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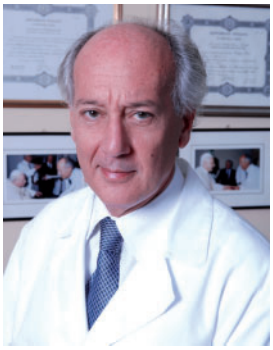
ISSUE @ A GLANCE

Stop smoking and sleep well to reduce cardiovascular risk



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This Focus Issue on epidemiology and prevention contains the ESC Fast Track manuscript '**Efficacy of a digital therapeutics system in the management of essential hypertension: the HERB-DH1 pivotal trial**' by Kazuomi Kario from the Jichi Medical University School of Medicine in Japan, and colleagues.[1] We are witnessing an exponential interest in digital health.[2,3] Digital therapeutics refers to an emerging branch of medicine, which utilizes technology-based software algorithms or applications to facilitate disease management. Although there are a plethora of apps claiming to help manage hypertension, few have been developed in collaboration with healthcare professionals or device companies, and none has undergone rigorous scientific assessment of clinical efficacy in patients with hypertension. Furthermore, the data that are available are not consistent with respect to the effects of digital therapeutics on blood pressure (BP) levels. Based on promising findings from a small pilot trial, the HERB Digital Hypertension 1 (HERB-DH1) pivotal trial, the authors investigated the efficacy of digital therapeutics in patients with hypertension not receiving antihypertensive medication. This prospective, open-label, randomized controlled study was performed at 12 sites in Japan. Patients with hypertension [office systolic BP (SBP) 140–<180 mmHg and 24 h SBP ≥130 mmHg] were randomly assigned 1:1 to the digital therapeutics group (HERB system + standard lifestyle modification) or control group (standard lifestyle modification alone). The primary efficacy endpoint was the mean change in 24 h ambulatory SBP from baseline to 12 weeks; key secondary efficacy endpoints were mean changes in office and home BP from baseline to 12 weeks. Between December 2019 and June 2020, a total of 390 patients were randomly assigned to the digital therapeutics group (n = 199) or control (n = 191) group. Between-group differences in 24 h ambulatory, home, and office SBPs at 12 weeks were -2.4, -4.3, and -3.6 mmHg, respectively, and all significant. No major programme-related safety events occurred up to 24 weeks.

The authors conclude that the HERB-DH1 pivotal study shows the superiority of digital therapeutics compared with standard lifestyle modification alone to reduce 24 h ambulatory, home, and office BP in the absence of antihypertensive medications. The article is accompanied by an **Editorial** by Luis Ruilope from the Hospital 12 de Octubre in Madrid, Spain, and colleagues.[4] The authors note that more effort is needed to efficiently implement healthy lifestyle changes for the prevention and management of arterial hypertension. Initiatives such as digital therapeutics might pave the way for a new era in which the technology of the new millennium can be used—paradoxically—to help us return to a more 'traditional' (non-westernized) way of living.

Direct oral anticoagulants (DOACs) have revolutionized the treatment of non-valvular atrial fibrillation (NVAF).[5–7] Persistence with DOACs has become a concern in NVAF patients, but whether this affects prognosis is rarely studied. In a clinical research article entitled '**Predictors, time course, and outcomes of persistence patterns in oral anticoagulation for non-valvular atrial fibrillation: a Dutch Nationwide Cohort Study**', Myrthe Toorop from the Leiden University Medical Center in the Netherlands, and colleagues investigated the persistence with oral anticoagulants (OACs) and its association with prognosis among a nationwide cohort of NVAF patients.[5] DOAC-naive NVAF patients who started to use DOACs for ischaemic stroke prevention between 2013 and 2018 were included using Dutch national statistics. Persistence with OACs was determined based on the presence of a 100 day gap between the last prescription and the end of study period. The cumulative incidence of persistence with OACs was 88, 83, 78, and 72% at 1, 2, 3, and 4 years after receiving DOACs, respectively. Baseline characteristics associated with better persistence with OACs included female sex, age range 65–74 years, permanent AF, previous exposure to vitamin K antagonists, stroke history (including transient ischaemic attack), and a CHA_2DS_2-VASc score ≥2. Non-persistence with OACs was associated with a significantly increased risk of the composite outcome of ischaemic stroke and ischaemic stroke-related death

