Do statins and hormonal replacement therapy in combination reduce cardiovascular risk in postmenopausal women?

See page 190 for the article to which this Editorial refers

The low attention given to cardiovascular risk in women should be a thing of the past. There is no doubt that cardiovascular disease is a frequent and important cause of death not only in men, but also in women after their menopause. Hypertension, smoking and non-HDL-cholesterol are considered to be the basic cardiovascular risk factors for both men and women; however, the role of total and LDL-cholesterol as a cardiovascular risk in women has been controversial for a long time. Special aspects of cardiovascular risk in women include diabetes, high triglycerides and low HDL-cholesterol[1]. Both HDL-cholesterol and triglycerides are independent lipid predictors of cardiovascular disease death in women older than 50 years. In women the level of HDL-cholesterol is more strongly related to cardiovascular disease death than LDL-cholesterol[2]. Also lower total and LDL-cholesterol was previously not considered as important in women as in men.

The large prospective randomized hypolipidaemic treatment trials published in the middle of the 1990s have shown that treatment with statins reduces morbidity and mortality from coronary heart disease significantly in both men and women with coronary heart disease. In the CARE study (Cholesterol and Recurrent Events) women profited even more than men from pravastatin treatment[3]. Statins are therefore preferred both in the treatment of dyslipidaemias and in the realm of secondary prevention in women.

The indication for statin therapy in the primary prevention of coronary heart disease is more controversial; it is recommended in high risk subjects, however we have fewer data about its effect in high


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risk women. The question how to define a high cardiovascular risk in subjects without evidence of cardiovascular disease has not been fully resolved. Lovastatin treatment in low risk subjects is not cost effective; low risk women have profited less than low risk men, in the primary preventive trial AFCAPS/ TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study)[4]. On the other hand there is no doubt about the effectiveness of statin therapy in the secondary prevention of coronary heart disease. Statins reduce coronary risk, risk of strokes, and cardiovascular and total mortality (not only due to lipid-lowering properties, but also several other additive effects such as modification of endothelial function, inflammatory responses, plaque stability, and thrombus formation[5]).

It is well known from the Framingham Study, that LDL-cholesterol levels rise with age in both men and women, and after age 55 years LDL levels may be higher in women. HDL-cholesterol appears to decline slightly in women, corresponding to the post-menopausal lowering of oestrogens. Not only endogenous but also exogenous oestrogen plays an important role in the creation of cardiovascular risk in women: oestrogen has antioxidant and calcium channel blocking properties and favourably alters multiple intermediary variables, including LDL- and HDL-cholesterol, Lp(a), plasminogen activator inhibitor-1, fibrinogen etc. Oestrogen improves well-being, and is the treatment of choice for menopausal symptoms and osteoporosis. On the other hand progestin has an unfavourable effect on lipoprotein metabolism, but it protects against uterine hyperplasia and reduces the risk of uterine cancer elevated by oestrogen[6]. That is why a combination of both kinds of hormones seems to be protective. Newer treatments with selective oestrogen-modulators (SERMs) such as raloxifene, tibolone or soy phytoestrogens, may preserve bone without increasing breast and uterine cancer risk; their effect on cardiovascular disease is unknown. The RUTH (Raloxifene Use for the Heart) study, which is still in progress, is aimed at solving the question of the role of raloxifene as a cardioprotector in post-menopausal women with preexisting coronary heart disease and/or with high cardiovascular risk.

