Advance reports

Included in this report are the highlights of the 20th FIGO World Congress of Gynecology and Obstetrics in Rome and the American Heart Association (AHA) Scientific Sessions in Los Angeles.

Peter Sayer GM
Alison Bloomer GM
Email: peter.sayer@pavpub.com

FIGO congress

Major advances in management of fibroids

Esmya (ulipristal acetate) could help women suffering from uterine fibroids, according to an international roundtable held recently at the 20th FIGO World Congress of Gynecology and Obstetrics in Rome.

Ulipristal acetate is a first in class oral selective progesterone receptor modulator that acts on progesterone receptors on fibroids and the endometrium. This allows it to rapidly control bleeding and reduce fibroid volume.

In the roundtable Professor Jacques Donnez, Head of Gynecology, Catholic University of Louvain, Brussels, Belgium, spoke about new developments in the treatment of uterine fibroids.

Two recent clinical trials (PEARL 1, PEARL 2), published in February 2012 in the *New England Journal of Medicine*, showed ulipristal acetate to control bleeding in 90% of patients and to control excessive bleeding significantly more rapidly with ulipristal acetate than with leuprolide acetate. Ulipristal acetate also significantly reduced fibroid size and for patients who did not undergo surgery, the volume reduction was maintained for six months after treatment.

In the PEARL I trial, 237 women with fibroids, excessive uterine bleeding, and anaemia were randomised to ulipristal 5mg daily, ulipristal 10mg daily, or placebo. At 13 weeks, uterine bleeding was controlled in 91% of the women receiving 5mg of ulipristal acetate, 92% of those receiving 10mg of ulipristal acetate, and 19% of those receiving placebo. The rates of amenorrhea were 73%, 82%, and 6%, respectively, with amenorrhea occurring within 10 days in the majority of patients receiving ulipristal acetate. The median changes in total fibroid volume were −21%, −12%, and +3%. Ulipristal acetate induced benign histologic endometrial changes that had resolved by six months after the end of therapy. Serious adverse events occurred in one patient during treatment with 10mg of ulipristal acetate (uterine haemorrhage) and in one patient during receipt of placebo (fibroid protruding through the cervix). Headache and breast tenderness were the most common adverse events associated with ulipristal acetate but did not occur significantly more frequently than with placebo.

In PEARL 2, uterine bleeding was controlled in 90% of patients receiving 5mg of ulipristal acetate, in 98% of those receiving 10mg of ulipristal acetate, and in 89% of those receiving leuprolide acetate. Median times to amenorrhea were seven days for patients receiving 5mg of ulipristal acetate, five days for those receiving 10mg of ulipristal acetate, and 21 days for those receiving leuprolide acetate. Moderate-to-severe hot flashes were reported for 11% of patients receiving 5mg of ulipristal acetate, for 10% of those receiving 10mg of ulipristal acetate, and for 40% of those receiving leuprolide acetate.

Uterine fibroids are benign tumours of the smooth muscle cells and connective tissue that grow within the uterine wall. They are the most common benign tumours in women of reproductive age, occurring in 20–40% of women between the ages of 35 and 55 years. The prevalence is highest in perimenopausal years and declines after the menopause.

In March 2012, ulipristal acetate received a European-wide medical licence permitting its use as a medical treatment of fibroids.

AHA Congress

RELAX-AHF study

The Phase III RELAX-AHF study has shown that investigational RLX030 (serelaxin) improved symptoms and reduced deaths by a third at the end of six months in patients with acute heart failure (AHF). Results of the study were presented recently at the American Heart Association (AHA) Scientific Sessions in Los Angeles and published simultaneously in *The Lancet*.

RLX030 is the first in a new class of medicines and is believed to act through multiple mechanisms on the heart, kidneys and blood vessels. RELAX-AHF demonstrated that RLX030 significantly reduced dyspnea (ie. shortness of breath), the most common symptom of AHF and the primary endpoint of the study. As one of two co-primary endpoints was met, the study achieved its primary objective based on pre-specified protocol criteria.

RELAX-AHF was an international randomised, double-blind study involving 1,161 patients and was designed to compare the efficacy and safety profile of RLX030 to placebo in addition to standard therapy for the treatment of AHF. RLX030 was given upon hospitalisation in the form of an intravenous infusion (30 mcg per kg per day) for 48 hours in addition to conventional therapy for AHF, ie. loop diuretics and other medicines.

The study had two primary endpoints using different scales to measure reduction in dyspnea. The visual analog scale (VAS) showed a significant benefit up to day five (p=0.0075), whereas the Likert scale (a baseline-related short-term assessment of dyspnea relief) did not reach significance at 6, 12 and 24 hours (p=0.702). As one of the primary endpoints was met, the study was positive according to protocol criteria.

The study did not meet its secondary efficacy endpoints, namely days alive and out of hospital up to day 60 (p=0.37), and cardiovascular death or re-hospitalisation due to heart or kidney failure up to day 60 (p=0.89).

