

NEWS

KEEPS: reassurance on heart effects of HRT

Four years of hormone-replacement therapy (HRT) started soon after the onset of the menopause improved depression and anxiety in healthy women without promoting or worsening cardiovascular disease, the results of the KEEPS study show.

The study, presented at the North American Menopause Society 2012 Annual Meeting held in Orlando, Florida, US, involved 700 women who took either oral conjugated equine oestrogens (Premarin®) 0.45 mg/day (lower than the 0.625 mg/day used in the Women's Health Initiative [WHI] study), transdermal oestradiol (Climara®) 50 micrograms/day, or placebo. Women taking

the active oestrogens received 200 mg of micronised progesterone for 12 days each month.

As expected, both types of hormone therapy relieved menopausal symptoms, such as hot flushes and night sweats and had favourable effects on bone mineral density compared with placebo.

WHI results hinted that the timing of therapy may be important. In general, the women in WHI started hormone therapy at an older age (mean age 63 years) than in most previous studies. In KEEPS, however, all the women were within three years of menopause when

they entered the study (mean age 52) and had no evidence of cardiovascular disease.

In KEEPS, oestrogen therapy did not increase blood pressure levels. Oral oestrogen had small but favourable effects on high-density lipoprotein and low-density lipoprotein but increased triglycerides and C-reactive protein. Transdermal oestrogen had no effect on biomarkers but improved glucose levels and insulin sensitivity. Carotid ultrasound showed no differences in the progression of arterial wall thickness among the three treatment groups. There was a non-significant trend toward less progression of coronary artery calcium in the hormone therapy groups.

New diabetes guidelines stress individual patient needs

The European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) have published new guidelines on the treatment of type 2 diabetes, which are less prescriptive than

previous guidelines. They advocate more patient involvement and give guidance on the rational approach to the choice of therapy.

While general recommendations regarding the intensiveness of glycaemic therapy focused

in the past on a HbA1c target below 7%, the new statement emphasises that goals must be individualised, with the precise target taking into account patient's attitude and expected treatment efforts, the risk



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reduction can be achieved when Edarbi® is co-administered with other antihypertensive

medicinal products, including diuretics and calcium channel blockers. **Contraindications:** Hypersensitivity to any component of Edarbi®. Second and third trimester of pregnancy. **Warnings and Precautions:** In patients with an activated renin-angiotensin-aldosterone system (e.g. congestive heart failure, severe renal impairment or renal artery stenosis) the use of angiotensin II receptor antagonists has been associated with acute hypotension, acidaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with Edarbi®. Edarbi® should be used with caution in hypertensive patients with severe renal impairment, congestive heart failure or renal artery stenosis or those who have recently undergone kidney transplantation as there is no experience of use of Edarbi® in these patients. In patients with ischaemic cardiomyopathy or ischaemic cerebrovascular disease excessive blood pressure decreases could result in myocardial infarction or stroke. Edarbi® is not recommended in patients with severe hepatic impairment or primary hyperaldosteronism. In patients with marked volume- and/or salt-depletion symptomatic hypotension could occur after initiation of treatment with

Edarbi®. Hypokalaemia should be corrected prior to treatment which should start under close medical supervision. Concomitant use of Edarbi® with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other medicinal products that may increase potassium levels (e.g. heparin) may lead to hyperkalaemia in hypertensive patients. The risk of hyperkalaemia is increased in the elderly, in patients with renal insufficiency, in diabetic patients and in patients with other co-morbidities. Monitoring of potassium should be undertaken as appropriate. Special caution in patients suffering from aortic or mitral valve stenosis, or hypertrophic obstructive cardiomyopathy (HOCM). Edarbi® should not be initiated during pregnancy. When pregnancy is confirmed treatment with Edarbi® should be stopped immediately. Edarbi® is not recommended during breastfeeding. **Drug Interactions:** No clinically significant interactions with amiloride, amiodone, chloralhydrate, digoxin, fluconazole, glyburide, lisinopril, metformin, and warfarin. Use with lithium is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Attenuation of the



associated with glycaemia and other adverse effects, disease duration, life expectancy, other co-morbidities, established vascular complications, and the patient's own resources and support system.

