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Coronary events in the WHI trial and the metabolic syndrome

A recent manuscript describes a nested case–control study of incident coronary heart disease (CHD) events during the first 4 years of follow-up in the Women's Health Initiative hormone therapy trials (estrogen plus progestin therapy, EPT and estrogen therapy, ET) [1]. There were 359 incident cases of CHD during follow-up. After the exclusion of women with cardiovascular disease (*n* = 90), diabetes, or hypertension at baseline (*n* = 103), 166 CHD cases were matched to 524 controls on age, randomization date, and hysterectomy status. Metabolic syndrome (MetS) classification required at least three of five Adult Treatment Panel III criteria. The main outcome measure was the odds for CHD with hormone therapy use versus placebo by MetS status. MetS modified the risk of CHD events with hormone therapy. In the pooled analysis, risk was increased with hormone therapy versus placebo in women with MetS (odds ratio (OR) 2.26; 95% confidence interval (CI) 1.26–4.07), whereas women without MetS were not found to have an increased risk for a CHD event with hormone therapy (OR 0.97; 95% CI 0.58–1.61; *p* for interaction = 0.03). Results of the EPT and ET trials, when examined separately, were similar. The constellation of MetS variables was more predictive of risk from hormone therapy than MetS components assessed individually. When women with diabetes or hypertension were included in the analysis, statistically significant effect modification was not detected. In conclusion, **MetS at baseline in women without prior cardiovascular disease, diabetes, or hypertension at baseline identifies women who are more likely to have had adverse coronary outcomes on hormone therapy. CHD risk stratification is recommended before initiating hormone therapy.**

Comment

Many studies have shown that people with metabolic syndrome are at increased risk of cardiovascular events. The most recent and largest of them [2] included nearly one million patients (total *n* = 951,083). It concluded that the metabolic syndrome is associated with a two-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality rates. The definition of the MetS may vary, and therefore study results may vary as well [3]. Hypertension and diabetes are closely related to MetS, yet, in the current study, separate analyses were performed either excluding or including these two major risk factors [1]. NCEP criteria of the MetS used in this study were defined as at least three of the following criteria: waist circumference > 88 cm, plasma triglycerides 150 mg/dl (1.7 mmol/l), HDL cholesterol < 50 mg/dl (1.29 mmol/l), blood pressure 130/85 mmHg, and fasting plasma glucose 110 mg/dl (6.1 mmol/l).

The prognostic importance of the metabolic syndrome compared with that of the sum of its individual components has repeatedly been challenged. For example, in a cohort study of 2815 patients [4], the risk of cardiovascular disease mortality associated with the metabolic syndrome (hazard ratio (HR) 2.53; 95% CI 1.74–3.67) was similar to the risk associated with impaired fasting glucose (HR 2.87; 95% CI 1.96–

4.20). In fact, the current analysis from the WHI data indicated that, once women with diabetes or hypertension at baseline were not excluded, having MetS no longer had a prognostic significance versus assessing only these individual risk factors [1].

Nevertheless, according to a recent review, it seems that most of the published reports indicated that the syndrome predicted cardiovascular events independently from other conventional risk factors [5]. Apart from these interesting data, the importance of the WHI analysis lies in what I call a 'reversed thinking'**. It actually showed that the increased risk for coronary events in the entire cohort was limited to women with adverse metabolic alterations, whereas healthy women without MetS had the same risk for coronary events whether or not they took hormones.** Thus 10 years after the first publication of the WHI results, it seems that several factors determine the safety of hormone use heart-wise: age at initiation of therapy, recency of menopause, duration of use, type of hormonal product, and personal coronary artery disease risk profile at baseline. Healthy, recently menopausal women should not be concerned of coronary artery disease events while initiating hormone therapy.

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