptide biomarker, which was raised in 25.9% of the placebo groups versus 16% of the eplerenone group (p<0.0002). There were, however, trends in favour of eplerenone for heart-failure rehospitalisation and ventricular arrhythmias.

Safety was good, with similar rates of hyperkalaemia in the eplerenone and placebo groups, and hypokalaemia occurring more often in the control group, noted lead investigator Dr Gilles Montalescot (Pitié-Salpêtrière University Hospital, France).

Discussing the trial, Dr Magnus Ohman (Duke University, Kansas City, USA) noted that eplerenone was not well used for heart failure because of concerns about hyperkalaemia. REMINDER could be considered more of a safety study for eplerenone rather than an efficacy study, showing that eplerenone is safe when you exclude patients with renal failure, he said.

Dr Ohman added that the clinical significance of a natriuretic-peptide elevation after 30 days was not clear but that it might be a predictor of clinical outcomes in the future.

TERISA: ranolazine reduces angina in diabetes

The anti-anginal drug, ranolazine, is effective at reducing angina episodes specifically in patients with diabetes, the TERISA (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina) trial has shown.

Lead investigator, Dr Mikhail Kosiborod (Saint Luke's Mid America Heart Institute, Kansas City, USA) noted that ranolazine is already approved as an anti-anginal but it was important to demonstrate a benefit in the particularly challenging diabetes population.

The study, which was simultaneously published online in the *Journal of the American College Cardiology* (http://dx.doi.org/10.1016/j.jacc.2013.02.011) to coincide with its ACC presentation, involved 949 type 2 diabetes patients who were randomised to a target dose of ranolazine 1,000 mg twice a day or placebo, for eight weeks. These patients had a high burden of angina, with around six to seven episodes per week, and were already receiving treatment with one or two anti-anginals.

The primary end point – average weekly angina frequency between weeks 2 and 8 – was significantly improved in the ranolazine group (3.8 episodes *vs*. 4.3 per week; p=0.008). Weekly use of rescue sublingual nitroglycerin was also lower among the ranolazine-treated patients (1.7 *vs*. 2.1 doses per week; p=0.003).

An editorial accompanying the publication (http://dx.doi.org/10.1016/j.jacc.2013.03.002) notes that the results confirm prior post hoc analyses of subgroups from the CARISA (Combination Assessment of Ranolazine in Stable Angina) and MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes) studies. But it adds that the absolute effects, although statistically significant, were small, with only 0.5 fewer episodes of angina and 0.4 fewer sublingual nitroglycerin tablets used per week. "The clinical relevance of such slight absolute differences may be questioned," it concludes.