atherosclerosis

Atherosclerosis newsletter

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Volume 294, Issue February 2020

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The two February issues contain several articles on the role of imaging either in improving risk prediction for different cardiovascular disease endpoints or for identifying novel biomarkers.

All-cause and cause-specific mortality in individuals with zero and minimal coronary artery calcium: A long-term, competing risk analysis in the Coronary Artery Calcium Consortium

There is increasing interest in zero coronary artery calcium (CAC) as a marker of sustained good health. Prior studies have reported very low rates of coronary heart disease (CHD) events, cardiovascular disease (CVD) events, and all-cause mortality in the presence of a CAC score of zero (CAC = 0). Intriguingly, recent reports have also linked the absence of CAC with low rates of cancer and other non-CVD events such as incident chronic obstructive lung disease, chronic kidney disease, hip fracture, and dementia. This has led to the hypothesis that the absence of CAC may be a marker of "healthy aging". Supporting this view, even minimal CAC (scores of 1–10) have been associated with higher CVD events and all-cause mortality as compared to CAC = 0. However, currently there are little data available on the long-term associations of CAC = 0, CAC 1–10, and higher CAC scores, particularly after accounting for competing risks, with other cause-specific mortality. Therefore, Blaha et al. conducted a competing risk analysis studying zero and minimal CAC in 66,363 individuals from the CAC Consortium, a large cohort with long follow-up for cause-specific death. Baseline evaluations occurred between 1991 and 2010.

Over a mean of 12 years of follow-up, individuals with CAC = 0 had stable low rates of CHD death, CVD death, and all-cause death. Cancer was the predominant cause of death in this group, yet rates were also very low. Compared to CAC = 0, individuals with CAC 1–10 had an increased multivariable-adjusted risk of CVD death only under age 40. Individuals with CAC>10 had multivariable-adjusted increased risks of CHD death, CVD death and all-cause death at all ages, and a higher proportion of CVD deaths.

CAC = 0 is a frequent finding among individuals undergoing CAC scanning for risk assessment and is associated with low rates of all-cause death at 12 years of follow-up. These results support the emerging consensus that CAC = 0 represents a unique population with favorable all-cause prognosis, who may be considered for more flexible treatment goals in primary prevention. Detection of any CAC in young adults could be used to trigger aggressive preventive interventions.

In his editorial, Raul D. Santos emphasizes the importance of these promising results and the need for more data to expand the "power of zero" beyond the vessels.

The association of coronary artery calcium score and mortality risk among smokers: The coronary artery calcium consortium

Smoking is the number one preventable risk factor, increasing the mortality risk for cardiovascular disease (CVD) and cancer. The coronary artery calcium (CAC) score can help stratify the risk for CVD and cancer mortality. Although prior studies have suggested that higher CAC score is a risk factor for all-cause mortality in smokers, the association between CAC score and cause-specific including CVD, and cancer mortality, has not been investigated. Mirbolouk et al. examined the implication of CAC score for CVD, coronary heart disease (CHD), and cancer mortality risk prediction among current smokers.

The study included current smokers without known heart disease from the CAC Consortium (a large multi-center cohort designed to study the association of CAC score with long-term cause-specific mortality). Cox regression (for all-cause mortality) and Fine-and-Gray competing-risk regression (for CVD, CHD, and cancer mortality) models, adjusted for traditional CVD risk factors, were used to assess the association between CAC and each mortality outcome, with CAC as a continuous or categorical variable. Number of vessels with CAC was used as a surrogate for the qualitative measure of CAC and mortality outcomes. Analyses were repeated for a lung cancer screening-eligible population, defined as ever smokers with >30 pack/years smoking history. Hazard ratios (HR) for all-cause mortality and subdistribution HRs (sHR) with 95% confidence intervals were reported.

Over a median of 11.9 years of follow-up, 337 of 5147 current smokers died. Doubling of CAC score was associated with increased HRs of all-cause mortality, and sHRs for CV, CHD and cancer mortality. Subjects with CAC ≥400 had increased sHR of CVD, CHD, and cancer mortality, compared with those with CAC = 0. A diffuse CAC pattern significantly increased the risk of all-cause, CVD, and CHD mortality among smokers. Results were consistent for the lung cancer screening-eligible population.

Smokers are at high risk of cardiovascular and cancer mortality, and CAC scoring in this population has strong prognostic implication for both outcomes.

Abdominal aortic calcification (AAC) and ankle-brachial index (ABI) predict health care costs and utilization in older men, independent of prevalent clinical cardiovascular disease and each other

Abdominal aortic calcification (AAC) and low ankle-brachial index (ABI) are markers of multisite atherosclerosis, and predict incident CVD events. No study has estimated the direct association of low ABI or high AAC with total health care costs. In particular, it is unclear if AAC and/or ABI predict subsequent total health care costs and utilization after accounting for CVD risk factors, previous clinical cardiovascular disease diagnoses, and each other. Schousboe et al. estimated the associations with health care costs and utilization adjusted for each other, and after accounting for CVD risk factors and prevalent CVD diagnoses in older men.

They conducted an observational cohort study of 2393 community-dwelling men enrolled in the Osteoporotic Fractures in Men (MrOS) study and U.S. Medicare Fee for Service (FFS). AAC was scored on baseline lateral lumbar spine X-rays using a 24-point scale. ABI was measured as the lowest ratio of arm to right or left ankle blood pressure. Health care costs, hospital stays, and SNF stays were identified from Medicare FFS claims over 36 months following the baseline visit.

Men with AAC score ≥9 had higher annualized total health care costs of $1473 compared to those with AAC score 0–1, after multivariable adjustment. Men with ABI <0.90 had higher annualized total health care costs of $2705 compared to men with normal ABI, after multivariable adjustment.

