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Review

A "window of opportunity:" The reduction of coronary heart disease and total mortality with menopausal therapies is age- and time-dependent☆

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ABSTRACT

The totality of data indicates that the "window of opportunity" for reducing coronary heart disease (CHD) and overall mortality is initiation of hormone therapy (HT) within 6 years of menopause and/or before 60 years of age. Reduction of CHD risk and overall mortality with prolonged HT use in this subgroup of women is consistent across randomized controlled trials and observational studies. As such, HT use for 5 to 30 years in postmenopausal women who initiate HT in their 50 s substantially increases quality-adjusted life-years (QALYs) by 1.5 QALYs and is highly cost-effective at $2438 per QALY gained. Cumulated randomized controlled trial results indicate a consistency along with observational data that young postmenopausal women with menopausal symptoms who use HT for long periods of time have lower rates of CHD and overall mortality than comparable postmenopausal women who do not use HT.

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1. Introduction

The consistency of data across approximately 40 observational studies that demonstrate a reduction in coronary heart disease (CHD) and overall mortality with exogenous postmenopausal hormone therapy (HT) with estrogen (Grodstein and Stampfer, 1995, 1998; Prentice et al., 2006) and estrogen plus progestogen (Thompson et al., 1989; Falkeborn et al., 1992; Psaty et al., 1994; Grodstein et al., 1996; Prentice et al., 2005) is unparalleled by any other potential primary prevention therapy for CHD in women. The consistency across observational studies led to formulation of the estrogen cardioprotective hypothesis that remained un-challenged until the 1990s when a series of randomized controlled trials (RCTs) tested this hypothesis. Two well-established and consistent results from these 40 observational studies are supported by the cumulated RCTs: (1) the incidence of CHD and overall mortality is reduced in postmenopausal women who initiate HT in close proximity to menopause and (2) the beneficial effect of HT on CHD and overall mortality accumulates with duration of HT use.

2. Observational studies and RCTs of HT involved different populations of women

Whereas observational studies have shown a 30–50% reduction in CHD and overall mortality in users versus nonusers of HT (Thompson et al., 1989; Falkeborn et al., 1992; Psaty et al., 1994; Grodstein and Stampfer, 1995, 1998; Grodstein et al., 1996; Prentice et al., 2005, 2006), RCTs have shown a null effect on these outcomes when analyzed over all randomized women without consideration of age (Hodis and Mack, 2008). However, as shown in Table 1, women selected for RCTs were a different population than the women included in observational studies. Because population-based observational studies reflect the pattern of HT use within the general population, women who used HT in observational studies were relatively young at the time of HT initiation (30–55 years old), recently postmenopausal (majority initiated HT at the time of menopause), were relatively lean (approximate body mass index of 25 kg/m^2) and were predominantly symptomatic mainly with flushing and other menopausal symptoms since these symptoms were the primary reason for initiating HT. Many of the women in the observational studies who used HT did so for decades (10–40 years).

On the other hand, women selected for RCTs were much older with more than 90% of women older than 55 years of age and on average more than 10 years beyond menopause when randomized (range of trial averages, 13–23 years). Women with significant menopausal symptoms, predominantly flushing, were excluded from RCT participation. Mean duration of therapy (1–6.8 years) in RCTs was also considerably less than that of the HT users in observational studies. Additionally, women in RCTs were on average overweight (approximate body mass index of 29 kg/m^2). It is clear that the characteristics of women selected for RCTs were markedly different from those of women studied from the general population in observational studies from which the estrogen cardioprotective hypothesis was generated. This accounts in part for the discordance of HT effects on CHD and overall mortality between observational studies and RCTs analyzed among all women regardless of age (Hodis and Mack, 2008).

Table 1 – Comparison of study populations included in randomized controlled trials and observational studies of postmenopausal hormone therapy.

	Randomized controlled trials	Observational studies
Mean age or age range at enrollment (years)	>62	30–55
Time since menopause (years)	>10	<6[a]
Duration of therapy (years)	≤8	>10
Menopausal symptoms (flushing)	Excluded	Predominant
Body mass index (mean)	~29 kg/m^2	~25 kg/m^2

[a] >80% of the women initiated hormone therapy within 2 years of menopause.

3. Cardioprotective effect of HT according to age and timing of initiation

Although the effect of HT on CHD over all ages is null in RCTs, these trials also indicate that there are distinct populations of women in terms of response to HT. Specifically, the beneficial effects of HT on CHD and overall mortality occurs when HT is initiated in younger women in close proximity to menopause and a null effect when HT is initiated in older women remote from menopause (Hodis and Mack, 2008). The beneficial effect of HT on CHD risk according to timing of HT initiation has been demonstrated in a large meta-analysis of RCTs (Salpeter et al., 2006). Using 23 RCTs (39,049 participants with 191,340 patient-years of follow-up) that reported at least 1 CHD event in