Results showed that 7.3% of patients died from all causes in the RLX030 group compared to 11.3% in the placebo group (p=0.02) at 180 days of follow-up. All-cause mortality up to day 180 was a safety endpoint of the study. The number of deaths due to cardiovascular causes to day 180 (an additional pre-specified efficacy endpoint) was also significantly lower with RLX030 than placebo (6.1% versus 9.6%, p=0.028). RLX030 was therefore associated with a 37% reduction in all-cause and cardiovascular mortality at the end of six months.

In addition to its effects on mortality and symptoms, RLX030 met several other efficacy endpoints including significantly reducing the worsening signs and symptoms of heart failure up to day 14 (p=0.024), thereby decreasing the need for intensified heart failure treatment. RLX030 also reduced the mean length of stay in hospital by 0.9 days (p=0.039) and in the intensive/cardiac care unit by 0.4 days (p=0.029).

Professor John R. Teerlink, MD of the Section of Cardiology, San Francisco Veterans Affairs Medical Center, University of California, San Francisco, and the co-lead investigator of the RELAX-AHF study, said: "This study with serelaxin is important because it may offer the prospect of a much-needed new medicine for acute heart failure, where the death rate remains high and there have been few new therapies for several decades."

RLX030 was well tolerated and adverse events, including low blood pressure (hypotension), were generally comparable between RLX030 and placebo. There was a lower incidence of adverse events related to renal impairment with RLX030 than placebo (4.6% versus 8.6%). The most common adverse events in both treatment groups were cardiac disorders, metabolism and nutrition disorders, and gastrointestinal disorders. No clinically significant differences in the incidence of serious adverse events were seen between treatment groups.

TRILOGY ACS: platelet function substudy

A study presented at the AHA investigated platelet function during extended prasugrel and clopidogrel therapy for patients with acute coronary syndromes (ACS) treated without revascularisation. It found that prasugrel was associated with lower platelet reactivity than clopidogrel, irrespective of age, weight, and dose.

The study looked at the relationship of platelet function testing measurements with outcomes in patients with ACS initially managed medically without revascularisation. The objective was to characterise the differences

and evaluate clinical outcomes associated with platelet reactivity among patients with ACS treated with clopidogrel or prasugrel.

Patients with medically managed unstable angina or non-ST-segment elevation myocardial infarction were enrolled in the study (2008 to 2011) comparing clopidogrel versus prasugrel. Of 9326 participants, 27.5% were included in a platelet function substudy: 1286 treated with prasugrel and 1278 treated with clopidogrel.

Despite consistently lower platelet reactivity with prasugrel for much of the study period, the rate of myocardial infarction, stroke, or cardiovascular death was not significantly different between patients taking the newer antiplatelet and those taking clopidogrel through 30 months (17.2% versus 18.9%, P=0.29), according to study investigator Matthew Roe, MD, of Duke University Medical Center, and colleagues.

RE-LY subanalysis of patients with non-valvular AF and diabetes

Study results from a new retrospective sub-analysis of the RE-LY trial indicated patients with non-valvular atrial fibrillation (NVAF) who also have diabetes experienced similar safety and efficacy with Pradaxa (dabigatran etexilate) 150mg or dabigatran 110mg relative to warfarin, in comparison to patients with NVAF who do not have diabetes.

This data was presented at the recent AHA and the results show that patients with diabetes in the RE-LY study had a higher prevalence of additional cardiovascular diseases (eg. hypertension), and for diabetic patients with NVAF randomised to warfarin, INR was not as well-controlled. Despite this, the sub-analysis indicates that patients with NVAF and diabetes, compared to patients with NVAF without diabetes, derive similar relative outcomes from dabigatran etexilate 150mg or dabigatran 110mg compared to warfarin.

Of the 18,113 patients in the RE-LY trial, 4221 patients (23%) had diabetes when the trial began. This sub-analysis examined patient characteristics and outcomes of patients with NVAF, comparing those with and without diabetes, and the relative efficacy of dabigatran etexilate 150mg twice daily or dabigatran 110mg twice daily versus warfarin, using an interaction p-value.

Harald Darius, Vivantes Berlin-Neukolln Medical Center, Germany, said: "It is common for patients with atrial fibrillation to have comorbidities, such as diabetes. These findings are important and relevant since nearly one out of four patients with NVAF in the RE-LY study also had diabetes."

The sub-analysis found that patients with diabetes were younger (70.9 versus 71.7 years, p<0.01) and more likely to have other cardiovascular diseases, including hypertension (86.6% versus 76.5% p<0.01), coronary artery disease (37.4% versus 24.9%, p<0.01) and peripheral vascular disease (5.6% versus 3.2%, p<0.01). Compared to RE-LY patients without diabetes, those with diabetes had a higher risk of strokes and major bleeds, except intracranial bleeding.

