ESC European Society of Cardiology
European Heart Journal (2018) **39**, 3483–3487
doi:10.1093/eurheartj/ehy607

Inflammation: the new cardiovascular risk factor

Thomas F. Lüscher[1,2,3], MD, FESC

[1]Consultant and Director of Research, Education & Development, Royal Brompton and Harefield Hospital Trust, London, UK; [2]Chairman, Center for Molecular Cardiology, University of Zurich, Switzerland; and [3]EHJ Editorial Office, Zurich Heart House, Hottingerstreet 14, 8032 Zurich, Switzerland

For the podcast associated with this article, please visit https://academic.oup.com/eurheartj/pages/Podcasts.

The famous German pathologist of the 19th century, Rudolf Virchow of the Charité in Berlin, was the first to point to the role of inflammation in atherosclerosis, when he wrote: 'Atherosclerosis is an inflammation induced by cholesterol'. The question remained: is it only cholesterol or is it also an independent mechanisms of plaque formation.[1–4] Alternatively, turned into a clinical question: is there only a cholesterol risk and inflammation will subside if treated appropriately, or is there a remaining inflammatory risk?[5] The CANTOS trial has addressed this and showed convincingly that in the absence of any change of LDL-cholesterol, Canakinumab, a monoclonal antibody targeting interleukin-1β, improves outcome further.[6] In this issue, the FAST TRACK '**Relationships of interleukin-6 reduction to atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)**' by Paul Ridker and colleagues provides further insights into this question.[7] They note that although interleukin-1β blockade is effective, it is uncertain to what extent these beneficial cardiovascular outcomes are mediated through interleukin-6 signalling. Interleukin-6 is markedly elevated at the site of plaque rupture[8] and is predictive of outcomes.[9] A total of 4833 patients of the CANTOS trial had interleukin-6 measured before randomization and after treatment with placebo or one of three doses of Canakinumab (50, 150, or 300 mg s.c. every 3 months). Compared with those allocated to placebo, those receiving canakinumab who achieved on-treatment interleukin-6 levels below the study median value of 1.65 ng/L experienced a 32% reduction in major adverse cardiovascular events or MACE, with an adjusted hazard ratio of 0.68, and a 30% reduction in MACE plus hospitalization for unstable angina requiring urgent revascularization, a 52% reduction in cardiovascular mortality with a hazard ratio of 0.48, and a 48% reduction in all-cause mortality with a hazard ratio of 0.52. In contrast, those with on-treatment interleukin-6 levels equal to or above the median had no significant benefit. Thus, CANTOS provides evidence that modulation of the interleukin-6 pathway can reduce cardiovascular events, independently of lipid lowering. These novel findings are put into context in an **Editorial** by Roland Klingenberg and myself, from Bad Nauheim, Germany and London, UK, respectively.[10]

This is further explored in a Basic Science article regarding a model of stroke.[11] In CANTOS, stroke was rather rare and was not reduced, probably due to the low number of events and the relatively young age of patients enrolled.[6] Inflammation seems also to be associated with stroke in the clinical setting.[12] In their article entitled '**Post-ischaemic administration of the murine Canakinumab-surrogate antibody improves outcome in experimental stroke**',[13] Giovanni G. Camici and colleagues from the University of Zurich, Switzerland tested the efficacy of the murine Canakinumab-equivalent antibody in their mouse model of ischaemic stroke. To mimic the clinical scenario of modern stroke management, Canakinumab was applied after transient middle cerebral artery occlusion in a randomized fashion upon reperfusion, as would be the case in patients eligible for thrombolytic therapy presenting to the emergency room. Following transient middle cerebral artery occlusion, cerebral interleukin-1β levels, unlike those of tumour necrosis factor-α, were increased. Post-ischaemic treatment with interleukin-1β antibody reduced infarct size and cerebral oedema, and improved neurological performance (*Figure 1*). Antibody-treated animals also exhibited a reduced neutrophil and matrix myeloperoxidase-2 but not matrix myeloperoxidase-9, activity in ipsilateral hemispheres as compared with vehicle-treated mice. It was noteworthy that transient middle cerebral artery occlusion was associated with vascular endothelial (VE)-cadherin reduction, which was blunted by Canakinumab. Thus, selective post-ischaemic interleukin-1β blockade improves outcome following experimental brain injury which should be further addressed in clinical studies as an adjuvant therapy to thrombolysis in acute ischaemic stroke patients. These provocative findings are further expanded in a thought-provoking **Editorial** by Paul Ridker from Brigham and Women's Hospital in Boston, Massachusetts (USA).[14]

The mechanism of chronic inflammation at the cellular level is as important as the cytokines addressed above.[15,16] This is further discussed in a review entitled '**Monocyte and haematopoietic progenitor**

With thanks to Amelia Meier-Batschelet for help with compilation of this article.

