atherosclerosis

Atherosclerosis newsletter

Simona Negrini and Arnold von Eckardstein

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The present time is characterized by major changes, notably in the climate and disrupting events, and in the appearance of COVID19. Also drug development is undergoing paradigm shifts from screening of small molecule libraries for effective compounds to specific targeting with antibodies, antisense oligonucleotides or small interfering RNAs (siRNA). The current issue of *Atherosclerosis* contains several articles addressing the impact of change on atherosclerotic cardiovascular disease from different angles: shift work or climate changes modulating cardiovascular risk, COVID19 or therapeutic siRNA raising questions on paradigm shifts in the management of dyslipidemia, mechanisms regulating the phenotypic switch of smooth muscle cells in the arterial wall, and the nutritional changes in pregnancy affecting inflammatory responses and atherosclerosis in the offspring.

Predicted impact of increasing average ambient temperature over the coming century on mortality from cardiovascular disease and stroke in the USA

Future climate change may adversely impact human health. The direct effects of extreme hot temperatures on mortality are well established, and their future impact well modelled. However, less extreme changes in ambient temperature (Ta) have been previously associated with increased mortality from circulatory and metabolic diseases, but their future impact is less clear. At present, a relatively small number of studies have investigated the impact of average temperature changes until the end of the century, and have done so in restricted regions of the United States (US) and Europe. Mazidi and Speakman evaluated the spatial association between cardiovascular diseases (CVD) and stroke mortality with average Ta across the US mainland, and then used this relationship to model future temporal trends in mortality from CVD and stroke until the end of the century (2099), using different warming scenarios for each US County.

Ta was significantly associated with crude levels of CVD mortality and stroke mortality. Moreover, there was a strong positive link between Ta and physical inactivity (PIA). Once adjusted for PIA, the associations between Ta and CVD and stroke mortality were much reduced but still highly significant.

By 2099, modelling suggests between 8844 and 25,486 extra deaths each year from CVD, and between 2063 and 13,039 extra deaths for stroke, beyond the increases expected from population

expansion. Mortality due to changes in the mean Ta may be as, or more, significant than the impacts of extreme hot weather events.

Shift work, and particularly permanent night shifts, promote dyslipidaemia: A systematic review and meta-analysis

Shift work that involves night time is common, accounting for approximately 20% of the work force. Unfortunately, shift work is linked to several health problems including deleterious cardiovascular effects that might be underlined by dyslipidemia. In this systematic review and meta-analysis, Dutheil et al. determined the impact of shift work on dyslipidemia.

A search in PubMed, Cochrane Library, Science Direct and Embase databases was conducted for studies describing blood lipids levels or a risk measure in shift workers compared with fixed-day workers (controls). Differences by study-level characteristics were estimated using stratified meta-analysis by type of shift work and meta-regression to examine relations between dyslipidemia and demographic, lifestyle and work characteristics. Estimates were pooled using random-effect meta-analysis.

A total of 66 articles, representing 197,063 workers, were included in the analysis. Shift work globally increased the levels of triglycerides, and globally decreased the levels of high density lipoprotein cholesterol (c-HDL). Permanent night shift workers were an at-risk type of shift for dyslipidemia, with significantly higher blood levels of total cholesterol and triglycerides, and significantly lower blood levels of c-HDL. Permanent night shift workers were more at-risk for total cholesterol than rotating 3 × 8 shift workers and rotating 2 × 12 shift workers; and more at-risk for triglycerides than rotating day shift workers. Results were non-significant for low density lipoprotein cholesterol (c-LDL), nor depending on type of shifts.

Shift work, and particularly permanent night shift, is associated with dyslipidaemia via elevated total cholesterol and triglycerides, and reduced c-HDL. Promoting rotating shifts instead of permanent night shifts could be an effective preventive strategy to reduce cardiovascular risk in shift workers.

