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Editorial

The heart of the WHI study: time for hormone therapy policies to be revised

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In 2002, immediately after the first publication of the Women's Health Initiative (WHI) results[1], attitudes to hormone therapy (HT) changed dramatically. Many millions of women in the USA[2] and around the world stopped taking hormones because the WHI investigators and the media presentation of the data told them that HT is dangerous. The message that came out of the NIH-sponsored project was very clear: HT should not be prescribed for prevention of chronic diseases of old age (i.e. coronary artery disease and osteoporosis), but may still be considered on a short-term basis for women who have severe menopause-related symptoms. The resulting fear of increased risks of coronary artery disease and breast cancer in hormone users left many women suffering from sudden adverse changes in their quality of life following cessation of HT.

Being captured by their own message, the WHI investigators failed to address during 2002–2006 an important issue that was already evident at the preliminary analyses – that age and years from menopause have major roles in the determination of benefits and risks of HT. It should not have been surprising that the WHI study did not reduce the incidence of coronary artery disease in women with a mean age of 63 years at enrolment, who are not the women usually seeking HT for the relief of menopausal symptoms. The problems have arisen because of inappropriate extrapolation and generalization of these results from mainly older women to those with symptoms around the time of menopause. Detailed evaluation of the WHI data and subgroup analyses showed that the initial conclusions drawn by the WHI investigators were in part misleading. It became apparent that, in the early postmenopausal period, coronary artery disease is no threat to hormone users. In fact, the data suggested a cardioprotective effect of estrogen-alone therapy in the younger age group (less than 60 years at recruitment to the study)[3,4]. Moreover, the most recent article, on coronary artery calcification, which reflects calcified atheroma and total plaque burden, showed that, 8.7 years after randomization, estrogen-alone users, who were 80% or more compliant, had 61% less atherosclerotic plaques in women whose mean age was 55 years at baseline, as compared to a placebo group ($p = 0.004$)[5]. Relative to placebo, for women in the WHI study below 60 years of age, conjugated estrogens alone *reduced* the following major adverse events per 10 000 treated women annually; coronary artery disease by 11, strokes by two, diabetes cases by 14, fractures by 56, breast cancer diagnoses by eight and deaths by ten. The only significant risk is an increase of four deep vein thromboses/pulmonary emboli, seen mostly in women with risk factors for thromboembolism in the early years of use[6]. Data from the WHI study for combined HT need to be released to allow a similar analysis of these risks and benefits in younger postmenopausal women.

This amazing shift in the interpretation of the WHI results should have been addressed by the WHI investigators, but, to date, generally they have preferred to remain silent. The WHI trial was stopped prematurely because an unvalidated global index, a measure balancing some of the risks and benefits of hormone use (quality of life was not included), exceeded a predetermined safety margin. The new analyses should have led to earlier assessment of the global index for the 50–59-year age group, which did show less morbidity in the treatment group versus the

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placebo group (95 versus 115 cases/10 000 person-years)[4]. Whilst acknowledging the reduced power of subgroup analyses, the hazard ratio and confidence intervals for this outcome should be published, as it seems that, in the younger women who initiate HT and who are the vast majority of HT users, the WHI global index is in favor of HT use. This might have avoided the scare media headlines of 2002. Also, it is reasonable to assume that the WHI trial might have been continued as scheduled in at least the younger groups and the hysteria of 2002 avoided if these data had been made available and considered. It is not possible to quantify the harm that has been inflicted by the 50% decrease in hormone use as a result of the WHI study. Calculation of potential changes related to quality-of-life issues may be too difficult. Some related morbidities may change and there are controversial observational data linking a small decline in breast cancer rates to decreased HT use. However, an increase in fracture risk is certainly anticipated. In this issue, Gambacciani and colleagues have calculated that, in the USA alone over the next few years, there will be an excess of 43 000 fractures per year[7]. Perhaps in the coming years, as women in the 50–59-year-old group age, the adverse consequences concerning coronary events will become apparent as well.

Mistakes, misinterpretations, reanalyses of data and the emergence of better data contradicting past conclusions often occur in medicine. When that happens, the investigators involved, and those who have advocated changes in clinical guidelines based on data that now do not apply to the vast majority of symptomatic women near menopause, have a responsibility to review and change their previous conclusions and advice. We shall be some of the first to applaud this mature and necessary change of heart! There is still time to re-establish a correct perspective on HT. With the dramatic decline in HT use, there is now little prospect of funding for any large study from early menopause, such as the WHI study. One of the strengths of the two long-term trials of HT, the WHI and WISDOM (which was stopped during recruitment partly because of the misleading coronary heart disease data), should have been that they were funded independently of the pharmaceutical industry. However, the full data from both are currently locked away from the scrutiny of the scientific community. Two smaller clinical HT trials are in progress, the Kronos Early Estrogen Prevention Study (KEEPS)[8] and the Early versus Late Intervention Trial with Estradiol (ELITE), but these will not report for several years. Therefore, we make no apology for repeating the theme of several previous editorials[9–11] and the recent statements and updated recommendations from the IMS on postmenopausal hormone therapy[12], when we call upon the regulatory agencies to re-evaluate their previous statements and revise them according to the new data. On current assessment, the WHI trial, being the most important and the most ambitious project in menopause medicine, has done a great disservice to the well-being and health of adult women. It chose to study mostly elderly asymptomatic women who were atypical of normal HT users. They had an atypical cardiovascular response compared to the cardioprotective effect seen in nearly all studies near menopause. Have the regulatory bodies the heart and soul to review their advice on HT use that was mostly based on the early results of the combined HT arm of the WHI trial and the controversial observational Million Women Study[13]? In our view, women can now be reassured that estrogen therapy is safe when initiated near menopause, with the potential to increase the quality of life in symptomatic women and reduce their risk of future heart disease and premature death.

The following members of the Board of the International Menopause Society have specifically endorsed the Editorial: Fredrick Naftolin, Regine Sitruk-Ware, Marco Gambacciani, Martin Birkhaeuser, Kobchitt Limpaphayom, Alice MacLennan, Andrea Genazzani (Past President).

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