

## Evidence-Based Medicine and Hormone Replacement Therapy

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During the past decade, hormone replacement therapy (HRT) became one of the most frequently prescribed therapies in the United States.<sup>1</sup> The approved indications were the relief of postmenopausal symptoms and prevention of osteoporosis; however, the long-term use of HRT was promoted for several unlabeled indications, including the prevention of cardiovascular disease and dementia. HRT was also promoted as a way to improve the quality of life for postmenopausal women. The evidence for these unlabeled indications comes mainly from observational studies and from randomized clinical trials with non-clinical outcomes.<sup>2,3,4</sup> In several clinical trials, including the Heart and Estrogen/Progestin Replacement Study (HERS) and Women's Health Initiative (WHI) trials, HRT was found to reduce total cholesterol, reduce LDL, and improve HDL levels.<sup>5,6</sup> In 1997 the results of a meta-analysis of randomized clinical trials (RCTs) found that HRT did not prevent cardiovascular events, with a trend towards an actual increase in cardiovascular events among women receiving HRT.<sup>7</sup> In 1998, the HERS trial showed no benefit of HRT in the secondary prevention of cardiovascular disease.<sup>5</sup> Many experts resisted the findings of this high quality, level I evidence and based their conclusions on studies with indirect and lower levels of evidence.<sup>8,9</sup> In 2002, the WHI trial was stopped because women taking estrogen (conjugated equine estrogen) plus progestin (medroxyprogesterone acetate) were at increased risk for myocardial infarction, stroke, venous thromboembolism, and breast cancer as compared with women taking placebo (Table 1). In March 2004, the estrogen-alone arm of the WHI study was stopped because of the increased risk of stroke in the estrogen-alone arm, which was similar to what was found in the estrogen plus progestin arm of the WHI study.

The wide use of HRT violated several principles of evidence-based medicine (EBM): First, therapeutic and preventive interventions need to be supported by well-designed RCTs before they are endorsed and used by the public. Observational studies are of great value in understanding the natural history of diseases and their prognostic factors, but are of limited value in the evaluation of therapeutic and preventive interventions. Second, disease-oriented outcomes such as total cholesterol, LDL, and HDL levels, do not necessarily predict patient-oriented outcomes such as the rates of myocardial infarctions, strokes and total mortality. Disease-oriented outcomes are of great value for

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the generation of hypotheses, but therapeutic and preventive interventions need to show clear and beneficial effect on patient-oriented outcomes before endorsement by health care professionals.

Quality of life is one of the most important outcomes in the era of EBM.<sup>10</sup> For years proponents of HRT suggested that HRT improves the quality of life for postmenopausal women, but HRT did not improve the quality of life in the majority of women enrolled in the HERS and WHI trials. There was a small improvement in quality of life among women who had moderate-to-severe postmenopausal symptoms (12-15% of participants).<sup>11,12</sup>

In the WHI trial, HRT reduced the risk of osteoporotic fractures in postmenopausal women.<sup>13</sup> In addition, HRT was associated with a decreased risk of colorectal cancer (Table 1), but the cancers diagnosed in women who were using estrogen and progestin had greater lymph-node involvement and a more advanced stage than the cancers in the placebo group.<sup>14</sup> The investigators of the WHI trial analyzed the benefits and risks of HRT using a global index that included several pre-specified outcomes (coronary heart disease, stroke, pulmonary embolism, colorectal cancer, endometrial cancer, hip fracture and death due to other causes), which indicated that the risks of HRT outweigh its benefits.<sup>6</sup>

We still have several evidence-based interventions for the prevention of cardiovascular disease and osteoporosis such as smoking cessation, the promotion of a healthy diet and exercise. There are several evidence-based therapeutic interventions that can be used for the prevention of cardiovascular disease such as aspirin therapy. For the prevention of osteoporosis in postmenopausal women, vitamin D and calcium can be added.

Postmenopausal symptoms affect approximately 70%

**Table 1.** Summary of the final results of the Women's Health Initiative trial.

Outcome	NNT*	NNH**
Coronary Heart Disease <sup>22</sup> (CHD)***		250
Stroke <sup>23</sup>		156
Venous thromboembolism <sup>6</sup> (VTE)		105
Pulmonary Embolism <sup>6</sup>		227
Deep Vein Thrombosis <sup>6</sup>		141
Breast cancer <sup>24</sup>		205
Dementia <sup>25</sup>		113
All fractures <sup>13</sup>	41	
Hip fractures <sup>13</sup>	345	
Colorectal cancer <sup>14</sup>	286	

\*NNT=number of patients who need to be treated to prevent one bad outcome; \*\*NNH=number of patients who need to be treated to lead to one bad outcome; \*\*\*CHD=includes acute myocardial infarction and death due to CHD.

of postmenopausal women; the majority of women have mild symptoms that usually wane within 1-2 years. Only 20% of women report significant symptoms that require

therapeutic intervention.<sup>15</sup> HRT is very effective in the treatment of postmenopausal symptoms, but several alternative interventions can be used for the control of postmenopausal symptoms.<sup>16,17</sup> Western societal tensions to find a cure for menopause and extensive pharmaceutical marketing campaigns had a major role in the mass prescription of HRT despite lack of solid evidence for its safety and effectiveness.<sup>18</sup>

In this issue Dr. Kirkby et al study the use of different preventive and screening interventions for postmenopausal women in Saudi Arabia. The findings of this study are interesting, as the prevalence of HRT use was similar or higher than what was reported in many developed countries. In Italy 20.8% of postmenopausal women were reported to be HRT ever-users.<sup>19</sup> In Sweden 48% of postmenopausal women were reported to be HRT ever-users and 32% were current users.<sup>20</sup> In Japan only 6.3% of postmenopausal women were reported to be HRT ever-users and 2.5% of women were current users.<sup>21</sup> We have to acknowledge the limitations of Dr. Kirkby et al study as it comes from a single center with a relatively small number of patients reviewed. This consequently limits the applicability and external validity of this study. The story of HRT reminds us in Saudi Arabia about the urgent need for an agency to develop, adapt and implement evidence-based clinical practice guidelines tailored according to local needs and perspectives.

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