Managing hyperlipidaemia in patients with COVID-19 and during its pandemic: An expert panel position statement from HEART UK

The emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes Coronavirus Disease 2019 (COVID-19) has resulted in a pandemic. SARS-CoV-2 is highly contagious and its severity highly variable. The fatality rate is unpredictable but is amplified by several factors including advancing age, atherosclerotic cardiovascular disease, diabetes mellitus, hypertension and obesity. A large proportion of patients with these conditions are treated with lipid lowering medication, and questions regarding the safety of continuing lipid-lowering medication in patients

infected with COVID-19 have arisen. Some have suggested they may exacerbate their condition. It is important to consider known interactions with lipid-lowering agents and with specific therapies for COVID-19. This paper by Iqbal et al. aims to collate current evidence surrounding the safety of lipid-lowering medications in patients with COVID-19. It offers a consensus view based on current knowledge and rates the strength and level of evidence for these recommendations.

Pubmed, Google scholar and Web of Science were searched for articles using search terms: SARS-CoV-2, COVID-19, coronavirus, lipids, statin, fibrates, ezetimibe, PCSK9 monoclonal antibodies, nicotinic acid, bile acid sequestrants, nutraceuticals, red-yeast rice, omega-3-Fatty acids, lomitapide, hypercholesterolaemia, dyslipidaemia and volanesorsen.

There is no evidence that lipid lowering therapy is unsafe in patients with COVID-19 infection. Lipid-lowering therapy should not be interrupted because of the pandemic or in patients at increased risk of COVID-19 infection. In patients with confirmed COVID-19, care should be taken to avoid drug interactions, between lipid-lowering medications and drugs that may be used to treat COVID-19, especially in patients with abnormalities in liver function tests.

Estimation of the major cardiovascular events prevention with Inclisiran

The recently published ORION-10 and ORION-11 trials demonstrated the long-term efficacy of Inclisiran on low-density lipoprotein cholesterol (LDLc) reduction; results also included the incidence of major cardiovascular events (MACE) in both trials, and a significant reduction in the composite endpoint (including cardiac death, nonfatal myocardial infarction, or stroke) was observed in patients receiving Inclisiran. Using the results of the ORION 10–11 trials, Cordero et al. performed a meta-analysis to assess the effect of therapies involving proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors or Inclisiran for >6 months on MACE incidence and provided an estimation of the possible effects of Inclisiran on real-world patients.

The primary endpoint was MACE incidence, as reported in outcomes-based randomized clinical trials (OB-RCT) and non OB-RCT. Analyses were performed using fixed effect models and fractional polynomial regression.

The meta-analysis included a total of 57,431 patients, 1592 treated with Inclisiran and 28,259 with PSCK9 inhibitors. Baseline mean LDLc was 104.1 (12.9) mg globally. On-treatment mean LDLc was 40.1 mg/dl and mean absolute LDLc reduction was 60.6 mg/dl. A total of 5389 MACE were reported, 2482 in patients receiving the study drug and 2907 in patients assigned to placebo. Treatment was associated with OB-RCT and no heterogeneity was observed. The estimation of MACE reduction associated with LDLc reduction, adjusted by age, diabetes, hypertension and baseline LDLc, provided a linear trend in the risk of MACE and LDLc reduction that was linear and all studies fitted properly.

The results of the ORION 10–11 trials are in concordance with results of trials involving treatment with PCSK9 inhibitors. The results of the ORION-4 trial will provide definite evidence on the effects of Inclisiran on MACE reduction.

The phosphorylation of CHK1 at Ser345 regulates the phenotypic switching of vascular smooth muscle cells both *in vitro* and *in vivo*

DNA damage and repair have been shown to be associated with carotid artery restenosis and atherosclerosis. The proliferation and migration of vascular smooth muscle cells (VSMCs) is the main cause of artery stenosis. Xin et al. aimed to define the relationship between DNA damage and VSMCs proliferation.

A rat carotid artery injury model was established, and human and rat VSMCs cultured *in vitro*. H_2O_2 was used to induce DNA damage *in vitro*. The selected checkpoint kinase 1 (CHK1) inhibitor, LY2603618, was used to inhibit CHK1 phosphorylation both *in vivo* and *in vitro*. γH2AX, αSMA and phosphorylated CHK1 were detected both in rat carotid artery and cultured VSMCs from different groups. Hyperplasia ratio of the rat carotid artery intima was measured.

