CARDIOVASCULAR DISEASE: REDUCED MORTALITY WITH LONG-TERM HRT TREATMENT

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Introduction

Several case-control as well as cohort studies indicate that estrogen replacement therapy reduces the risk of arterial disease, especially myocardial infarction. As with all observational studies there are limitations to each study. However, some of the cohort studies are large enough to control for a number of confounding factors. A meta-analysis on estrogen replacement therapy in cardiovascular disease would yield a relative risk of 0.5 [1] in women using estrogen replacement therapy. Data on stroke are less clear. This is at least partly due to the fact that stroke occurs at a relatively more advanced age than myocardial infarction and few women use estrogens beyond 70 [2]. There are also uncertainties about the venous side. Recent data imply that there is a 2-3 fold increase of venous thromboembolism at least during the first year of usage [3-5]. It is also established that estrogen confers protection against osteoporotic fractures and as hip fractures carry a mortality of about 20%, estrogen usage may impact on mortality. Furthermore, long-term use of hormone replacement therapy seems to increase the risk of the diagnosis of breast cancer; the relative risk being 1.3. Most data indicate that prognosis of breast cancers in women on HRT is better than in controls and that mortality in breast cancer may not be increased [6].

The risk of dying during the forthcoming year at 90 is much higher than dying during the next decade when you are 50. In other words, adjusted risk for mortality is dependent on age and even if one can reduce aged standardized death rate by 50% at the age of 90, this only translates into a prolongation of life expectancy with a few months. The majority of hip fractures and myocardial infarctions occur after the age of 85, but the clinical significance of reductions of fatal events are limited in terms of prolongation of life.

HRT is used largely by women after 50. For society it is of interest if age-adjusted mortality can be reduced overall and to what extent this reduction is confined to women below mean age.

As was outlined above, there are a number of uncertainties about HRT both on the benefit side as well as on the risk side. For this reason, one optimistic and one pessimistic scenario are often considered. The pessimistic scenario consists of minimal benefits and maximal risks. The optimistic scenario considers the reverse situation. In these considerations cardiovascular disease will be looked upon specifically and the other variables

will be mentioned briefly. This is not to say that they are less important but fall out of the scope of the present paper.

Even if the relative risk of developing cardiovascular disease is 0.5 it should be remembered that if a thromboembolic event occurs or women develop breast cancer or any other possibly estrogen-dependent side effect, HRT treatment will be discontinued so that a 50% reduction is not likely to be achieved in a routine clinical setting.

Profound effects are exerted not only by the estrogen but also by the progestogen. Progestogens are believed to protect the endometrium from endometrial cancer, to have no effects on breast cancer and theoretically attenuate some of the cardiovascular benefits by estrogens. Two cohorts of women are therefore considered, one being the hysterectomized woman and the other the woman with uterus \textit{in situ}. It is assumed that the non-hysterectomized woman receives a combined therapy with estrogen and progestogen. However, different progestogens and possible differences between sequential and continuous combined therapies are commonly not considered. The hysterectomized woman is assumed to receive an estrogen monotherapy.

Prevalence and incidence rates as well as risk of dying are based on figures from Western Europe and the United States and may or may not be applicable to other parts of the world as several of the diseases are influenced not only by genetic factors but also by lifestyle and availability of medical care.

All models are based on morbidity and mortality statistics. It is conceivable that the women who contributed to these figures had other risk factors at age 50 than today's women.

Compliance is never 100%, neither in clinical practice nor in observational studies. The benefits as well as risks may therefore well have been underestimated. On the other hand, it is conceivable that 100% compliance will never be achieved even in the future unless long-term implants or other modes of continuous administration become much more widespread than the traditional oral medication. The relative risks obtained in the observational studies were therefore not adjusted for.

In most of the observational studies to date the indication for using hormone replacement therapy was climacteric symptoms. It is conceivable that these women have had a time of lower estrogen influence in the period preceding estrogen use. This fact tends to reduce the impact of the estrogen medication especially in short-term studies. On the other hand, women who use estrogens are generally more educated and of higher socioeconomic status. They should have no contraindications to the use of estrogen replacement therapy. In general they are healthier than the control population. In other words, there are confounders and bias which are inevitable in most of the observational studies, but as this could lead both to overestimates and underestimates of potential risks and benefits, they are usually not adjusted for.

**Mortality Analyses**

Daly et al. [7] made an analysis in the United Kingdom. They looked at deaths induced and/or prevented by cause up to age 69 following ten years' treatment from age 50 with