RE-LY was a global, phase III, randomised trial of 18,113 patients enrolled in 951 centers in 44 countries, investigating whether dabigatran etexilate (two blinded doses) was as effective as open-label warfarin—INR 2.0–3.0—for stroke prevention. Patients with non-valvular AF and at least one other risk factor for stroke (ie. previous ischemic stroke, transient ischaemic attack, or systemic embolism, left ventricular ejection fraction <40%, symptomatic heart failure, New York Heart Association Class >2, age >75 years, age >65 years with either diabetes mellitus, history of coronary artery disease, or hypertension) were enrolled in the study for two years with a minimum follow-up period of one year.

RELY-ABLE study: additional support to safety profile

New data from the RELY-ABLE study have provided additional support to the safety profile and efficacy of Pradaxa (dabigatran etexilate) for stroke prevention in patients with nonvalvular atrial fibrillation (AF) over a period in excess of two years.

The new long-term results presented at the AHA, are consistent with the findings from the RE-LY trial. The rates of stroke and haemorrhage observed during an additional 2.3 years of blinded follow-up in RELY-ABLE correspond to the initial RE-LY results, with the benefit of both doses of dabigatran etexilate sustained throughout the study duration.

The combined data from RE-LY and RELY-ABLE provides over four years of clinical trial experience and constitutes the longest evaluation of the benefits and safety of any novel oral anticoagulant for stroke prevention in AF to date.

The international multi-centre

RELY-ABLE study followed 5851 patients on dabigatran etexilate for a further 28 months after completion of the RE-LY trial. It examined the long-term benefits of the two treatment doses (110mg bid and 150mg bid) in an ongoing randomised and blinded approach.

Professor Gregory Lip, Professor of Cardiovascular Medicine at the University of Birmingham, said: "The results from RELY-ABLE will be a valuable contribution to evidence-based decision making in the selection of a treatment that is effective in patients with AF over the longer term. Despite the prevalence of AF and the associated five-fold increase in risk of stroke, there remains significant scope for improvement in reducing the risk of stroke in the AF patient population. RELY-ABLE will serve to give added confidence to physicians in the appropriate prescribing of dabigatran etexilate."

Cardiorenal rescue study in acute decompensated heart failure (CARRESS-HF)

Ultrafiltration was no more effective in removing excess fluid from the heart than using standard treatment including diuretics to reduce congestion in heart failure patients, according to research presented at the AHA.

Excess fluid build-up in the body can occur in many heart failure patients and lead to a need to hospitalisation. For decades, physicians have used diuretics to remove excess fluid. Many heart failure patients may have some degree of abnormality in kidney function and diuretics can lead to further worsening of kidney function.

In the prospective randomised comparison of the treatments, researchers randomly assigned ultrafiltration or a diuretic-based approach to 188 hospitalised patients (average age 68 years, mostly male) with persistent excess fluid and worsening kidney function. 84% had high blood pressure; 66% had diabetes; and 75% had at least one recent admission to the hospital for heart failure.

Researchers measured the patients' weight change (as a measure of improved congestion and fluid loss) and kidney function four days after starting treatment, and followed patients for 60 days to see if they remained stable and out of the hospital.

Both groups lost about 12 pounds during the first four days of treatment. Kidney function worsened in ultrafiltration patients and they also had more side effects. After 60 days, there were no differences between the two groups in either heart failure hospitalisations or death.

Bradley Bart, lead author of the study and chief of cardiology at Hennepin County Medical Center in Minneapolis, Minn said: "We need better treatments for managing hospitalized heart failure patients, but our findings indicate that ultrafiltration may not be the answer. Ultrafiltration is more expensive, more complex and doesn't offer any advantage as administered in this study."

UMPIRE trial results: use of multidrug pill in reducing cardiovascular events

People are much more likely to take heart medicines if they are combined in one pill, according to a late-breaking clinical trial presented at the AHA.

Researchers studied whether changing the delivery of several medications into one fixed-dose, combination pill might improve adherence and, therefore, improve blood pressure and cholesterol control. The researchers followed more than 2000 men and women (average age 62 years) with cardiovascular disease in Europe and India for an average 15 months. Half of the participants were given a combination pill of aspirin, a cholesterol-lowering agent (statin) and two blood pressure-lowering drugs. The other half took their medications as usual, with multiple pills and doses.

Researchers noted that the group taking a single pill improved adherence by a third and had improved blood pressure and cholesterol levels compared to those taking multiple pills.

Simon Thom, lead author of the UMPIRE trial and Professor of Cardiovascular Medicine and Pharmacology at Imperial College London, said: "This is the first time the impact of a fixed-dose, combination strategy has been tested in people with cardiovascular disease. People who have suffered heart attacks or strokes or those at high risk of such problems need to take preventive medications, including antiplatelet drugs (such as aspirin), cholesterol-lowering and blood pressure-lowering drugs. But the reality is that many people in this high risk category get out of the habit of taking the recommended medications. This happens for a variety of reasons; some of which may be corrected by a single, simple, fixed dose combination pill—a combination known as a 'polypill.'"