IN BRIEF

INTERVENTIONAL CARDIOLOGY

Young women have worse outcomes after STEMI

Among patients with ST-segment elevation myocardial infarction (STEMI) and aged < 60 years, women have worse outcomes than men, according to data from the ISACS-TC registry. This sex-specific difference declines with increasing age. A total of 2,657 women and 6,177 men were hospitalized and treated for STEMI in 41 hospitals in 12 countries between 2010 and 2016. Among these patients, 30-day mortality was significantly higher in women than in men (11.6% versus 6.0%). Mortality remained higher in women than in men in the group of patients who underwent percutaneous coronary intervention (PCI; 7.1% versus 3.3%). After multivariable adjustment, women aged < 60 years had a higher risk of early mortality than men in the same age group (OR 1.88, 95% CI 1.04–3.26). The risk was not significantly different between the sexes in those aged ≥ 60 years. The investigators highlight that the differences in STEMI mortality between younger men and women were unrelated to disparities in treatment, given that a difference was observed even in those undergoing primary PCI.

ORIGINAL ARTICLE Cenko, E. et al. Sex differences in outcomes after STEMI: effect modification by treatment strategy and age. *JAMA Intern. Med.* https://doi.org/10.1001/jamainternmed.2018.0514 (2018)

CANCER

Breast cancer therapy and cardiac mortality

Treatment for breast cancer and subsequent survival are improving, but cardiotoxicity of anticancer therapies remains an important concern. However, data from the SEER-18 database indicate that cardiac mortality is not increased among survivors of breast cancer compared with the general population. In a registry-based cohort study, a total of 347,476 women were diagnosed with breast cancer between 2000 and 2011, treated with chemotherapy or radiotherapy, and followed up until 2014. The highest cause of death among the study population was breast cancer. Compared with the general population, survivors of breast cancer had a lower risk of cardiac mortality (standardized mortality ratio 0.84, 95% CI 0.79–0.90).

ORIGINAL ARTICLE Weberpals, J. et al. Long-term heart-specific mortality among 347 476 breast cancer patients treated with radiotherapy or chemotherapy: a registry-based cohort study. *Eur. Heart J.* https://doi.org/10.1093/eurheartj/ehy167 (2018)

PREVENTION

Fitness ameliorates genetic risk of heart disease

High cardiorespiratory fitness can lower the risk of coronary heart disease (CHD) and atrial fibrillation (AF), even among individuals at high genetic risk of these conditions, according to an analysis of data from the UK Biobank. The study included data on 502,635 individuals. As expected, grip strength, physical activity, and cardiorespiratory fitness were inversely associated with incident CHD and AF events. Individuals were then stratified according to their genetic risk scores for these conditions. Again, higher grip strength and cardiorespiratory fitness were associated with lower risk of cardiac events. Of note, high cardiorespiratory fitness was associated with a 49% lower risk of CHD and a 60% lower risk of AF among individuals at high genetic risk of these conditions. "Elevated genetic risk [of CHD and AF] can be compensated for by exercise," suggest the researchers, which "could encourage individuals to initiate a healthier lifestyle to reduce their overall risk".

ORIGINAL ARTICLE Tikkanen, E. et al. Associations of fitness, physical activity, strength, and genetic risk with cardiovascular disease: longitudinal analyses in the UK Biobank study. *Circulation* https://doi.org/10.1161/CIRCULATIONAHA.117.032432 (2018)

Credit: S. Bradbrook/Macmillan Publishers Limited

ATHEROSCLEROSIS

Atherosclerosis linked to faulty DNA repair in VSMCs

DNA repair mechanisms offer potential therapeutic targets for atherosclerosis, according to the results of a study published in *Circulation*. "We find that human plaque vascular smooth muscle cells (VSMCs) show defective repair of oxidative DNA damage, owing to reduced activity and increased degradation of the major base excision repair (BER) enzyme, 8-oxoguanine DNA glycosylase (OGG1)," asserts Martin Bennett, corresponding author of the study.

The researchers also showed that correcting levels of this enzyme in mouse VMSCs not only rescued this defect in BER (which normalized 8-oxoguanine levels) but also markedly reduced atherosclerosis. "This result," Bennett continues, "demonstrates that levels of oxidative DNA damage that actually occur in atherosclerosis directly promote atherogenesis."

Previous studies had linked 8-oxoguanine accumulation (a marker of oxidative stress) in VSMCs, macrophages, and endothelial cells to atherosclerosis, but the present study is the first to show that VSMCs from human atherosclerotic plaques have decreased protein levels and enzyme activity of OGG1, and that this defect not only impairs BER and drives 8-oxoguanine accumulation, but also promotes atherosclerosis.

In particular, the researchers showed that the stability and activity of OGG1 are regulated by acetylation at Lys338 and Lys341, and identified p300 acetyltransferase and sirtuin 1 deacetylase as important for regulating BER efficiency in VSMCs. Specifically, p300 levels are reduced by oxidative stress and are also decreased in plaque VSMCs; these reduced p300 levels lead to decreased formation of the p300–OGG1 complex, which both reduces OGG1 enzyme activity and promotes its proteasomal degradation. Reactive oxygen species can also directly reduce OGG1 activity. The resulting decreased efficiency of BER drives 8-oxoguanine accumulation.

In mice, the researchers showed that targeted deletion or knockdown of *Ogg1* led to accumulation of 8-oxoguanine as well as increased cell death, senescence, and expression of inflammasome components, which are all proatherogenic. By contrast, overexpression of *Ogg1* reduced these responses to oxidative stress and attenuated the development of atherosclerosis.

Thus, the researchers posit, the detrimental effect of chronic oxidative stress on atherosclerosis involves a vicious cycle of oxidative DNA damage, decreased efficiency of BER, and downregulation of OGG1.

In their published report, the researchers suggest that approaches that protect against oxidative DNA damage or promote DNA repair mechanisms could offer benefits in patients with coronary artery disease that go beyond the reduction of traditional cardiovascular risk factors, such as hypercholesterolaemia, diabetes mellitus, and smoking.

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ORIGINAL ARTICLE Shah, A. et al. Defective base excision repair of oxidative DNA damage in vascular smooth muscle cells promotes atherosclerosis. *Circulation* https://doi.org/10.1161/CIRCULATIONAHA.117.033249 (2018)