Atherosclerosis newsletter

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Volume 318, Issue February 2021

Volume 319, Issue February 2021

Volume 320, Issue March 2021

Current guidelines consider all patients with atherosclerotic cardiovascular disease (ASCVD), whether or not clinically manifest, as very high risk patients who should undergo strictest risk factor control and reach very low target values of LDL-cholesterol. However, also in patients with ASCVD, the risk of future major cardiovascular events is not uniform. This is best illustrated by the most recent randomized controlled trials on PCSK9 inhibitors: *post hoc* analyses of the Fourier and Odyssey Outcome trials identified subgroups of patients who benefited over-proportionately from the PCSK9 inhibitor treatment, as well as subgroups of patients who did not benefit at all. Thus there is considerable need to stratify patients with ASCVD who require most aggressive lipid lowering treatment and those who are in less need or need better control of other targets, for example inflammation. Such a personalized strategy needs biomarkers, recorded for example by imaging or by laboratory tests. Issues 318, 319, and 320 contain several review articles and original publications addressing this issue.

Predicting 1-, 3- and 5-year outcomes in patients with coronary artery disease: A comparison of available risk assessment scores

Thromboischemic and bleeding events are rare but life-threatening complications after percutaneous coronary intervention (PCI). Various risk assessment models have been established to predict short- and long-term adverse events, including thromboischemic and/or bleeding complications, in patients with symptomatic CAD. Zdanyte et al. compared available risk assessment systems based on their performance in identifying high-risk patients within this category.

1565 consecutive patients with symptomatic CAD were included in the study. CALIBER, DAPT, GRACE 2.0, PARIS-CTE, PARIS-MB, PRECISE-DAPT and PREDICT-STABLE scores were calculated in appropriate patient subgroups. All patients were followed-up for 1, 3 and 5 years for all-cause death (ACD), myocardial infarction (MI), ischemic stroke (IS) and bleeding. The primary combined ischemic endpoint (CE) consisted of ACD, MI and/or IS. Secondary endpoints were defined as single occurrence of either ACD, MI, IS, or bleeding.

GRACE 2.0 score showed good discrimination performance for CE in a 3- and 5-year follow-up. CALIBER, GRACE 2.0 and PARIS-CTE showed best performance (AUC>0.7) in predicting ACD throughout the follow-up, whereas IS was best predicted by PARIS-CTE and CALIBER scores. None of the scores performed well in predicting MI or bleeding complications in short- and long-term follow-up.

Residual inflammatory risk at 12 months after acute coronary syndromes is frequent and associated with combined adverse events

Acute coronary syndromes (ACS) constitute life-threatening manifestations of coronary atherosclerosis and remain associated with substantial mortality and morbidity in the subsequent 12 months. Residual inflammatory risk (RIR) after ACS may identify patients likely to benefit from anti-inflammatory therapies. Klingenberg et al. aimed to identify the proportion of patients with RIR based on hsCRP ≥ 2 mg/L and determine whether persistently high inflammation at baseline and 12 months after ACS is associated with combined adverse events.

Patients from the Special Program University Medicine ACS cohort were divided into four groups according to level of hsCRP at baseline and after 12 months: persistently high RIR, increased RIR (first low, then high hsCRP), attenuated RIR (first high, then low hsCRP), or persistently low RIR. High RIR was defined as hsCRP ≥ 2 mg/L. An independently adjudicated incident of combined adverse events was defined as the composite of myocardial infarction, clinically indicated coronary revascularization or cerebrovascular events.

Among 1209 patients with available hsCRP, clinical and demographic data, 295 patients had persistently high RIR and 72 patients had increased RIR. A total of 390 patients had attenuated RIR and 452 patients had persistently low RIR. Of 90 combined adverse events, 31 occurred in the persistently high compared with the three other groups combined, attenuated RIR 30, persistently low RIR 26.

Persistently elevated hsCRP after ACS is found in a quarter of patients with the highest risk of combined adverse events. This underlines the need to perform anti-inflammatory intervention trials in RIR patients.