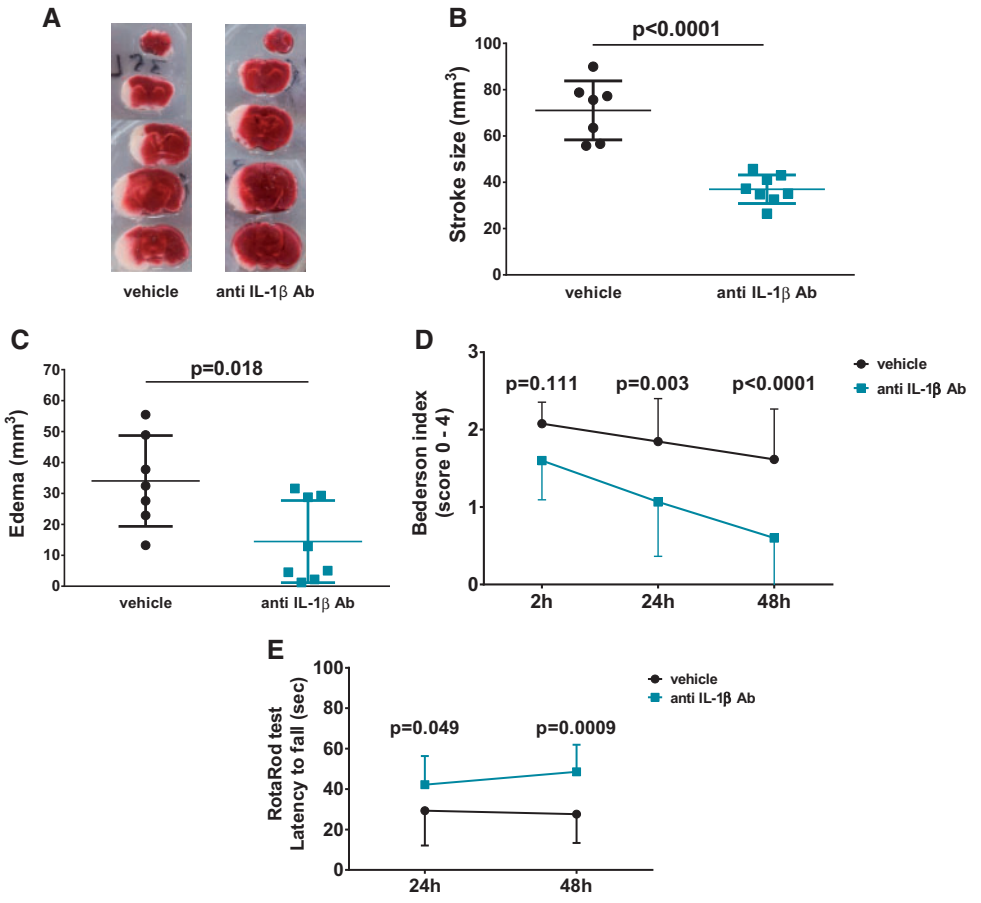

Figure 1 Impact of post-ischaemic treatment with IL-1β antibody on cerebral lesion and neurological deficit after tMCAO in mice. (*A*) Representative pictures of TTC-stained brain slices. (*B*) Animals treated with monoclonal antibody against IL-1β (anti IL-1β Ab) showed decreased stroke volumes by 50% (n = 7–8, unadjusted $P < 0.0001$) and (*C*) decreased oedema (n = 7–8, unadjusted $P = 0.018$) as assessed by TTC staining 48 h after tMCAO, compared with animals treated with vehicle alone. Accordingly, treatment with anti IL-1β Ab improved post-stroke neurological function as assessed by (*D*) RotaRod test or (E) Bederson-based neurological score, as compared with treatment with vehicle alone (n = 13–15 for both; adjusted $P = 0.003$ and <0.0001 for Bederson index at 24 h and 48 h, respectively; adjusted $P = 0.049$ and 0.0009 for Rotarod test at 24 h and 48 h, respectively). IL-1β, interleukin-1β; MCA, middle cerebral artery, tMCAO, transient MCA occlusion, TTC, 2,3,5-triphenyltetrazolium chloride. (from Liberale L, Diaz-Cañestro C, Bonetti NR, Paneni F, Akhmedov A, Beer JH, Montecucco F, Lüscher TF, Camici GG. Post-ischaemic administration of the murine Canakinumab-surrogate antibody improves outcome in experimental stroke. See pages 3511–3517).