The results showed that DNA double-strand breaks occur in the rat carotid artery after injury. DNA damage induces CHK1 phosphorylation and down-regulates αSMA expression in VSMCs both *in vitro* and *in vivo*. The inhibition of CHK1 phosphorylation rescues αSMA expression in VSMCs both *in vitro* and *in vivo*, and rat carotid intima hyperplasia after injury is suppressed.

These data demonstrated that phosphorylation of CHK1 under DNA damage stress modulates VSMCs phenotypic switching. CHK1 inhibition may be a potential therapeutic strategy for intima hyperplasia treatment.

Mutual regulation between β-TRCP mediated REST protein degradation and Kv1.3 expression controls vascular smooth muscle cell phenotype switch

Phenotypic switch of vascular smooth muscle cells (VSMC) plays a key role in the pathogenesis of atherosclerosis and restenosis after artery intervention. In VSMC, levels of K+ channel proteins have been shown to change during phenotype switch in response to environmental alterations.Transcription repressor element 1-silencing transcription factor (REST) has been identified as a key regulator of VSMC proliferation. In the present study, Ye et al. investigated the potential association of E3-ubiquitin ligase β-TRCP-mediated REST protein degradation with Kv1.3 (voltage-gated K+ channel) expression during VSMC phenotypic switch.

Protein and mRNA expression was measured in *ex vivo* and *in vitro* models. Protein interaction and ubiquitination were analyzed by immunoprecipitation assays. ChIP assays were performed to assess the relationship between REST and the targeted DNA binding site.

The expression level of E3-ubiquitin ligase β-TRCP was significantly increased during VSMC phenotypic switch. REST protein ubiquitination mediated by β-TRCP was critical for VSMC proliferation and migration. Moreover, the authors found that the *KCNA3* gene, encoding Kv1.3, contains a functional REST binding site and is repressed by REST. Downregulation of REST by β-TRCP and consequent upregulation of Kv1.3 are important events during VSMC phenotypic switch. Furthermore, upregulated Kv1.3 accelerated β-TRCP-modulated REST degradation through Erk1/2 signaling.

These findings reveal a fundamental role for regulatory interactions between β-TRCP modulated REST degradation and Kv1.3 in the control of the multilayered regulatory programs required for VSMC phenotype switch.

Maternal exposure to soy diet reduces atheroma in hyperlipidemic F1 offspring mice by promoting macrophage and T cell anti-inflammatory responses

The "fetal origins of adult disease" hypothesis refers to the theory that in utero environment may be a vital contributor to the predisposition for chronic diseases in offspring. Maternal hypercholesterolemia has been implicated in a higher incidence of atherosclerotic lesions during the fetal period, and faster progression of these lesions after birth when compared with controls. In this study, Burris et al. investigated whether maternal exposure to soy protein isolate (SPI) diet attenuated the progression of atherosclerosis in F1 offspring mice.

Pregnant apolipoprotein E knockout (*Apoe*$^{-/-}$) female mice were fed an SPI diet until postnatal day 21 (PND21) of the offspring (SPI-offspring). SPI-offspring were switched at PND21 to casein (CAS) diet until PND140. Mice fed CAS throughout their lifetime (gestation to adulthood) were used as controls (CAS-offspring).

Atherosclerotic lesions in the aortic sinuses were reduced in SPI-offspring compared with CAS-offspring. Total serum cholesterol levels in CAS-offspring or dams were comparable to levels in their SPI-counterparts, suggesting that alternative mechanisms contributed to the athero-protective effect of maternal SPI diet. Aortic VCAM-1, MCP-1, and TNF-α mRNA and protein expression, and expression of macrophage pro-inflammatory cytokines was reduced in SPI-offspring. Interestingly, CD4+ T cells from SPI-offspring showed reduced IFN-γ expression (Th1), while the expression of IL-10 (Th2/Treg), and IL-13 (Th2) was increased. DNA methylation analyses revealed that anti-inflammatory T cell-associated *Gata3* and *Il13* promoter regions were hypomethylated in SPI-offspring. These findings suggest that anti-

inflammatory macrophage and T cell response may have contributed to the athero-protective effect in SPI-offspring.

These results demonstrate that gestational and lactational soy diet exposure inhibits susceptibility to atherosclerotic lesion formation by promoting anti-inflammatory responses by macrophages and T cells.