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## Hormone Replacement Therapy and Coronary Heart Disease

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Cover Illustration by Stacey Caiazzo

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# Hormone Replacement Therapy and Coronary Heart Disease

Jooyoung Julia Shin, MD, and Nanette Kass Wenger, MD

## I. INTRODUCTION

Natural menopause usually occurs between ages 45 and 55 years and is marked by a significant reduction in hormone production by the ovaries. Levels of estrogen in postmenopausal women are decreased to about one tenth of those in premenopausal women, while progesterone becomes nearly absent. Hot flashes are a common complaint and can be severe enough to disturb sleep. More seriously, life after menopause has been associated with several chronic disease states. On average, women in the United States live approximately 30 years after menopause, and these subsequent years come with an increased risk of cardiovascular disease, coronary heart disease, osteoporosis, cancer, and dementia.<sup>1</sup>

Cardiovascular disease ranks first among causes of death in women in the United States. Indeed, the yearly mortality from cardiovascular disease in women is more than twice that from all cancers.<sup>2,3</sup> Morbidity and mortality associated with coronary heart disease differ by gender. Although women present with symptomatic coronary heart disease at a later age than men, women exhibit a higher mortality rate and a higher rate of readmission within the first 6 months after a myocardial infarction.<sup>4</sup> Upon presentation to the hospital with a myocardial infarction, women are less likely than men to receive therapies such as thrombolytic agents, heparin,  $\beta$ -blockers, aspirin, or coronary angioplasty.<sup>5</sup>

Coronary heart disease is less common in premenopausal women, and its incidence starts to increase after menopause.<sup>6</sup> Women, on average, present with symptomatic coronary heart disease about 10 years later than men (Figure 1).<sup>7</sup> In addition, surgical menopause (ie, bilateral oophorectomy) also confers an increased risk of cardiac events, suggesting a cardioprotective effect of female hormones.<sup>8</sup> A delay in the occurrence of menopause is associated with a decrease in the cardiovascular mortality rate for postmenopausal women,<sup>9</sup> but the role of estrogen in coronary heart disease of the postmenopausal state remains controversial. This manual reviews important clinical trials that have shaped current rec-

ommendations regarding the use of hormone replacement therapy (HRT) in postmenopausal women. (While the Food and Drug Administration [FDA] now uses the term *postmenopausal hormone therapy* in place of the term *hormone replacement therapy*, the latter term is used in this review.)

## II. HRT AND CORONARY HEART DISEASE: OBSERVATIONAL DATA AND BIOLOGIC PLAUSIBILITY

Premenopausal women seem to be protected from cardiac events, theoretically through the effects of estrogen. This plausible explanation was reinforced by data from several observational studies conducted during the 1990s that found a 35% to 50% decreased risk of developing coronary heart disease with HRT.<sup>10–13</sup> For example, the Nurses' Health Study enrolled more than 48,000 healthy women and concluded that individuals taking HRT had a relative risk of 0.5 of developing cardiac events.<sup>14</sup> In addition to evidence from observational studies, there is physiologic evidence suggesting that estrogen may have potential cardiovascular risk-modifying effects. For example, several randomized, controlled trials have shown that HRT lowers serum low-density lipoprotein cholesterol (LDL-C) levels,<sup>15</sup> lowers lipoprotein (a) levels,<sup>16</sup> and increases high-density lipoprotein cholesterol (HDL-C) levels.<sup>17</sup> Direct infusion of 17 $\beta$ -estradiol during cardiac catheterization in women with coronary atherosclerotic heart disease has been shown to increase coronary blood flow in response to acetylcholine<sup>18</sup> and to increase brachial-artery-flow-mediated vasodilation in postmenopausal women.<sup>19</sup> Another randomized, controlled study demonstrated that short-term transdermal estradiol therapy significantly increased exercise time to myocardial ischemia in postmenopausal women with exertional angina.<sup>20</sup>

Based on the findings from observational studies that HRT may reduce the incidence of coronary heart disease, osteoporotic fractures, and colorectal cancer, HRT quickly became one of the most commonly prescribed drug