IN BRIEF

HEART FAILURE

No association between heart failure and cancer

Heart failure (HF) and cancer share common risk factors, and previous studies have indicated that patients with HF have an increased risk of cancer. However, a new study reports that the presence of HF has no effect on the incidence of cancer or on cancer-specific mortality. The study included data from 28,341 male participants from the Physicians' Health Studies I and II. During a median follow-up of almost 20 years, 1,420 patients developed HF and 7,363 cancers developed. The investigators used time-varying analysis (in which HF was modelled as a time-varying exposure) and landmark analysis methods to minimize possible confounding by age, the strongest risk factor for cancer. HF was not associated with the overall incidence of cancer in either unadjusted or multivariable-adjusted models, or with site-specific cancer or cancer-specific mortality after multivariable adjustment. Nevertheless, as Paolo Boffetta and Jyoti Malhotra caution in an accompanying editorial, larger studies are needed before completely disregarding the potential association between HF and cancer.

ORIGINAL ARTICLE Selvaraj, S. et al. Lack of association between heart failure and incident cancer. *J. Am. Coll. Cardiol.* **71**, 1501–1510 (2018)

CONGENITAL HEART CONDITIONS

Baby's heart defects can signal mother's CVD risk

Mothers of infants with congenital heart defects have an increased risk of hospitalization for cardiovascular causes later in life, indicating that congenital heart defects in offspring might signal a familial predisposition to cardiovascular disease (CVD). This finding comes from a study in >1 million women who had delivered babies in 1989–2013 in Quebec, Canada, including 1,516 women with critical and 14,884 with noncritical heart defects in the offspring. In adjusted models, the risk of hospitalization for any cardiovascular cause was higher in women whose infants had critical heart defects (HR 1.43, 95% CI 1.13–1.82) or noncritical heart defects (HR 1.24, 95% CI 1.15–1.34) compared with mothers of infants with no heart defects. Having offspring with congenital heart defects was also associated with a greater risk of hospitalization for specific cardiovascular causes, such as myocardial infarction and heart failure. "More study is needed to determine if women whose infants [have] heart defects could benefit from targeted primary prevention initiatives," conclude the investigators.

ORIGINAL ARTICLE Auger, N. et al. Long-term risk of cardiovascular disease in women who have had infants with heart defects. *Circulation*. https://doi.org/10.1161/CIRCULATIONAHA.117.030277 (2018)

DYSLIPIDAEMIA

Novel genetic variant linked with high LDL-C levels

A study reports a new genetic factor that influences LDL-cholesterol (LDL-C) levels, revealing a potential novel mechanism of lipid homeostasis. An array-based association analysis in 1,102 Amish individuals identified a variant in chromosome 5 that was associated with a 15 mg/dl increase in LDL-C levels. Genetic analyses indicated eight candidate genes in this region and functional studies in zebrafish showed that overexpression of one of the candidates, the transcribed pseudogene *APOOP1*, increased LDL-C levels and vascular plaque formation. Further assays provided a possible regulatory link to its parent gene, *APOO* (encoding apolipoprotein O), suggesting *APOO* as a novel target for hyperlipidaemia.

ORIGINAL ARTICLE Montasser, M. E. et al. An *APOO* pseudogene on chromosome 5q is associated with LDL-C levels. *Circulation* https://doi.org/10.1161/CIRCULATIONAHA.118.034016 (2018)

ATHEROSCLEROSIS

Alarmin(g) stroke response drives atheroprogression

Stroke is associated with acute and chronic inflammatory responses, and epidemiological studies have shown that patients who experience a stroke as a result of underlying atherosclerosis are at substantially increased risk of recurrent stroke events. Arthur Liesz and colleagues now show that the immune response triggered by stroke can cause atherosclerotic plaque progression.

Apoe$^{-/-}$ mice were fed a high-cholesterol diet and then underwent either surgery to induce a stroke or a sham procedure. Both atherosclerotic plaque load and monocyte cell counts were higher in the aorta of mice after stroke compared with control. The C-C motif chemokine 2 pathway was critical in attracting pro-inflammatory monocytes to the aorta after stroke. Additionally, plaques had a more vulnerable morphology after stroke, indicated by increased activity of metalloproteinases 2 and 9 and reduced thickness of the fibrous cap.

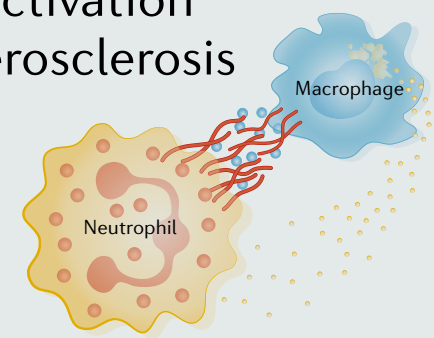
Acute stroke produces a massive release of pro-inflammatory alarmin proteins, such as high mobility group protein B1 (HMGB1), from hypoxic and necrotic brain tissue. HMGB1 induced monocyte and endothelial activation via receptor for advanced glycosylation end products (RAGE) signalling. The investigators showed that reducing systemic levels of alarmins using a soluble form of RAGE as a decoy receptor reduced atherosclerotic

INFLAMMATION

Cholesterol-dependent inflammasome activation accelerates atherosclerosis

IL-1β promotes atherosclerosis in mice, and monotherapy targeting IL-1β can reduce cardiovascular disease in humans. IL-1β is activated by the NLRP3 inflammasome, but the link between inflammasome activation and atherogenesis is unclear. A new study shows that cholesterol accumulation in myeloid cells activates the inflammasome, which promotes neutrophil extracellular trap (NET) formation in the plaque.

Marit Westerterp and colleagues had previously demonstrated that myeloid deficiency of ATP-binding cassette A1 (ABCA1) and ABCG1 — mediators of cholesterol efflux — increased macrophage cholesterol accumulation and atherosclerosis. To investigate the role of the inflammasome, *Ldlr*$^{-/-}$ mice were transplanted with bone marrow from control mice or mice deficient in myeloid *Abca1* and *Abcg1*, with or without inactivation of inflammasome components encoded by *Nlrp3* or *Casp1* and *Casp11*. *Abca1* and *Abcg1* deficiency induced NLRP3 inflammasome activation, and inactivation of *Nlrp3* or *Casp1* and *Casp11* decreased atherosclerotic lesion size by 50% compared with *Abca1* and *Abcg1* deficiency only. Myeloid *Abca1* and *Abcg1* deficiency led to an increase in neutrophil accumulation



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