

# HRT after myocardial infarction

**Hormone replacement therapy (HRT) comprises estrogen either alone or with progestogen addition. The primary indication for HRT use is relief of menopausal symptoms. Can it be given to postmenopausal women who have previously sustained a myocardial infarction (MI)?**

## What does HRT do to normal arteries?

Estrogen has major benefits for arterial health. Estrogen has direct arterial effects and indirect effects through metabolic risk factor modification.<sup>1</sup> Estrogen improves vascular function through its stimulation of nitric oxide (NO)-dependent vasodilatation and inhibition of calcium-dependent channels.<sup>2</sup> It also improves vascular remodelling of arterial collagen through its direct effects on matrix metalloproteinases.<sup>3</sup> Estrogen reduces atheroma formation.<sup>4,5</sup> In some HRT preparations the vascular benefits of estrogen may be attenuated by the addition of oral androgenic progestogens such as medroxyprogesterone acetate<sup>6</sup> or norgestrel (transdermal or vaginal progestogen administration may not have this adverse effect) but not by the addition of non-androgenic progestogens such as micronized progesterone<sup>7</sup> or dydrogesterone. When initiated below age 60 years or within 10 years of onset of menopause HRT reduces atherosclerosis progression and coronary events. This has been clearly shown by observational studies<sup>8</sup> and confirmed by randomised clinical trials.<sup>5,9,10</sup>

## What happens when arterial disease is present?

In a two-year placebo-controlled randomised trial of estrogen-alone HRT with estradiol valerate in over a 1000 postmenopausal women following their first MI there was a non-significant decrease in re-infarction, cardiac death and all-cause mortality.<sup>11</sup> A 14-year follow-up of the study participants showed no increase in cardiac or non-cardiac outcomes in those allocated to estrogen treatment, establishing its long-term safety.<sup>12</sup> In another placebo-controlled randomised trial of women with established coronary disease, HRT initiation with conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) appeared to cause an initial increase in coronary events but this was followed by a steady significant decline in events.<sup>13</sup> But this initial increase with HRT has been questioned because of an apparent initial decrease in events in the placebo arm.<sup>14</sup> It can be argued that this trial used inappropriately high doses of CEE for the age of the patients enrolled. In a further analysis of the trial data, women randomised to HRT who self-selected statin therapy showed a significant reduction in coronary events and death compared to those who did not take statins.<sup>15</sup> A small randomised placebo-controlled pilot study initiating a lower dose of estradiol plus norethisterone acetate (NETA) in women with an acute coronary syndrome showed a decrease in further events of around 40%.<sup>16</sup> Observational studies have shown an overall reduction in coronary events associated with HRT use in women with established CHD.<sup>17</sup>

## What happens if a woman on HRT sustains an MI?

A retrospective study of women aged above 55 years admitted to hospital with acute myocardial infarction showed that current HRT users at the time of the event had a significantly lower mortality rate compared with non-users.<sup>18</sup> Thus there is no evidence to support the discontinuation of HRT in women who sustain a myocardial infarction. However, patients who sustain an MI may be in a hypercoagulable state. It may therefore be prudent to change the types of hormones and/or routes of administration of HRT in some cases. Furthermore, statin therapy used in combination with HRT significantly reduced venous thrombo-embolism (VTE) by 55%.<sup>15</sup>

### What happens if a woman with a previous MI needs HRT?

A myocardial infarction is usually the result of a thrombosis in a coronary artery. This may be caused by the rupture of an atheromatous plaque (which statins stabilise), therefore anything that increases adverse vascular remodelling and/or thrombosis risk should be avoided in such patients. Will HRT increase these risks? Estrogen affects remodelling in a dose-dependent manner, therefore inappropriately high doses may be adverse whereas lower doses may be beneficial.<sup>3</sup> Similarly, in terms of thrombogenesis estrogen has dose-dependent effects, with high doses increasing risk but lower doses being fairly neutral.<sup>19</sup> In this respect, transdermal administration appears to have lesser risk than oral.<sup>20</sup> Thus it seems obvious that initiating HRT in women who have had a myocardial infarction requires the use of low dose estrogen, preferably non-oral, combined with a non-androgenic progestogen when necessary. Around 80% of coronary deaths in women occur in those aged 75 years or above, and that age group will rarely require HRT for relief of menopausal symptoms. Prevention or treatment of osteoporosis for those women can be achieved with alternative medications to HRT. But in the small minority of women requiring the initiation of HRT for menopausal symptom relief who have sustained a myocardial infarction, it can be safely given providing due care is taken in the choice of hormone type, dose and route of administration, together with the co-administration of a statin.

### Practice points

Women taking HRT who sustain a myocardial infarction do not necessarily have to discontinue it.

Women who have sustained a myocardial infarction and who then require HRT can be given it.

- The starting dose is very important, needing to be appropriate for the age of the patient.
- The type of progestogen may be important, with the use of non-androgenic progestogens being preferred.
- The route of administration of estrogen may be important, with non-oral administration being preferred in those with any perceived risk of thrombo-embolism.
- The co-administration of a statin may bring further synergistic benefits.
- Supervision from a specialist menopause clinic is recommended.

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