Vascular imaging of atherosclerosis: Strengths and weaknesses

Atherosclerosis is an inflammatory disease that can lead to several complications such as ischemic heart disease, stroke, and peripheral vascular disease. Therefore, researchers and clinicians rely heavily on the use of imaging modalities to identify and quantify the burden of atherosclerosis in the aorta, carotid arteries, coronary arteries, and peripheral vasculature. These imaging techniques

vary in invasiveness, cost, resolution, radiation exposure, and presence of artifacts. Consequently, a detailed understanding of the risks and benefits of each technique is crucial prior to their introduction into routine cardiovascular screening. Additionally, recent research in the field of microvascular imaging has proven to be important in the field of atherosclerosis. Using techniques such as contrast-enhanced ultrasound and superb microvascular imaging, researchers have been able to detect blood vessels within a plaque lesion that may contribute to vulnerability and rupture. Mantella et al. review the strengths and weaknesses of the various imaging techniques used to measure atherosclerotic burden. The future of advanced imaging modalities as potential biomarkers for atherosclerosis is discussed.

Cardiac outcomes in patients with acute coronary syndrome attributable to calcified nodule

Calcified nodule (CN) is a distinct plaque phenotype, which is a pathogenesis of acute coronary syndrome (ACS). It is characterized by a protruding nodular calcification penetrating the lumen surface with the attached thrombus. Given that the presence of lesion calcification with this unique distribution pattern could affect clinical outcomes after percutaneous coronary intervention (PCI), ACS subjects with CN may exhibit worse cardiac outcomes following PCI. Sugane et al. retrospectively analyzed 657 ACS patients receiving PCI with newer-generation drug-eluting stent (DES) implantation under intravascular ultrasound (IVUS) guidance.

CN was defined as (1) protruding calcification with its irregular surface and (2) the presence of calcification at adjacent proximal and distal segments. The primary endpoint was a composite of major adverse cardiac event [MACE = cardiac death + ACS recurrence + target lesion revascularization (TLR)].

CN was identified in 5.3% of the study subjects. CN patients were more likely to have coronary risk factors including hypertension, chronic kidney disease, maintenance hemodialysis and a history of PCI. During the observational period, CN was associated with an increased risk of MACE, ACS recurrence and TLR. These cardiac risks related to CN were consistently observed in Cox proportional hazards model and a propensity score–matched cohort analysis.

ACS patients attributable to CN have an increased risk of ACS recurrence and TLR, mainly driven by the continuous growth and protrusion of the calcified mass.

CN as a rare but important cause of acute coronary syndrome are discussed in the editorial by Sato et al.

Acute ischemic stroke *versus* transient ischemic attack: Differential plaque morphological features in symptomatic intracranial atherosclerotic lesions

Intracranial atherosclerotic disease (ICAD) is a major etiologic cause for acute ischemic stroke (AIS) and transient ischemic attack (TIA). Xiao et al. investigated whether differential morphological features exist in symptomatic atherosclerotic lesions between AIS and TIA patients.

The culprit plaques from 45 AIS patients and 42 TIA patients were analyzed for the degree of stenosis, vessel wall irregularity, normalized wall index (NWI), remodeling index, plaque-wall contrast ratio (CR), high signal intensity on T1-weighted images, plaque enhancement ratio and enhancement grade. These plaque features along with clinical characteristics were compared between the AIS and TIA groups.

Overall, grade 2 enhancement and hyperlipidemia were independent indicators for AIS, whereas high NWI was associated with TIA. In the comparison between the subgroups with moderate stenosis, high plaque-wall CR was associated with AIS, whereas high NWI was associated with TIA.

The study shows differential morphological features in symptomatic ICAD lesions between AIS and TIA patients. Probing these features with MR vessel wall imaging may provide insights into the prognosis of patients with ICAD.

New prediction tools and treatment for ACS patients with plaque erosion

It is known from autopsy observations that the proximate cause of the majority of acute coronary syndromes (ACS) is occlusive thrombosis generated by plaque rupture or, less frequently, superficial erosion. Patients with ACS caused by plaque erosion seem to have a better long-term prognosis compared to those with plaque rupture, and may be stabilized by dual antiplatelet therapy without any need for stenting in a non-trivial proportion of cases, limiting the expenses and potential complications of invasive procedures. The accurate prediction of plaque erosion and the identification of specific biomarkers that could be used at the point-of-care without the need of invasive imaging would take us a step closer to the holy grail of precision medicine in patients with ACS. In this review, Vergallo et al. discuss new prediction tools and treatment for ACS patients with plaque erosion.