It notes, for example, some patients may feel that the weight gain associated with a particular diabetes therapy is unacceptable, whereas others may consider risk of hypoglycaemia as the primary factor in selecting treatment. And patients who are older with multiple co-morbidities will have different

issues compared with a younger newly-diagnosed person that is otherwise healthy.

EASD president, Professor Andrew Boulton (University of Manchester) said: "The overarching goal should be to reduce blood glucose concentrations safely to a range that will substantially minimise long-term complications, but always keeping in mind the potential adversities with treatment burden, particularly in the elderly".

Other key points from the guidelines include:

- Diet, exercise and education to remain

the foundation of any type 2 diabetes treatment programme

- Unless there are prevalent contraindications, metformin is the optimal first-line drug
- After metformin, there are limited data to guide treatment. Combination therapy with an additional one or two oral or injectable agents is reasonable, aiming to minimise side effects where possible
- Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.

More on diabetes risk with statins

Another study has found a slight increase in fasting glucose levels in patients at increased risk of type 2 diabetes taking statins. The study (published in *BMJ* online 13th September 2012) was conducted by a Finnish group who concluded that their findings suggest statin use "might have unfavourable effects on glucose metabolism and hamper beneficial effects of lifestyle intervention in people at high risk of type 2 diabetes".

While the researchers say that that the benefits of statin therapy for the prevention of cardiovascular disease in people with an increased risk of type 2 diabetes are still unequivocal, they suggest that such patients on statins need to focus even more on intensive lifestyle intervention, with a healthy diet, non-smoking, and physical activity.

In the study, 2,798 patients at high risk of diabetes were followed for one year. Patients

were given counselling on lifestyle interventions; fasting blood glucose was measured at baseline and one year. Results showed that 484 individuals (17.3%) used statins at baseline. Of these patients, 7.5% developed type 2 diabetes during follow-up compared with 6.5% of those not taking statins, a non-significant difference. However, fasting glucose increased significantly by 0.08 mmol/L in statin users but remained unchanged in non-users.

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antihypertensive effect may occur with NSAIDs and use with NSAIDs may lead to worsening of renal function and increase in serum potassium. Therefore adequate hydration and monitoring of renal function at the beginning of treatment is recommended. **Side Effects:** Prescribers should consult the Summary of Product Characteristics in relation to other side-effects. In clinical studies of up to 56 weeks, adverse reactions were mostly mild or moderate, with an overall incidence similar to placebo. The incidence of adverse reactions with Edarbi[®] was not affected by gender, age, or race. These are ranked by frequency, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports. The most common adverse reaction was diarrhoea. Other adverse reactions seen commonly in clinical trials include dizziness and increased blood creatine phosphokinase. Uncommon adverse reactions include hypotension, fatigue, peripheral oedema, increased blood creatinine and hyperkalaemia. Angioedema, including circumoral oedema and periorbital oedema, was rarely seen in patients during open label treatment. Co-administration with chlorzoxazone increased the frequency of increased blood creatinine and hypotension from uncommon to common. Co-administration with amlodipine increased the frequency of peripheral oedema from

uncommon to common, but was lower than amlodipine alone. **Legal Category:** POM **Packs and Basic NHS Price:** Edarbi[®] 20mg, £16.80 for 28 tablets (EU/1/11/734/002), Edarbi[®] 40mg, £16.80 for 28 tablets (EU/1/11/734/006) and Edarbi[®] 60mg, £19.95 for 28 tablets (EU/1/11/734/009). **PI approval code:** AZ1120107a **PI Date of Preparation:** February 2012 **Marketing Authorisation Holder:** Takeda Global Research and Development Centre (Europe) Ltd., 61 Aldwych, London, WC2B 4AF, UK. **Further information can be obtained from:** Takeda UK Ltd, Takeda House, Mercury Park, Woodburn Green, High Wycombe, Bucks HP10 0HH. Tel: 01628 537900 Fax: 01628 525617 @Registered trademark owned by Takeda Pharmaceutical Company Ltd. Reference: 1. Bönnner G, et al. *J Hypertens* 2010; 28:e253

Please refer to the Summary of Product Characteristics for details on the full side-effect profile and drug interactions of Edarbi[®]. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Takeda UK Ltd. on 01628 537900.

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