PHARMACOTHERAPY

Benefits of menopausal hormone therapy—timing is key

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A large Danish study overturns the concept that postmenopausal hormone replacement therapy increases the risk of experiencing cardiovascular events. Indeed, the study shows that such therapy decreases the risk of myocardial infarction by ~50% and mortality by ~40%. So what is the truth?

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Much controversy exists regarding the costs, benefits and safety of hormone replacement therapy (HRT) in postmenopausal women. However, a Danish study into the effects of postmenopausal HRT indicates that such interventions might lead to reductions in cardiovascular risk throughout the ageing process. Schierbeck *et al.*[1] show that women in whom HRT is initiated around the time of menopausal transition have a significantly lower risk of myocardial infarction, heart failure or death than those who receive no such treatment.

This intention-to-treat analysis of a cohort of 1,006 postmenopausal women who were randomly allocated to receive HRT or no treatment and followed up for nearly 16 years provides an interesting set of results that were awaited by many in the field. The cohort of women in the study by Schierbeck *et al.*[1] were originally enrolled in a randomized, open-label trial of the effect of HRT with synthetic 17-β-oestradiol or a combination of 17-β-oestradiol and a synthetic progestin (norethisterone acetate) on osteoporotic fractures.

Patients were enrolled between 1990 and 1993 and the planned study duration was 20 years. In 2002, when the first report of the Women's Health Initiative (WHI) trial was published,[2] the patients were advised to stop taking the medication owing to emerging evidence of an adverse risk-to-benefit balance. However, follow-up for both primary and secondary outcomes was continued using data from national registers which include information on hospital admissions and death. The incidence of the composite primary endpoint of death, myocardial infarction or heart failure was reduced in women receiving HRT. The magnitude of this reduction was ~50% during both the 10-year period of active treatment and the later 6-year observational phase. Importantly, no differences were recorded between the two groups in terms of stroke, venous thromboembolism or breast cancer incidence over the duration of the study.

At least two key differences exist between this study and those previously conducted. The first difference is the age of the women enrolled. In the trial by Schierbeck *et al.*,[1] women who started HRT soon after the menopausal transition (<24 months since last menstrual bleeding) were studied. By contrast, in the WHI trial[2] (the largest study of this kind previously carried out) nearly 75% of enrolled patients were aged >60 years and <5% of the population studied were <5 years from the menopausal transition when treatment was initiated. Nevertheless, no discrepancy exists between the results of Schierbeck *et al.*[1] and those from subpopulation analyses of the WHI[3] and Nurse's Health Study[4] datasets, in which there were clear indications that women receiving HRT soon after menopause experienced reduced rates of cardiovascular disease. However, these subpopulation analyses were not sufficiently powered to enable definitive conclusions to be drawn.[3,4] Additionally, the finding by Schierbeck *et al.*[1] that venous thromboembolism, stroke and breast cancer were not increased in women receiving HRT is not surprising at all. In most previous studies, including the WHI trial, provision of HRT to women around the time of menopause did not increase the incidence of any of these conditions, highlighting that the use of this therapy in women 10 years after menopause (which has no clinical indication) rather than the use of HRT *per se* leads to harmful effects.

A second difference between the study by Schierbeck *et al.*[1] and other studies conducted is that the medications used are different from those used in previous trials. In this trial, women were treated with 17-β-oestradiol and norethisterone acetate, whereas conjugated equine oestrogens and medroxyprogesterone acetate were used in most previous studies. The use of a progestin during HRT—particularly medroxyprogesterone acetate—is increasingly appreciated to be associated with a higher risk of cardiovascular disease as compared to use of oestrogen-only therapies.[5] This phenomenon was also found in the study by Schierbeck *et al.*,[1] in which there was a trend towards a lower incidence of cardiovascular events in women who received 17-β-oestradiol alone than in those who received 17-β-oestradiol and norethisterone acetate.