High levels of AAC and low ABI in older men are associated with higher subsequent health care costs, after accounting for clinical CVD risk factors, prevalent CVD diagnoses, and each other. Further investigations of whether preventing progression of peripheral vascular disease and calcification reduces subsequent health care costs are warranted.

Retinal microvascular findings and risk of incident peripheral artery disease: An analysis from the Atherosclerosis Risk in Communities (ARIC) Study

Lower-extremity peripheral artery disease (PAD) is caused by macrovascular atherosclerosis in many PAD patients. However, for the development of critical limb ischemia (CLI), a severe form of PAD, microvascular disease also appears to play an important role by impairing collateral formation and wound healing. Indeed, a few studies of diabetic patients have identified retinopathy as a predictor of PAD severity and progression. However, the association of objectively assessed retinal measures with the development of PAD has not been systematically evaluated in a large community-based cohort. Yang et al. aimed to quantify the associations of retinal findings, reflecting *in vivo* visualized information on the microvasculature, with incident PAD and CLI in the Atherosclerosis Risk in Communities (ARIC) Study (an ongoing, prospective cohort study from four U.S. communities), considering the hypothesis that retinal findings would be particularly strongly associated with incident CLI.

Among 9371 ARIC participants free of a history of PAD, the authors assessed the association of several retinal measures with PAD risk using Cox models. Incident PAD was defined as the first hospitalization with PAD diagnosis or leg revascularization (considered CLI if an additional diagnosis of ulcer, gangrene, or amputation).

During a median follow-up of 18.8 years, 303 participants developed PAD (including 91 CLI cases). Although generalized retinal arteriolar narrowing was not associated with PAD, most measures of retinopathy demonstrated strong associations with PAD beyond potential confounders, including diabetes, with adjusted hazard ratios (HR) of 3.26 for blot-shaped hemorrhages, 3.11 for hard exudates, and 2.18 for any retinopathy. Adjusted HRs were significantly greater for CLI than for PAD. Retinopathy measures showed particularly strong associations in participants with diabetes.

Several retinopathy measures were strongly associated with PAD, especially with CLI and in diabetes. These findings support the contribution of microvascular abnormalities to the development and progression of PAD and would have implications on its preventive and therapeutic approaches.

The results of the study are discussed in depth in the editorial by Hafner et al. in the same issue.

Free cholesterol, cholesterol precursor and plant sterol levels in atherosclerotic plaques are independently associated with symptomatic advanced carotid artery stenosis

Circulating sterols result either from cholesterol (CH) synthesis or intestinal uptake. They are mainly esterified and can be oxidized. Sterols accumulate in atherosclerotic plaques whereby their clinical impact is uncertain. Ceglarek et al. assessed the associations between circulating and plaque

sterol levels in patients with advanced carotid artery stenosis in respect to a prior ischemic event and statin treatment.

Free and esterified CH, CH precursors and plant sterols, as well as oxysterols, were quantified by liquid chromatography-tandem mass spectrometry in 63 consecutive patients undergoing carotid endarterectomy.

CH, CH precursors, plant sterols and oxysterols accumulated in carotid artery plaques. Absolute circulating sterol levels were not predictive for their corresponding plaque levels. After normalisation to CH, plant sterol but not oxysterol levels correlated between plasma and plaques. Among the circulating sterols, oxysterols occurred proportionally less in plaques. Furthermore, CH and plant sterols were less esterified in plaques than in plasma.

Patients who experienced a prior ischemic event and asymptomatic patients had comparable circulating sterol levels, except for lanosterol. In contrast, the absolute plaque levels of free CH, CH precursors and plant sterols and oxysterols were increased in symptomatic compared to asymptomatic patients. These differences remained significant for free CH, precursors and 3 out of 4 analyzed plant sterols after adjustment to the most influencing covariates - statin treatment, type 2 diabetes and age.

Increased absolute plaque levels of free CH, precursors and plant sterols predict an ischemic event in patients with advanced carotid artery stenosis.

The plasma protein profile and cardiovascular risk differ between intima-media thickness of the common carotid artery and the bulb: A meta-analysis and a longitudinal evaluation

Genetic loci associated with CHD show different relationships with intima-media thickness in the common carotid artery (IMT-CCA) and in the bulb (IMT-bulb). Lind et al. investigated whether IMT-CCA and IMT-bulb differ also with respect to circulating protein profiles and risk of incident atherosclerotic disease.

In three Swedish cohorts (MDC, IMPROVE, PIVUS), IMT-CCA and IMT-bulb were assessed by ultrasound at baseline, and 86 cardiovascular-related proteins were analyzed. In the PIVUS study only, IMT-CCA and IMT-bulb were investigated in relation to incident atherosclerotic disease over 10 years of follow-up.

In a meta-analysis of the analysis performed separately in the cohorts, three proteins, matrix metalloproteinase-12 (MMP-12), hepatocyte growth factor (HGF) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), were associated with IMT-CCA when adjusted for traditional cardiovascular risk factors. Five proteins were associated with IMT-bulb (MMP-12, growth/differentiation factor 15 (GDF-15), osteoprotegerin, growth hormone and renin). Following

adjustment for cardiovascular risk factors, IMT-bulb was significantly more closely related to incident stroke or myocardial infarction than IMT-CCA in the PIVUS study. MMP-12 levels were related to this combined end-point.

Elevated levels of MMP-12 were associated with both IMT-CCA and IMT-bulb, but other proteins were significantly related to IMT in only one of these locations. The finding that IMT-bulb was more closely related to incident atherosclerotic disease than IMT-CCA emphasizes a difference between these measurements of IMT.