Heart Disease: *Not Just for Men*

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Cardiovascular disease, mainly heart attack and stroke, is the biggest killer of women in Ireland, and worldwide. In fact, one in two women will die of cardiovascular disease in Ireland. Yet research carried out by the Irish Heart Foundation showed that less than one in five Irish women were aware of this. Heart disease is perceived as a man's disease. However, this is not necessarily the case.

The incidence of cardiovascular disease (CVD) in premenopausal women is three times lower than in men of the same age. By the time women reach age 75-79, the incidence is equal. This appears to be due to a protective effect of estrogen which is lost at menopause, when ovarian estrogen production fails.

Premature menopause occurring under the age of 40, increases the risk of myocardial infarction by two to threefold. Oophorectomy under the age of 40 increases it even more so. Interestingly, total mortality is increased even if oophorectomy is carried out after the onset of natural menopause, up to the age of 60, largely due to Coronary Artery Disease (CAD). This suggests a degree of protection by the ovary even beyond menopause.

Preventative measures against CAD such as statins and aspirin are successful in terms of mortality reduction in men. However, the same benefit is not seen in women. Only lifestyle changes show any benefit. However, this is only half the benefit seen with the use of estrogen Hormone Replacement Therapy (HRT).

Studies suggest a window of opportunity within which women will benefit from estrogen replacement, if started within 10 years of their last period or below the age of 60. Women initiating HRT within this window gain a 50% reduction in the development of CVD and approx 40% reduction in all cause mortality. The benefit has been seen to persist for at least 16 years in a long-term Danish study. Despite women's fears of breast cancer, CVD is the leading cause of death in women, with the risk of death from CAD at 31% compared to a 3% risk of dying from breast cancer. So, a 50% reduction in risk is highly significant. Beyond that window, however, the initiation of HRT may increase the incidence of coronary events. There are several potential reasons for this window:

Increases in weight, blood pressure and blood glucose are all risk factors for the development of CAD, but the most important change occurring with menopause appears to be the increase in total cholesterol. This is largely accounted for by a rise in LDL-C which contributes to the formation of atherosclerotic plaques. The further post menopause, the more atherosclerosis women are likely to have developed, with a resulting narrowing of the coronary arteries.

Multiple factors lead to reduced blood flow in all vascular beds and a vasoconstrictor effect of acetylcholine. Estrogen generally improves all the responsible parameters, often restoring them to the premenopausal range, resulting in increased blood flow and a vasodilatory response. As cholesterol levels increase post menopause, so does endogenous 27-hydroxycholesterol. This competes with estrogen at estrogen receptor sites in the endothelium and may prevent its direct vasodilatory action. The direct effects of estrogen on the endothelium are thought to be more important than the changes in lipids and lipoproteins. The more advanced the atherosclerotic plaque formation, the less unaffected endothelium is available to estrogen and the less effective it can be.

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Not only do we see a lack of benefit for older women commencing HRT de novo, there may be an increase in coronary events. This is likely due to metabolites of oral estrogen which dissolve part of the gelatinous plaque, leading to instability, rupture and potentially coronary thrombosis. The same increase in risk is not seen with transdermal estrogen. The increased risk is also not seen in women who are on a statin, as statins stabilise plaques.

There are significant differences between oral and transdermal estrogen. Oral estrogen undergoes first pass liver metabolism, resulting in metabolites which affect the coagulation cascade, resulting in an increased risk of venous thromboembolism (VTE) and stroke. In young women without other risk factors, the background risk of VTE or stroke is extremely low and the small associated increase in risk is negligible. Transdermal estrogen does not undergo first pass metabolism and is not associated with an increase in VTE or stroke risk. It is, therefore, safer for younger women with risk factors or for older women in whom the risk is naturally higher due to age alone. For older women suffering from significant symptoms of menopause and who wish to use HRT, low dose transdermal estrogen is also the safer option as it is also less likely to lead to coronary events, as noted earlier.