Recurrent cardiovascular events in contemporary cardiology: obesity patients should not rest in PEACE

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This editorial refers to 'Obesity and cardiovascular events in patients with established coronary disease†' by M.J. Domanski et al., on page 1416

Obesity is becoming a global epidemic and is associated with numerous co-morbidities such as cardiovascular disease (CVD), Type 2 diabetes, hypertension, certain cancers, and sleep apnoea. In fact, obesity is an independent risk factor for CVD, but the estimated years of life lost due to obesity may differ among races and gender. Overweight and obesity are classically classified using the body mass index (BMI). BMI (weight in kg/height² in meters) is frequently used as a surrogate measure of fatness in adults. Overweight is being defined as a BMI of 25.0–29.9 kg/m², whereas obesity is defined as a BMI ≥ 30.0 kg/m².

Domanski et al.,2 reported a post hoc analysis from the PEACE trial. The PEACE trial is considered as one of the landmark studies evaluating the impact of angiotensin-converting enzyme inhibitors (ACEi) on cardiovascular outcomes in patients with known coronary artery disease (CAD).3–5 The investigators explored the association between obesity and major adverse coronary events (MACE) defined as cardiovascular death, non-fatal myocardial infarction, coronary revascularization, or stroke. The authors show that, in a large cohort of non-diabetic patients (n = 7864) with established CAD, independently of traditional risk factors, BMI, was associated with MACE in men but not in women. The relation between categories of BMI (underweight to morbid obesity) and MACE depicted a J-shaped curve, whereas no BMI category was associated with an increased risk of MACE in women.

Overweight and obesity have risen dramatically worldwide, resulting in a marked increase in the metabolic syndrome (MetS), a clustering of cardiovascular risk factors including central adiposity, insulin resistance, hypertension, dyslipidaemia, and a proinflammatory state. This syndrome maybe viewed as 'at risk' obesity. In order to better circumcribe the syndrome, several definitions of MetS have been published and this topic has been reviewed recently.

Currently, there is debate as to which anthropometric measure defining obesity best assesses the risk of CVD. It was suggested that abdominal obesity may be a better clinical surrogate marker of obesity than BMI as a risk factor for myocardial infarction worldwide or as a higher-risk factor for CVD incidence and mortality.1 Waist circumference (WC) is strongly correlated with abdominal fat content and may be the easiest clinical way to assess a patient’s abdominal fat.

Accordingly, it was reported from the Heart Outcomes Prevention Evaluation (HOPE) study of over 8000 patients with known CVD or following acute myocardial infarction, that overall obesity as assessed by BMI was related to myocardial infarction and congestive heart failure (CHF).7 In contrast, when abdominal obesity indexes [waist-to-hip ratio (WHR) or WC] were integrated into the statistical analysis, BMI was no longer an independent predictor of myocardial infarction. Indeed, when adjusted for all variables, including BMI, increased WC as well as WHR were independent predictors for CVD death, myocardial infarction, and total mortality, but not for stroke or CHF. Moreover, for WHR, there was an interaction with sex, whereas WHR was an independent predictor for each CVD event except stroke in women but not in men. Thus, in the Trandolapril Cardiac Evaluation (TRACE) register, the mortality rate was not associated with BMI in men or women, but increased in 23% of men with abdominal obesity compared with men who were not abdominally obese. Excluding diabetes and hypertension from the multivariate analysis did not change the findings. This may imply that the impact of obesity on all-cause mortality is mediated via mechanisms other than traditional risk factors such as hypertension and diabetes.

From a pathogenesis point of view, examination of arteries post-mortem from individuals 15–34 years of age [Determinants of Atherosclerosis in Youth (PDAY) study] who died from accidental injuries, homicides, or suicides revealed that the extent of fatty streaks and advanced lesions (fibrous plaques and plaques with calcification or ulceration) in the right coronary artery and in the abdominal aorta were associated with obesity (BMI ≥ 30 kg/m²) concomitantly with the size of the abdominal panniculus (≥ 17 mm), reinforcing the concept that central fat distribution is more important than total fat as a risk factor for atherosclerosis.1 Also, it was reported that the maximal density of macrophages/mm² in the plaques lesions was associated with visceral obesity.1 Of clinical importance,
macrophage-rich plaques in individuals with large amounts of visceral fat may have the potential to progress rapidly.

Owing to limited number of outcomes observed in this study, Domanski et al. were not able to examine the association between BMI and the individual components of the MACE endpoint. Nevertheless, the findings suggested a sex-specific difference in the impact of obesity on adverse cardiovascular events in patients with CAD. However, one must be cautious, because the study number of women was rather small (n = 1171). Finally, WC was not assessed in the PEACE trial. The lack of association between BMI and CVD events in women is not clear, but could be explained by a delayed atherosclerosis process in women compared with men or simply to the obesity assessment using BMI instead of WHR. Indeed, the relationships between the MetS, presence of angiographically significant CAD, and incident CVD events were prospectively evaluated in a larger cohort of women (n = 755): the Women’s Ischaemia Syndrome Evaluation (WISE) study. Interestingly, compared to women with normal metabolic status, women with MetS or diabetes had a significantly lower 4-year survival rate (3.5% absolute) and event-free survival from major adverse CVD events (death, non-fatal myocardial infarction, stroke, CHF; 5.7% absolute). To add to the contemporary controversy regarding hormone replacement therapy and CVD, hormone replacement therapy in women was associated with a decreased risk of MACE in the study of Domanski et al. Mortality related to obesity has declined since the first National Health and Nutrition Examination Survey (NHANES) study in 1971, a result most likely due to a more aggressive approach to the treatment of associated CVD risk factors in obese patients as graded through the years with a more aggressive management of associated CVD risk factors in landmark ACEi trials: HOPE, EUROPA, and PEACE. At a low level of risk, obesity may have very little impact on CVD outcomes, but for obese subjects at moderate risk, the CHD risk mortality may increase substantially. However, it seems from the PEACE sub-analysis that even higher-risk obese patients, assessed with BMI, may not benefit from ACEi.

Unfortunately, the improvement in risk-factor recognition and management that developed through the last decades in modern cardiology maybe counteracted in the future by the incidence of obesity. It appears that the life-shortening influence of obesity could rise as the obese, who are now at younger ages, carry their elevated risk of death into middle and older ages. Indeed, with obesity occurring at younger ages, the children and young adults of today will carry and express obesity-related risks for more of their lifetime than previous generations have done. Finally, an important parameter often overlooked in outcome studies in overweight and obese subjects is the level of physical activity. In a recent report from the Harvard School of Public Health, the level of physical activity was an important predictor of CHD, an effect independent of the presence of obesity. Numerous studies have reported that even light-to-moderate activity is associated with lower CHD rates.

Following the results of Domanski et al., showing ACEi was of no additional benefit on MACE in obese patients, we can assume that the time has come for clinicians and health care professionals to strongly advocate to CAD obese patients to increase physical activity, not just to assist with weight loss but to enhance CVD health. Obesity is a chronic metabolic disorder associated with CVD and increased morbidity and mortality. Although there are no prospective studies to date demonstrating that intentional weight loss increases survival, weight reduction through non-pharmacological approaches like diet and exercise should continuously be integrated in the active management of these patients. Hopefully, within the next decade, new information may be provided that weight reduction is beneficial for hard CVD outcomes, i.e. CHD events, CHD death, CHF, stroke, and total mortality. Until then, the clinical approach must hope that such a favourable result will ensue.

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References