‘Tib the balance’: the search for the optimal hormone replacement therapy

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This editorial refers to ‘Menopausal complaints, oestrogens, and heart disease risk: an explanation for discrepant findings on the benefits of post-menopausal hormone therapy’† by Y.T. van der Schouw et al., on page 1358 and ‘Significant differential effects of lower doses of hormone therapy or tibolone on markers of cardiovascular disease in post-menopausal women: a randomized, double-blind, crossover study’‡ by K.K. Koh et al., on page 1362.

In 1902, W. Bayliss and E. Starling formulated a new term in their effort to prove the existence of internal secretions. The selected term ‘hormone’ was phrased after the Greek word for ‘I excite’.1 Since these early observations about the physiological relevance of sex hormone regulation, the excitement in this field of research and related therapy has never really stopped. On the one hand, we have learnt a lot about the complex regulatory network of sex hormones and their respective receptors in heart disease.2 On the other, in parallel with the growing knowledge about hormones, the life expectancy of the population in demand for treatment is increasing. Almost 50 years ago, the Framingham Heart study showed that ovariectomy without hormonal substitution leads to an increased risk of developing cardiovascular disease. New data support this observation and underline the fact that hysterectomy leads to an increased risk for ischaemic heart disease.3–6 However, it is well documented that oestrogen substitution alone is not sufficient to prevent cardiovascular disease in these patients. With more post-menopausal women than ever till date, we found that the following questions remain unanswered: what tips the balance of the hormonal equilibrium and how can it be restored properly.

Following the publication of large prospective randomized trials of hormone replacement therapy (HRT), such as HERS and WHI, a heated discussion about the quality and scale of the statistical relevant readout of these studies is warranted.7 This controversy asks for more, better controlled, and cleverly recruited prospective studies.

Current treatment strategies are based on the relief of climacteric symptoms and not on the primary prevention of cardiovascular disease. Standard HRT with either unconjugated oestrogens or combined oestrogen/progestin preparations have been found to be associated with an increased risk for breast cancer or venoembolism, in particular the oestrogen/progestin preparation. These studies showed that both a selection bias (depending on the centre which recruited) and unsatisfying risk stratification exist in the recruitment of post-menopausal women with or without clinical symptoms.

Van der Schouw et al.8 state that the severity and onset of the underlying climacteric symptoms have to be taken into account more properly. The timing of the enrolment after menopause and the severity of symptoms, such as vasomotor symptoms, play a major role in the assessment of the risk stratification of morbidity. Although perimenopausal sweating is associated with low estradiol levels, hot flashes may be an indicator for increased oxidative stress. Earlier studies, such as the WHI, used quality of life (QOL) scores such as theSF36 questionnaire to report these changes in women on average 15 years after menopause.7 Both the statistical analysis (normal distribution vs. non-parametric statistical procedures) and the age at the time of recruitment show that this trial will not answer the question regarding which women benefit most from which hormone replacement strategy. In future studies, a well-balanced QOL is desirable to assign the patient who benefit the most from a certain protocol. Finally, success of the recruitment procedure heavily depends on the centres which enrol. As most HRT prescriptions are made by OB/GYN professionals and not by cardiovascular prevention centres, the recruitment centres for these trials should be equilibrated to avoid any bias.

New ongoing study protocols focus on the use of oestrogen–androgen preparations, the combination of oestrogen with selective oestrogen receptor modulators (SERM) or synthetic steroids.9,10 The prodrug is quickly metabolized in the gastrointestinal tract to hormone active metabolites. These metabolites exert a variety of actions, which depend on the state of sulphation in the respective target tissues. In patients with a climacteric syndrome, Tib has been shown to alleviate vasomotor symptoms without any effect on endometrium proliferation or an increase in

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thrombo-embolic events. The Million Women study stated that Tib may enhance the relative risk of developing breast cancer; however, this observation has to be proven in a randomized clinical trial. Tib has been available in Europe and other countries for many years; however, it has not been approved for use in the USA.

These longstanding clinical observations of Tib lead to the assumption that no major cardiovascular side effects may be found. Whether Tib has the potential to alleviate menopausal complaints and prevent cardiovascular disease is under study.

Tib has been shown to improve flow-mediated brachial artery dilator response, comparable to those with standard combined HRT. Furthermore, it might modulate lipid levels, and Koh et al. now show that in a small (41 patients), short-term prospective study, Tib alone (2.5 mg) compared with low dose (0.3 mg) conjugated equine oestrogen (CEE) has a favourable effect on flow-mediated responses and PAI-1 levels. No changes in hs-C-reactive protein were observed. In addition, when compared with CEE, a decrease in total cholesterol levels, triglycerides, was shown.

The women were on average 7.5 years past menopause. Twenty and 14 women of both groups were hypertensive and overweight, respectively. Overall, Koh et al. demonstrated in this study that Tib has a positive profile with respect to cardiovascular risk marker reduction. Interestingly, Tib decreased HDL levels, whereas CEE increased HDL levels, this might be attributed to its androgenic potential. The study also showed that in a small cohort of both hypertensive and normotensive obese women, Tib might significantly exert its positive effects through its complex steroidogenic potential. These oestrogenic, androgenic, and progestogenic features might tip the balance in post-menopausal women. Well-defined and recruited prospective large-scale randomized trials may therefore lead to the equilibrium needed in the elderly. These studies with cardiovascular endpoints (cardiovascular or thrombo-embolic event) will clarify the complex role of promising synthetic steroids in HRT.

References