Many observational studies have found lower rates of coronary heart disease in women taking hormone replacement therapy (HRT) than in women without HRT in the primary and secondary prevention of coronary heart disease. Unexpected results from the HERS study (Heart and Estrogen/progestin Replacement Study) were recently published: in about 2700 post-menopausal women with pre-existing coronary heart disease and average age of 67 years, no overall effect of combined HRT was found for coronary heart disease. Compared with placebo, the intervention group had significantly more coronary heart disease events in the first year of the trial and fewer events during years 4 and 5. HRT increased the risk of venous thrombo-embolic events and gallbladder disease. There were some limitations in the HERS study. The main reason for the lack of benefit may have been the very high risk of these old post-menopausal women with coronary heart disease, who had not been properly treated with highly effective therapies such as aspirin, beta-blockers and especially statins (the screening for HERS was finished before evidence-based medicine suggested women benefit from statin-treatment). HERS also promoted the big potential of lifestyle changes (smoking cessation, rational diet, physical activity), control of hypertension and diabetes. Other big randomized trials on post-menopausal HRT such as The Women’s Health Initiative Randomized Trial, which includes more than 27 000 younger post-menopausal women without coronary heart disease[7], will resolve the questions raised by HERS.

In the last few years new data have come to light concerning the effect of combined statin and HRT therapy. The combined application of these protective drugs seems to be very useful in terms of the influence on the lipid profile in women, as has been shown in the study by Fak et al. in this issue[8]. The positive effects on HDL-cholesterol and the reduction in LDL-cholesterol were greater in the women treated with combined therapy than in the group treated with statins only. The evaluation of the effects of combined HRT and statins in a larger trial with hard end-points such as morbidity, total and cardiovascular mortality, seems to be justified.

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References

The not so obvious truth

See page 213 for the article to which this Editorial refers

‘If an idea presents itself to us, we must not reject it simply because it does not agree with . . . logical deductions . . .’ Claude Bernard (1813–1878: An Introduction to the Study of Experimental Medicine).

Two patients of similar age and gender are admitted to hospital complaining of chest pain. One of them is eventually diagnosed with an acute myocardial infarction; the other is not. It would seem logical or even obvious that the post-discharge prognosis for the patient with the diagnosis of acute myocardial infarction would be worse than the prognosis for the individual who was discharged with the diagnosis of infarction ruled-out. However, as noted in the quote cited above from the great French experimental physiologist, Claude Bernard, one should not reject an idea merely because it goes against ‘common logic’. If one uses Bernard’s reasoning, therefore, one should not reject automatically the idea that the prognosis for the two patients under discussion might be similar. In fact, Bernard’s admonition is wisely stated. Many investigations performed in North America and Europe during the last 25 years have documented that the long-term prognosis for patients with the diagnosis of ‘myocardial infarction, ruled-out’ or ‘possible myocardial infarction’ is no better or only slightly better than the prognosis for patients with a diagnosis of ‘definite myocardial infarction’[1–6].

Who are these individuals, admitted to the Coronary Care Unit, and subsequently discharged without a definitive diagnosis of acute myocardial infarction? Many of them have unstable angina or, to use the term currently in vogue, an acute coronary syndrome. Others are eventually shown to have some form of cardiopulmonary disease such as acute pericarditis, pulmonary embolism, pneumonia, pleurisy, valvular heart disease, aortic dissection or a tachyarrhythmia. Still other patients have non-cardiac/non-pulmonary aetiologies as the cause of their chest discomfort, e.g. musculoskeletal or neuropathic pain.

One might argue that a careful history would have kept individuals without cardiac chest pain out of the coronary care unit and, perhaps, in an earlier, gentler, and less pressurized era this might have been the case. However, given the data presented by Packham et al.[7] in this issue, it would still seem reasonable to admit these individuals to the coronary care unit since many of the patients discharged from the coronary care unit with the diagnosis of ‘myocardial infarction ruled-out’ subsequently suffer a cardiac event or death. Thus, it is apparent to me that cardiologists need to examine these patients with a more critical eye. As Packham et al. conclude: ‘. . . the mortality of patients admitted with a suspected myocardial infarction in whom the diagnosis is not confirmed is so high that more detailed work is needed to characterize this group and to develop models predictive of those at highest risk.’[7] Presumably, Packham et al. would suggest that these individuals undergo further diagnostic evaluation in order to identify those patients with ischemic heart disease.

I agree with this approach particularly since the work of Packham et al. confirms a number of