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Raloxifene and cardioprotection in early postmenopausal women

The Raloxifene Use for The Heart (RUTH) trial results were published in 2004 [1]. This was a randomized, double-blind, placebo-controlled study which recruited 10,101 women above the age of 55 years (mean age 67.5 years), with established coronary artery disease (CAD) or at high risk for CAD. Women were followed for a median period of 5.6 years. The study was completed by about 80% of the participants, 70% of whom took at least 70% of their assigned medications. The original publication concluded that raloxifene had no effect on the risk for coronary events. Now, a new article brings post-hoc analyses and more details on RUTH subgroups, with a focus on the age factor [2]. In women < 60 years old at baseline, a significant reduction in risk for CAD events was demonstrated (hazard ratio 0.59; 95% confidence interval (CI) 0.41–0.83), but such an effect was not recorded in older women. Another intriguing finding unrelated to age was that women with the highest risk score for CAD (> nine risk points) were those who benefited most, with a 27% reduction in hazard ratio, which almost reached statistical significance (95% CI 0.68–1.01).

Comment

Just a few months before the first release of the Women's Health Initiative (WHI) data in 2002, a sub-analysis from the Multiple Outcomes of Raloxifene Evaluation (MORE) study suggested a lower risk for cardiovascular events in a subset of osteoporotic women with increased cardiovascular risk (> four risk points; relative risk 0.60; 95% CI 0.38–0.95) [3]. The entire MORE study cohort (7705 women, mean age 67 years) was considered to be at low risk for CAD and, indeed, the CAD mortality in the study was lower than that reported for the general US population. It seems that the RUTH trial, which was designed to provide data on the cardiovascular outcomes of raloxifene therapy, supports this observation.

Looking at a potential triple advantage of raloxifene in the early postmenopausal period (reducing the risk for fractures, breast cancer and CAD) opens a discussion on similarities and differences between the RUTH trial and the WHI estrogen-alone results [4]. In fact, both studies yielded very similar figures, although the mechanisms of actions of both products may not be the same. The cardioprotective effects of estrogen are attributed to its vasodilatory and anti-inflammatory activities, which slow the development of atherosclerosis when the endothelium is still intact. However, these beneficial effects of estrogen are lost once there are established arterial plaques (the 'window of opportunity' theory) [5].

The RUTH and MORE results perhaps indicate that, cardiac-wise, raloxifene 'works' better in higher-CAD-risk populations. However, these women received aspirin, antihypertensive, lipid-lowering and antidiabetic medications as well, which makes the interpretation of the data quite complex. Unlike estrogen, raloxifene has no effect on C-reactive protein and was found capable of lowering serum levels of cholesterol and homocysteine, attenuating oxidation of low-density lipoprotein, inhibiting endothelial–leukocyte interaction, improving endothelial function and reducing vascular smooth muscle tone [6].

In conclusion, activation of arterial wall estrogen receptors by estrogen or raloxifene, as well as inducing various metabolic alterations, seems beneficial for the cardiovascular system in the early postmenopausal period, but may not provide any advantage in older women. The exact natures of action of these products on vessel wall physiology and atherosclerosis may not be similar and deserve further evaluation.

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