atherosclerosis

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Call for original papers on "Influence of sex and gender on biology of atherosclerotic cardiovascular disease"

There are differences in the risk for atherosclerotic cardiovascular diseases (ASCVD) between men and women. These differences stem from various biological aspects related to sex and gender and should be considered when assessing the risk for ASCVD in clinical practice, planning clinical trials, and performing *in vivo* and even *in vitro* experiments in research settings. *Atherosclerosis*, the journal of the European Atherosclerosis Society (EAS), is now **calling for the submission of Original Research Papers for a Special Issue related to the role of sex and gender biology in ASCVD**. These manuscripts will undergo a regular review process and in case of acceptance will go online within the usual time of processing. Submissions are encouraged from all fields related to the topic including clinical, translational, and basic research.

The submitted Original Research Articles will be handled by Elena Osto, Jeanine Roeters van Lennep, and Lale Tokgözoğlu as Guest Editors and Katariina Öörni as Co-Editor of *Atherosclerosis*. They will decide on the peer reviewers of the submitted articles. If a manuscript is accepted for publication, these Original Research Articles will appear printed together in a combined issue of the journal containing roughly a dozen in-depth review articles on the sex and gender biology of ASCVD. The collection aims to provide the most comprehensive, insightful, and current overview of the clinical and translational aspects and basic research related sex and gender differences in ASCVD. The topics and authors for these review articles have already been decided for this project. The publication is planned for spring/summer 2023 and is expected to receive a high visibility. **Accepted papers will be published with promotional open access for a one-year period, free of charge.**

For preparation of the Original Research manuscripts please see the "Guide for authors"

Deadline for submission of the first draft of Original Research Papers is December 31st, 2022. This call is only open for Original Research Articles and no review articles are allowed. Please select "Special issue: Gender biology in ASCVD" as article type at submission.

To submit your paper go to: Editorial Manager®

Atherosclerosis newsletter

Simona Negrini and Arnold von Eckardstein

Volume 358, Issue October 2022 contains several articles on refined risk prediction in individuals who are already at increased risk for atherosclerotic cardiovascular disease, for example because of familial hypercholesterolemia or a history of stroke.

Risk of stroke in genetically verified familial hypercholesterolemia: A prospective matched cohort study

Even though a genetic familial hypercholesterolemia (FH) diagnosis does not seem to be associated with higher risk of total stroke, data on the risk of ischemic stroke, and particularly hemorrhagic stroke, are less clear. Svendsen et al. aimed to investigate the risk of incident total, ischemic and hemorrhagic stroke in individuals with FH compared to controls, and to explore the association between cumulative statin use and risk of total stroke in FH.

This prospective cohort study included 4186 individuals with genetically verified FH and 82,180 age and sex matched controls followed from 2008 to 2018 for incident stroke. Daily defined doses (DDD) described cumulative statin exposure: 0–5000 DDD ("low"), 5000–10,000 DDD ("intermediate"), and >10 000 DDD ("high"). Results were presented as hazard ratio (95% CI) derived from Cox proportional hazards models.

The results showed that individuals with FH did not have a higher risk of total stroke nor ischemic stroke. Excess risk of hemorrhagic stroke was observed but attenuated after adjusting for antithrombotic medication. Among individuals with FH, there was no association between statin use and total stroke for intermediate *vs.* low DDD or for high vs. low DDD.

No significant excess risk of incident total and ischemic stroke in FH, and no difference in total stroke risk among the FH population with low, intermediate, and high statin exposure were observed. The observed relationship between FH and hemorrhagic stroke was no longer significant after adjusting for use of anti-thrombotic medication.

Assessing the external validity of the SAFEHEART risk prediction model in patients with familial hypercholesterolaemia in an English routine care cohort

Familial hypercholesterolaemia (FH) is associated with a coronary heart disease risk, which is much greater than that observed in the general population. Whilst tools enabling estimation of individual vascular event risk in the general population are well-established, and have been recommended as part of routine preventive care for several years, they have not been validated for the population with FH. A tool aiming to predict event risks for the population with FH (the SAFEHEART model) was recently developed in a multicenter Spanish cohort with an established genetic FH

diagnosis. McKay et al. assessed whether such tool could aid clinical decision-making in an English routine care cohort with FH.