reprogramming as a common mechanism underlying chronic inflammatory and cardiovascular diseases' by Alberico Luigi Catapano and colleagues from the University of Milan in Italy.[17] In search of innovative anti-inflammatory strategies, immune cells have been recognized as key players contributing to atherosclerotic plaque progression and destabilization. In particular, the role of innate immune cells is of major interest, following the recent paradigm shift that innate immunity, long considered to be incapable of learning, does exhibit immunological memory mediated via epigenetic reprogramming. Of note, atherosclerotic risk factors promote immune cell migration by pre-activation of circulating innate immune cells. Innate immune cell activation via metabolic and epigenetic reprogramming perpetuates a systemic low grade inflammatory state in cardiovascular disease that is also common in other chronic inflammatory disorders. This opens up a new therapeutic area in which metabolic or epigenetic modulation of innate immune cells may result in decreased systemic chronic inflammation, alleviating cardiovascular disease and its co-morbidities.

Environmental factors such as noise and pollution may also contribute to chronic inflammation in the cardiovascular system.[18–20] Aircraft noise in particular causes endothelial dysfunction, oxidative stress, and inflammation. Epidemiological studies suggest that transportation noise increases the incidence of coronary artery disease, hypertension, and stroke. However, the underlying molecular mechanisms are not well understood.[21,22] In their Basic Science article '**Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation**', Thomas Münzel and colleagues from the Johannes Gutenberg Universität in Mainz, Germany investigated the effects of noise in phagocyte-type NADPH oxidase knockout ($Nox2^{-/-}$) mice.[23] Wild-type and $Nox2^{-/-}$ mice were