Reviewing imaging modalities for the assessment of plaque erosion

Plaque rupture followed by intracoronary thrombus formation is recognized as the most common pathophysiological mechanism in acute coronary syndromes (ACS). The second most common underlying substrate for ACS is plaque erosion whose hallmark is thrombus formation without cap disruption. Invasive and non-invasive methods have emerged as a promising tool for evaluation of plaque features that either predict or detect plaque erosion. Optical coherence

tomography (OCT), high-definition intravascular ultrasound (IVUS), near-infrared spectroscopy (NIRS), and near-infrared autofluorescence (NIRF) have been used to study plaque erosion. The detection of plaque erosion in the clinical setting, mainly facilitated by OCT, has shed light upon the complex pathophysiology underlying ACS not related to plaque rupture. Coronary computed tomography angiography (CCTA), which is to date the most commonly used non-invasive technique for coronary plaque evaluation, may also have a role in the evaluation of patients predisposed to erosion. Also, computational models enabling quantification of endothelial shear stress may pave the way to new research in coronary plaque pathophysiology. In this review, Collet et al. focus on the recent imaging techniques for the evaluation of plaque erosion including invasive and non-invasive assessment.

Coronary ^{18}F-sodium fluoride PET detects high-risk plaque features on optical coherence tomography and CT-angiography in patients with acute coronary syndrome

^{18}F-Sodium Fluoride Positron Emission Tomography (^{18}F–NaF PET) non-invasively detects micro-calcification activity, the earliest stage of atherosclerotic arterial calcification. Majeed et al. studied the association between coronary ^{18}F–NaF uptake and high-risk plaque features on intra-coronary optical coherence tomography (OCT) and CT-angiography (CTCA) and the potential application to patient-level risk stratification.

Sixty-two prospectively recruited patients with acute coronary syndrome (ACS) underwent multi-vessel OCT, ^{18}F–NaF PET and CTCA. The maximum tissue to background ratio was measured in each coronary segment on ^{18}F–NaF PET scans. High-risk plaque features on OCT and CTCA were compared in matched coronary segments. The number of patients testing positive for micro-calcification activity was determined.

In 62 patients, the coronary segments with elevated ^{18}F–NaF uptake had higher lipid arc (LA), higher prevalence of macrophages and lower plaque free wall (PFW) on OCT, and a higher total plaque burden and higher dense calcified plaque burden on CTCA, when compared with ^{18}F–NaF negative segments. Patients grouped by increasing number of coronary lesions positive for microcalcification activity (0,1, ≥2) showed decreasing plaque free wall, increasing calcification and increasing macrophages on OCT.

^{18}F–NaF uptake is associated with high-risk plaque features on OCT and CTCA in a per-segment and per-patient analysis in subjects hospitalized for ACS.

The results of this study are discussed in the editorial by Raggi and Abele.

Machine learning integration of circulating and imaging biomarkers for explainable patient-specific prediction of cardiac events: A prospective study

Atherosclerotic cardiovascular disease (ASCVD) causes significant morbidity and mortality in the United States, and early risk stratification of individuals for cardiovascular events is crucial in determining treatment strategies. Traditional risk assessment tools utilize demographic, anthropometric, and clinical patient characteristics. Despite the many reliable predictors, few studies have combined serum biomarker levels with clinical and imaging variables for prognostication of CVD. Tamarappoo et al. assessed the performance of a comprehensive machine learning (ML) risk score integrating circulating biomarkers and computed tomography (CT) measures for the long-term prediction of hard cardiac events in asymptomatic subjects.

1069 subjects from the prospective EISNER trial, who underwent coronary artery calcium (CAC) scoring CT, serum biomarker assessment, and long-term follow-up, were include in the study. Epicardial adipose tissue (EAT) was quantified from CT using fully automated deep learning software. Forty-eight serum biomarkers, both established and novel, were assayed. An ML algorithm (XGBoost) was trained using clinical risk factors, CT measures (CAC score, number of coronary lesions, aortic valve calcium score, EAT volume and attenuation), and circulating biomarkers, and validated using repeated 10-fold cross validation.

At 14.5 ± 2.0 years, there were 50 hard cardiac events (myocardial infarction or cardiac death). The ML risk score outperformed the CAC score and ASCVD risk score for the prediction of hard cardiac events. Serum biomarkers provided incremental prognostic value beyond clinical data and CT measures in the ML model. Among novel biomarkers, MMP-9, pentraxin 3, PIGR, and GDF-15 had highest variable importance for ML and reflect the pathways of inflammation, extracellular matrix remodeling, and fibrosis.

In this prospective study, ML integration of novel circulating biomarkers and noninvasive imaging measures provided superior long-term risk prediction for cardiac events compared to current risk assessment tools.

These results are further discussed in the editorial by Williams and Newby.