Chapter 73
Risk-Benefit Analysis of Combination vs. Unopposed HRT in Post-Menopausal Women

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ABSTRACT

Many trials on the use of hormone replacement therapy (HRT) have provided contradictory results on its risks and benefits in post-menopausal women. The use of HRT declined globally following publication of the first data from the Women's Health Initiative (WHI) trial in 2002, with the revelation that there was an increased risk of breast cancer and coronary heart disease (CHD) in postmenopausal women taking HRT. Following this, other leading studies published results that were consistent with these findings, which reduced enthusiasm for HRT use. However, recent publications from the International Menopause Society indicate that HRT is the first-line and most effective treatment for menopausal symptoms. Moreover, when the full results of the WHI trial were subsequently published, it appeared that HRT may confer benefits for CHD prevention below age 60. The statements from the British Menopause Society and the International Menopause Society (IMS) published in 2008 also supported this opinion. These revelations renew interest in HRT use. This paper analyzes the effects of combination versus unopposed HRT on osteoporosis, breast and CHD, endometrial cancer induction, venous thromboembolic disease, lipids and lipoproteins, neuroprotection, and cognitive function in post-menopausal women.

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INTRODUCTION

Hormone replacement therapy (HRT) is an intervention for surgical menopause, perimenopausal and postmenopausal symptoms based on the assumption that it may prevent discomfort and health problems caused by diminished circulating estrogen and progesterone hormones. In women who have had a hysterectomy, estrogen is usually given without progesterone, a therapy referred to as "unopposed estrogen therapy". HRT is seen as either a short-term relief (often one or two years, usually less than five) from menopausal symptoms (hot flashes, irregular menstruation, fat redistribution) or as a long term treatment to reduce the risk of osteoporosis (Minelli, Abrams, Sutton, & Cooper, 2004).

The HRT is a debated topic, fuelled by many studies reporting contradictory results regarding its risks and benefits particularly in post-menopausal women. For quite a long period till the end of previous century, HRT was used indiscriminately by women expecting the benefit of reducing cardiac risks, while providing a protective effect against bone fractures and improving overall quality of life. This belief was based on the demonstration of beneficial biological effects of HRT on vascular function, and supported by the effects observed in a large number of epidemiological studies (Stevenson, 2005). However, this decade brought scientific reformation in our understanding of the role of HRT in post-menopausal women. After decades of the public and professional belief that HRT would improve women's health, evidence to the contrary surfaced that was persuasive. There was a progressive accumulation of data from pivotal experimental studies reported since 1998 that led to a major swing against HRT. Consequently the use of HRT declined worldwide.

More than a dozen randomized controlled megatrials have investigated the risks and benefits of HRT in postmenopausal women since 1998. Out of these, three trials in the USA, two in the UK, and one in Estonia (Hulley, Grady, Bush, Furberg, Herrington, Riggs, & Vittinghoff, 1998; Hoibraaten et al., 2000; Viscoli, Brass, Kernan, Sarrel, Suissa, & Horwitz, 2001; Writing Group for the Women's Health Initiative Investigators, 2002; Clarke, Kelleher, Lloyd-Jones, Slack, & Schofield, 2002; Waters et al., 2002; Holmberg & Anderson, 2004; WHI, 2004; Veerus, Hovi, Fischer, Rahu, Hakama, & Hemminki, 2006) showed that such therapy does not protect against development of cardiovascular disease and may in-fact increase it. To further try to enunciate the risks and benefits in postmenopausal women, the US National Institutes of Health (NIH) set up a series of randomized clinical trials known as the Women's Health Initiative (WHI, 2004). First WHI trial was launched in 1991 that included more than 161,000 U.S. women aged between 50 to 79 years and consisted of two cohorts of women; the estrogen-alone group of women without a uterus and the estrogen-plus-progestin group of women with a uterus. Results from these trials showed that the combination of estrogen plus progestin was associated with increased rates of coronary events, stroke, breast cancer, pulmonary embolism (PE) and dementia. An increased rate of coronary events was also recorded in the first year of treatment in the Heart and Estrogen-Progestin Replacement Study (HERS). Million Women Study (Beral & Million Women Study Collaborators, 2003) also established an increased risk of breast cancer with HRT. WHI study showed that estrogen alone was associated with stroke and possibly pulmonary embolism and did not protect against coronary events. The WHI Memory Study (WHIMS) showed that estrogen alone did not decrease the risk of dementia. Accordingly, it was concluded that HRT should no longer be recommended for the prevention of cardiovascular disease or dementia or as first-line therapy for osteoporosis. Women's international study of long duration oestrogen after menopause – WISDOM (Vickers et al., 2007), which began recruitment in 1999 of postmenopausal women, was prematurely closed during recruitment, after the publication of