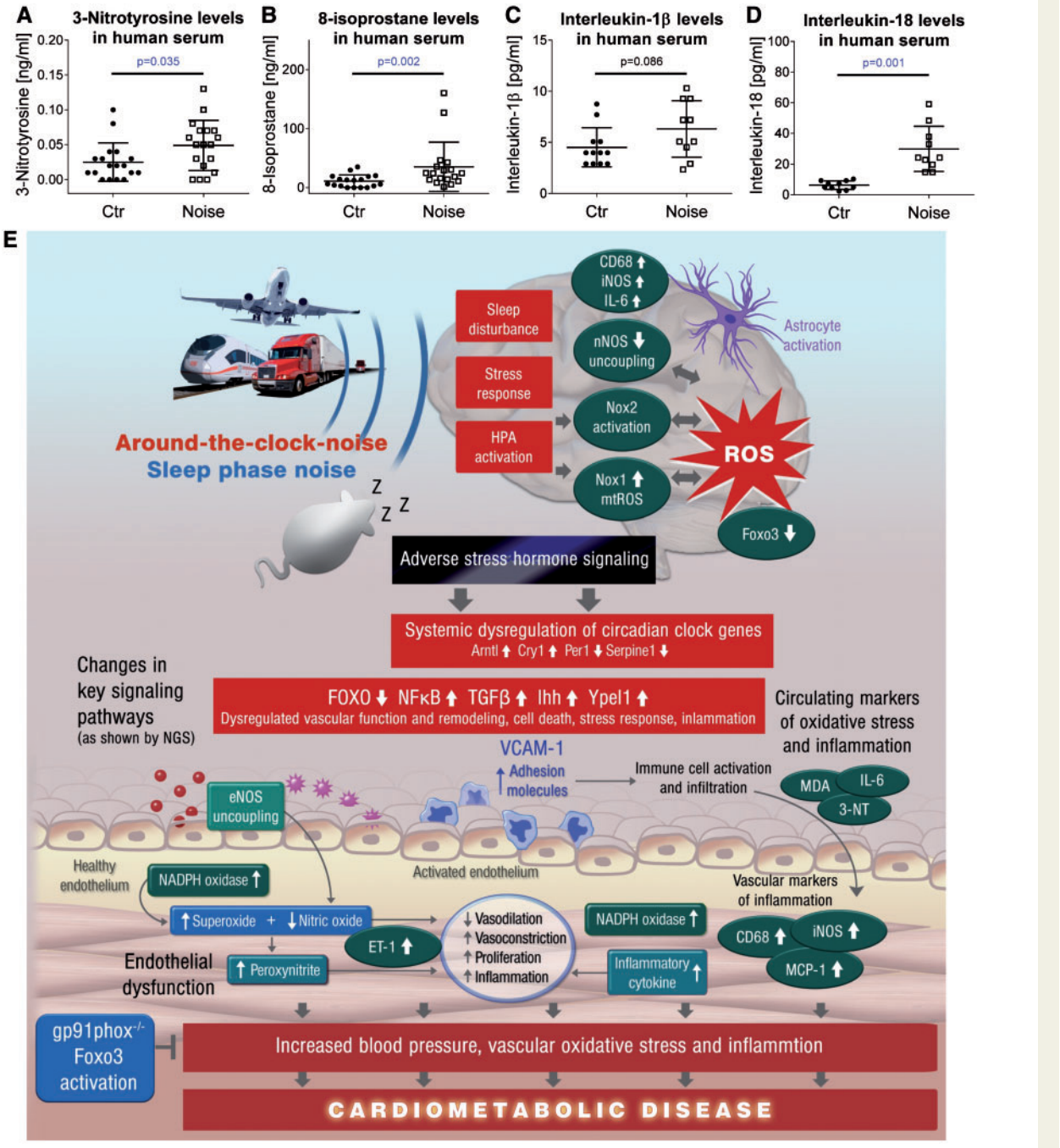

Figure 2 Oxidative stress markers in serum of noise-exposed human subjects. ELISA measurements revealed increased 3-nitrotyrosine (3NT)-positive proteins (*A*) and 8-isoprostane concentrations (*B*) in serum of human subjects. Multiplex measurements revealed increased markers of inflammation [IL-1β by trend (*C*), IL-18 significant (*D*)] in serum of human subjects. Data are the mean ± SD. Samples from $n = 18$ individuals (*A*, *B*) were compared before and after noise [aircraft noise for 6 h, mean sound pressure level 47 dB (*A*)] using the Wilcoxon matched-pairs signed rank test. Cytokine measurements yielded results for $n = 10–12$ individuals using the unpaired *t*-test [without (IL-1β) and with (IL-18) Welch's correction] (*C*, *D*). (*E*) Summarizing central scheme: around the clock and sleep phase noise triggers cerebral oxidative stress and a neuroinflammatory phenotype that translates the adverse effects of noise to the vascular and systemic level (e.g. by adverse stress hormone signalling and dysregulation of the circadian clock inducing changes in key signalling pathways). Noise via the neuronal pathways triggers vascular oxidative stress and inflammation with subsequent endothelial dysfunction, and increases in blood pressure, all of which contribute to the development and progression of cardiometabolic disease. (from Kröller-Schön S, Daiber A, Steven S, Oelze M, Frenis K, Kalinovic S, Heimann A, Schmidt FP, Pinto A, Kvandova M, Vujacic-Mirski K, Filippou K, Dudek M, Bosmann M, Klei M, Bopp T, Hahad O, Wild PS, Frauenknecht K, Methner A, Schmidt ER, Rapp S, Mollnau H, Münzel T. Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation. See pages 3528–3539).