A historical (2000–2017) open cohort of 3643 participants aged 18–79 years and ≥6-months since FH diagnosis was derived from the Clinical Practice Research Datalink. Individual 10-year cardiovascular risks were predicted using the SAFEHEART model, with multiple imputation used to manage missing data. Outcomes were the first occurrence of myocardial infarction, coronary revascularisation, ischaemic stroke, carotid revascularisation, peripheral arterial revascularisation, non-traumatic lower limb amputation, or cardiovascular death. Model performance was assessed using standard measures of calibration and discrimination, and decision curve analysis.

147 outcome events were observed over a median 3.73 years follow-up. While the model had some discriminatory value, observed outcome risks departed substantially from predicted risks. Calibration slopes for men and women by age decile were 10.09 and 2.85, respectively. Recalibration-in-the-large led to closer alignment of observed and predicted risks . Decision curve analysis suggested the recalibrated model had net benefit at predicted risks of 10–30%.

The original SAFEHEART model has limited generalisability to the routinely identifiable English primary care FH population. With recalibration, it appears to have moderate utility at 10–30% predicted risk. The model would likely be of limited utility in current practice in England.

The difficulties in gauging atherosclerotic cardiovascular disease risk heterogeneity in FH are discussed in the editorial by Mizuta and Santos.

Effective high-density lipoprotein cholesterol is associated with carotid intima-media thickness and vascular events after acute ischemic stroke

Effective high-density lipoprotein cholesterol (HDL-C) is a measure of HDL functionality. Schwedhelm et al. evaluated if HDL-C was associated with carotid intima-media thickness (cIMT) and incident major adverse cardiovascular events (MACE) in patients with acute ischemic stroke from two prospective cohort studies.

In the MARK-STROKE cohort, 299 patients with acute ischemic stroke or TIA were included. Outcome was available in 219 patients during a median follow-up of 294 days. In CIRCULAS, 382 acute ischemic stroke patients were included and a 90-day follow-up was available in 213 patients. HDL-C was calculated based on symmetric dimethylarginine (SDMA) and HDL cholesterol concentrations. Main outcome was incident MACE (death, stroke, and myocardial infarction) and the main measure was cIMT.

In both studies, HDL-C was inversely associated with cIMT in linear regression analysis adjusted for age, sex and creatinine. In MARK-STROKE, the adjusted hazard for MACE was significantly reduced for patients with one unit increase (mg/dL) of HDL-C. In the CIRCULAS cohort, stroke patients with

higher HDL-C had less incident MACE during 90 days of follow-up. Neither SDMA nor HDL cholesterol predicted outcome.

These findings imply a protective role of biologically effective HDL after acute cerebral ischemia for secondary events and emphasize the relevance of lipoprotein functionality in these patients.

Acid suppressants use and risk of atherosclerotic cardiovascular disease in middle-aged and older adults

Acid suppressants, including proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), are widely recommended in many acid-related conditions. In recent years, the use of PPIs and H2RAs has exploded due to their superior acid suppression and concerns regarding adverse events associated with their use have increased. However, the impact of PPIs and H2RAs on the risk of atherosclerotic cardiovascular disease (ASCVD) remains unknown. Ma et al. aimed to estimate the association between use of acid suppressants and risk of ASCVD events among patients without history of cardiovascular diseases or anti-hypertensive treatment at baseline by taking advantage of the data available in the UK Biobank. The outcomes were ASCVD and each subtype (coronary artery disease, myocardial infarction, peripheral artery disease, and ischemic stroke). The association was estimated by Cox proportional-hazards models.

Among 316,730 individuals, with a median of 12.5 years of follow-up, 13,503 incident ASCVD were documented. Regular PPIs use was associated with a higher risk of ASCVD and every subtype of ASCVD. Among each type of PPIs, omeprazole, lansoprazole, and pantoprazole were associated with a higher risk of ASCVD. Stratification analysis showed that PPIs use was associated with a higher risk of ASCVD among individuals without indications of medications for PPIs. In addition, use of H2RAs was not related to the risk of ASCVD.

In conclusion, PPIs were associated with increased risk of ASCVD, particularly amongst participants without indications for medication. These findings suggest clinicians and patients should balance the risks and benefits when choosing the type of PPIs. Carefully evaluating the need for long-term use of PPIs, seeking alternative therapy, and routinely screening for CVD risk among those who need long-term medications of PPIs, is warranted.