Why are the findings of Schierbeck *et al.*[1] important? This study is the first prospective randomized trial in which the only

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question that has clinical relevance has been addressed: what are the long-term effects of HRT in women who start treatment at the time of menopause? In all previous randomized studies, the role of hormones in preventing diseases during ageing has been investigated, without taking into consideration the fact that the action of hormones is strictly dependent on the status of the tissues and cells they act upon. Experimental evidence from studies in cells, animals and humans shows that oestrogens protect the healthy cardiovascular system but have detrimental effects in the presence of degenerative changes, such as atherosclerosis.[6,7] How this finding applies to HRT in women aged 50 years as compared to those aged 65 years is not difficult to appreciate.[8]

Despite these study findings, and after nearly 20 years of debate, the contradiction remains: unambiguous studies show that young postmenopausal women can benefit tremendously from treatment with oestrogens in terms of reductions in the risk of heart disease, fracture and, possibly, dementia, but all existing guidelines state that HRT should not be used to prevent such disorders. The most recent guidelines, published by the US Preventive Services Task Force, explicitly recommend against the use of either oestrogen-based treatments or combinations of oestrogens and progestins for prevention of chronic conditions.[9]

In real-world clinical settings, HRT is generally initiated because women suffer from hot flashes or vulvo–vaginal atrophy, with the only aim being to counteract these symptoms. However, we believe that this study should raise awareness in the media, regulatory authorities and the general population that HRT has powerful off-target benefits: it saves lives and reduces disability. Additionally, this treatment costs much less than drugs that are not as effective in reducing blood cholesterol levels or the risk of fractures. This advantage is not trivial and a shift in communication and clinical attitude could lead to enormous benefits for women and health-care systems throughout the world.

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Competing interests
A. Genazzani declares associations with the following companies: Abbott Laboratories, Bayer HealthCare, Gedeon Richter, Novo Nordisk, Pfizer and Théramex (Teva Pharmaceuticals).
T. Simoncini declares associations with the following companies: Abbott Laboratories and Bayer HealthCare. See the article online for full details of the relationships.

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DIABETES

Effect of vitamin D on diabetic kidney disease in T1DM

Peter Rossing and Christel Joergensen

Low circulating levels of vitamin D metabolites were found to be associated with development of microalbuminuria in patients with type 1 diabetes mellitus from the DCCT/EDIC study. Could interventions aimed at improving vitamin D levels be a new option for the prevention of diabetic kidney disease?

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Diabetic kidney disease is a leading cause of end-stage renal disease across the world, and, in addition, patients with diabetic kidney disease have an increased risk of cardiovascular morbidity and mortality. Although improved glycaemic control and aggressive treatment of hypertension with agents that block the renin–angiotensin–aldosterone system (RAAS) have improved the prognosis, diabetic kidney disease remains a considerable problem. de Boer *et al.*[1] examined whether impaired vitamin D metabolism is related to the development of diabetic kidney disease. The findings support investigation into the use of vitamin D supplementation to prevent microalbuminuria in patients with type 1 diabetes mellitus (T1DM).

de Boer *et al.*[1] measured the plasma concentrations of several vitamin D metabolites in 1,193 patients with T1DM at or towards the end of the Diabetes Control and Complications Trial (DCCT). The patients were then followed up for the development of persistent microalbuminuria, sustained impairment of renal function (estimated glomerular filtration rate <60 ml/min/1.73 m^2) or persistent hypertension (>140/90 mmHg) during the 16 years in the Epidemiology of Diabetes Interventions and Complications (EDIC) study. Levels of 25-hydroxyvitamin D had been measured to reflect total intake of vitamin D_2 and vitamin D_3 from cutaneous synthesis and dietary consumption. Levels of two other vitamin D metabolites were also measured: 24,25-dihydroxyvitamin D, the most abundant product of 25-hydroxyvitamin D catabolism, and 1,25-dihydroxyvitamin D, the activated form of the hormone.

Microalbuminuria, impaired renal function and hypertension had developed in 166, 54 and 541 patients, respectively, by the end of follow up. Low levels of 25-hydroxyvitamin D were associated with an increased risk of persistent microalbuminuria in a dose-dependent manner: patients with levels <50 nmol/l had a 65% higher risk than patients with levels >75 nmol/l. Low levels of 24,25-dihydroxyvitamin D