exposed to aircraft noise at a maximum sound level of 85 dB and an average sound pressure level of 72 dB around the clock or during sleep/awake phases for 1, 2, and 4 days. Adverse effects of around the clock noise on the vasculature and brain were mostly prevented by Nox2 deficiency. Around the clock aircraft noise caused the most pronounced vascular effects and dysregulation of Foxo3/circadian clock as revealed by next-generation sequencing, suggesting impaired sleep quality in exposed mice. Accordingly, sleep but not awake phase noise caused increased blood pressure and endothelial dysfunction, and increased markers of vascular and systemic oxidative stress and inflammation (*Figure 2*). Noise also caused cerebral oxidative stress and inflammation, endothelial and neuronal nitric oxide synthase uncoupling, down-regulation of neuronal nitric oxide synthase mRNA and protein, and Nox2 activation. Next-generation sequencing revealed similarities in adverse gene regulation between around the clock and sleep phase noise. In a translational attempt, the authors also show that in patients with established coronary artery disease, night-time aircraft noise increased oxidative stress and inflammation biomarkers. Thus, aircraft noise increases vascular and cerebral oxidative stress via Nox2. Sleep deprivation and/or fragmentation caused by noise triggers vascular dysfunction. Thus, preventive measures that reduce night-time aircraft noise are warranted, an aspect that is further discussed in an **Editorial** by David G. Harrison from the Vanderbilt University Medical Center in Nashville, Tennessee in the USA.[24]

The role of environmental factors is further outlined in a review entitled '**Effects of gaseous and solid constituents of air pollution on endothelial function**', again by Thomas Münzel and colleagues from the Johannes Gutenberg Universität in Mainz, Germany.[25] The largest proportion of deaths and morbidity due to air pollution is now known to be due to cardiovascular disorders. Several particulate and gaseous air pollutants can trigger acute cardiac events. While the mechanisms are undergoing continual refinement, the preponderant evidence supports rapid effects of a diversity of pollutants including all particulate pollutants, e.g. coarse, fine, and ultrafine particles, and gaseous pollutants such as ozone, on vascular function. Alterations in endothelial function seem to be critically important in transducing signals and eventually promoting hypertension, diabetes, and atherosclerosis. There is evidence from proof-of-concept trials evaluating the impact of personal-level strategies to reduce exposure to fine particulate matter and its impact on vascular function. However, randomized evidence using hard endpoints should be the next step.

This issue is further complemented by two Discussion Forum contributions relating to the manuscript published some time ago entitled '**Circulating non-coding RNAs in biomarker-guided cardiovascular therapy: a novel tool for personalized medicine?**' by Thomas Thum from the Hannover Medical School in Germany.[26] In their discussion piece '**Circulating non-coding RNAs as functional markers to monitor and control physical exercise for the prevention of cardiovascular disease**', Boris Schmitz and colleagues from the Institute for Sports Medicine in Muenster, Germany comment on the article,[27] and Thum *et al.* respond to it in a separate contribution.[28]

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

References

1. Ridker PM, Luscher TF. Anti-inflammatory therapies for cardiovascular disease. *Eur Heart J* 2014;**35**:1782–1791.
2. Nilsson J. Atherosclerotic plaque vulnerability in the statin era. *Eur Heart J* 2017;**38**:1638–1644.
3. Xiao H, Li H, Wang JJ, Zhang JS, Shen J, An XB, Zhang CC, Wu JM, Song Y, Wang XY, Yu HY, Deng XN, Li ZJ, Xu M, Lu ZZ, Du J, Gao W, Zhang AH, Feng Y, Zhang YY. IL-18 cleavage triggers cardiac inflammation and fibrosis upon beta-adrenergic insult. *Eur Heart J* 2018;**39**:60–69.
4. Cimato TR. Persistent stem cell-driven inflammation in patients with prior MI and stroke. *Eur Heart J* 2017;**38**:433–435.
5. Ridker PM. Canakinumab for residual inflammatory risk. *Eur Heart J* 2017;**38**:3545–3548.
6. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ. Antiinflammatory therapy with Canakinumab for atherosclerotic disease. *N Engl J Med* 2017;**377**:1119–1131.
7. Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, Koenig W, Shimokawa H, Everett BM, Glynn RJ. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). *Eur Heart J* 2018;**39**:3499–3507.
8. Maier W, Altwegg LA, Corti R, Gay S, Hersberger M, Maly FE, Sutsch G, Roffi M, Neidhart M, Eberli FR, Tanner FC, Gobbi S, von Eckardstein A, Luscher TF. Inflammatory markers at the site of ruptured plaque in acute myocardial infarction: locally increased interleukin-6 and serum amyloid A but decreased C-reactive protein. *Circulation* 2005;**111**:1355–1361.
9. Swerdlow DI, Holmes MV, Kuchenbaecker KB, Engmann JE, Shah T, Sofat R, Guo Y, Chung C, Peasey A, Pfister R, Mooijaart SP, Ireland HA, Leusink M, Langenberg C, Li KW, Palmen J, Howard P, Cooper JA, Drenos F, Hardy J, Nalls MA, Li YR, Lowe G, Stewart M, Bielinski SJ, Peto J, Timpson NJ, Gallacher J, Dunlop M, Houlston R, Tomlinson I, Tzoulaki I, Luan J, Boer JM, Forouhi NG, Onland-Moret NC, van der Schouw YT, Schnabel RB, Hubacek JA, Kubinova R, Baceviciene M, Tamosiunas A, Pajak A, Topor-Madry R, Malyutina S, Baldassarre D, Sennblad B, Tremoli E, de Faire U, Ferrucci L, Bandenelli S, Tanaka T, Meschia JF, Singleton A, Navis G, Mateo Leach I, Bakker SJ, Gansevoort RT, Ford I, Epstein SE, Burnett MS, Devaney JM, Jukema JW, Westendorp RG, Jan de Borst G, van der Graaf Y, de Jong PA, Mailand-van der Zee AH, Klungel OH, de Boer A, Doevendans PA, Stephens JW, Eaton CB, Robinson JG, Manson JE, Fowkes FG, Frayling TM, Price JF, Whincup PH, Morris RW, Lawlor DA, Smith GD, Ben-Shlomo Y, Redline S, Lange LA, Kumari M, Wareham NJ, Verschuren WM, Benjamin EJ, Whittaker JC, Hamsten A, Dudbridge F, Delaney JA, Wong A, Kuh D, Hardy R, Castillo BA, Connolly JJ, van der Harst P, Brunner EJ, Marmot MG, Wassel CL, Humphries SE, Talmud PJ, Kivimaki M, Asselbergs FW, Voevoda M, Bobak M, Pikhart H, Wilson JG, Hakonarson H, Reiner AP, Keating BJ, Sattar N, Hingorani AD, Casas JP. The interleukin-6 receptor as a target for prevention of coronary heart disease: a Mendelian randomisation analysis. *Lancet* 2012;**379**:1214–1224.
10. Klingenberg R, Luscher TF. CANTOS: a seductive song with several verses. *Eur Heart J* 2018;**39**:3508–3510.
11. Spescha RD, Shi Y, Wegener S, Keller S, Weber B, Wyss MM, Lauinger N, Tabatabai G, Paneni F, Cosentino F, Hock C, Weller M, Nitsch RM, Luscher TF, Camici GG. Deletion of the ageing gene p66(Shc) reduces early stroke size following ischaemia/reperfusion brain injury. *Eur Heart J* 2013;**34**:96–103.
12. Penson PE, Long DL, Howard G, Toth PP, Muntner P, Howard VJ, Safford MM, Jones SR, Martin SS, Mazidi M, Catapano AL, Banach M. Associations between very low concentrations of low density lipoprotein cholesterol, high sensitivity C-reactive protein, and health outcomes in the Reasons for Geographical and Racial Differences in Stroke (REGARDS) study. *Eur Heart J* 2018; doi: 10.1093/eurheartj/ehy533.
13. Liberale L, Diaz-Canestro C, Bonetti NR, Paneni F, Akhmedov A, Beer JH, Montecucco F, Luscher TF, Camici GG. Post-ischaemic administration of the murine Canakinumab-surrogate antibody improves outcome in experimental stroke. *Eur Heart J* 2018;**39**:3511–3517.
14. Ridker PM. Interleukin-1 inhibition and ischaemic stroke: has the time for a major outcomes trial arrived? *Eur Heart J* 2018;**39**:3518–3520.
15. van der Valk FM, Kuijk C, Verweij SL, Stiekema LCA, Kaiser Y, Zeerleder S, Nahrendorf M, Voermans C, Stroes ESG. Increased haematopoietic activity in patients with atherosclerosis. *Eur Heart J* 2017;**38**:425–432.
16. Paneni F, Costantino S, Krankel N, Cosentino F, Luscher TF. Reprogramming ageing and longevity genes restores paracrine angiogenic properties of early outgrowth cells. *Eur Heart J* 2016;**37**:1733–1737.

17. Hoogeveen RM, Nahrendorf M, Riksen NP, Netea MG, de Winther MPJ, Lutgens E, Nordestgaard B, Neidhart M, Stroes ESG, Catapano AL, Bekkering S. Monocyte and haematopoietic progenitor reprogramming as common mechanism underlying chronic inflammatory and cardiovascular diseases. *Eur Heart J* 2018;**39**:3521–3527.
18. Cai Y, Hansell AL, Blangiardo M, Burton PR, de Hoogh K, Doiron D, Fortier I, Gulliver J, Hveem K, Mbatchou S, Morley DW, Stolk RP, Zijlema WL, Elliott P, Hodgson S. Long-term exposure to road traffic noise, ambient air pollution, and cardiovascular risk factors in the HUNT and lifelines cohorts. *Eur Heart J* 2017; **38**:2290–2296.
19. Fuks KB, Weinmayr G, Basagana X, Gruzieva O, Hampel R, Oftedal B, Sorensen M, Wolf K, Aamodt G, Aasvang GM, Aguilera I, Becker T, Beelen R, Brunekreef B, Caracciolo B, Cyrys J, Elosua R, Eriksen KT, Foraster M, Fratiglioni L, Hilding A, Houthuijs D, Korek M, Kunzli N, Marrugat J, Nieuwenhuijsen M, Ostenson CG, Penell J, Pershagen G, Raaschou-Nielsen O, Swart WJR, Peters A, Hoffmann B. Long-term exposure to ambient air pollution and traffic noise and incident hypertension in seven cohorts of the European study of cohorts for air pollution effects (ESCAPE). *Eur Heart J* 2017;**38**:983–990.
20. Munzel T, Daiber A, Steven S, Tran LP, Ullmann E, Kossmann S, Schmidt FP, Oelze M, Xia N, Li H, Pinto A, Wild P, Pies K, Schmidt ER, Rapp S, Kroller-Schon S. Effects of noise on vascular function, oxidative stress, and inflammation: mechanistic insight from studies in mice. *Eur Heart J* 2017;**38**: 2838–2849.
21. Munzel T, Sorensen M, Gori T, Schmidt FP, Rao X, Brook J, Chen LC, Brook RD, Rajagopalan S. Environmental stressors and cardio-metabolic disease: part I—epidemiologic evidence supporting a role for noise and air pollution and effects of mitigation strategies. *Eur Heart J* 2017;**38**:550–556.
22. Munzel T, Sorensen M, Gori T, Schmidt FP, Rao X, Brook FR, Chen LC, Brook RD, Rajagopalan S. Environmental stressors and cardio-metabolic disease: part II—mechanistic insights. *Eur Heart J* 2017;**38**:557–564.
23. Kroller-Schon S, Daiber A, Steven S, Oelze M, Frenis K, Kalinovic S, Heimann A, Schmidt FP, Pinto A, Kvandova M, Vujacic-Mirski K, Filippou K, Dudek M, Bosmann M, Klein M, Bopp T, Hahad O, Wild PS, Frauenknecht K, Methner A, Schmidt ER, Rapp S, Mollnau H, Munzel T. Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation. *Eur Heart J* 2018;**39**:3528–3539.
24. Patrick DM, Harrison DG. Nocturnal noise knocks NOS by Nox: mechanisms underlying cardiovascular dysfunction in response to noise pollution. *Eur Heart J* 2018;**39**:3540–3542.
25. Munzel T, Gori T, Al-Kindi S, Deanfield J, Lelieveld J, Daiber A, Rajagopalan S. Effects of gaseous and solid constituents of air pollution on endothelial function. *Eur Heart J* 2018;**39**:3543–3550.
26. de Gonzalo-Calvo D, Vea A, Bar C, Fiedler J, Couch LS, Brotons C, Llorente-Cortes V, Thum T. Circulating non-coding RNAs in biomarker-guided cardiovascular therapy: a novel tool for personalized medicine? *Eur Heart J* 2018; doi:10.1093/eurheartj/ehy234.
27. Schmitz B, Brand SM. Circulating non-coding RNAs as functional markers to monitor and control physical exercise for the prevention of cardiovascular disease. *Eur Heart J* 2018;**39**:3551.
28. de Gonzalo-Calvo D, Thum T. Circulating non-coding RNAs as biomarkers to predict and monitor the response to exercise: chances and hurdles. *Eur Heart J* 2018;**39**:3552.