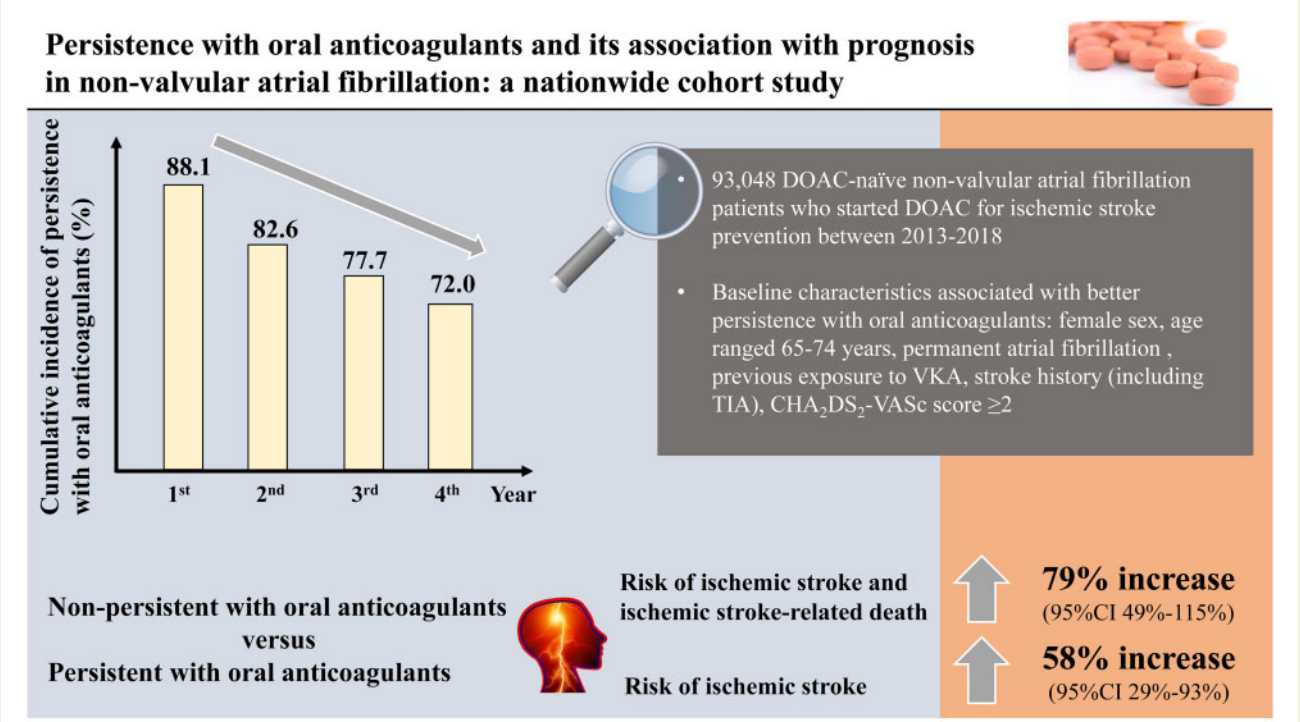

Figure 1 Graphical Abstract (from Toorop MMA, Chen Q, Tichelaar V, Cannegieter SC, Lijfering WM. Predictors, time course, and outcomes of persistence patterns in oral anticoagulation for non-valvular atrial fibrillation: a Dutch Nationwide Cohort Study. See pages 4126–4137).

[adjusted hazard ratio (aHR) 1.79] and ischaemic stroke [aHR 1.58, 95% confidence interval (CI) 1.29–1.93] compared with being persistent with OACs (*Figure 1*).

The authors conclude that at least a quarter of NVAF patients are non-persistent with OACs within 4 years, which is associated with poor efficacy of ischaemic stroke prevention. The identified baseline characteristics may help to identify patients at risk of non-persistence. The article is accompanied by an **Editorial** by Peter Vibe Rasmussen from the Herlev-Gentofte University Hospital in Denmark and Elaine Hylek from Boston University in the USA.[8] The authors highlight that while it is unclear what specific initiatives and interventions could be beneficial in improving treatment persistence, it is obvious that the current rates of persistence with treatment are suboptimal, as stressed by the study by Toorop *et al*. Successful treatment of AF requires not only scrutiny of risk factors and identification of patients requiring stroke prophylaxis, but also subsequent recognition of patients at risk of being non-persistent with a potentially life-saving treatment. It is concerning that an inappropriately low persistence with treatment is still an obstacle in the quest to gain full benefit of prophylactic treatment with OACs in AF. Interventional studies aiming at improving treatment persistence should be a distinct priority in future AF research.

Smoking is an established potent risk factor.[9,10] However, it is still uncertain whether smoking reduction rather than cessation is sufficient to reduce cardiovascular risk. In a clinical research article entitled '**Smoking cessation, but not reduction, reduces cardiovascular disease incidence**' Su-Min Jeong from the Samsung Medical Center in the Republic of Korea, and colleagues assessed the association of smoking cessation and reduction with risk of cardiovascular disease (CVD).[11] A total of ~900 000 current smokers aged ≥40 years who had undergone two consecutive national health examinations (in 2009 and 2011) were included. Participants were classified as quitters (20.6%), reducers I (≥50% reduction, 7.3%), reducers II (20–50% reduction, 11.6%), sustainers (45.7%), and increasers (≥20% increase, 14.5%). During 5 575 556 person-years of follow-up, 17 748 stroke and 11 271 myocardial infarction (MI) events were identified. Quitters had significantly decreased risk of stroke (aHR 0.77) and MI (aHR 0.74) compared with sustainers after adjustment for demographic factors, comorbidities, and smoking status. The risk of stroke and MI incidence in reducers I and reducers II was not significantly different from the risk in sustainers.

The authors conclude that smoking cessation, but not reduction, was associated with reduced CVD risk. Their study emphasizes the importance of sustained quitting in terms of CVD risk reduction. The manuscript is accompanied by an **Editorial** by Charlotte Andersson and Amalie Lykkemark Møller from the Boston University School of Medicine in Boston, MA, USA.[12] The authors conclude that the low prevalence of women (5%) must be acknowledged as a limitation of the present study. Although this is likely to reflect the epidemiology of smoking in East Asia, under-reporting of smoking in women may be a concern. In addition, non-cigarette tobacco products have become very common in some populations. In South East Asia, smokeless tobacco has been reported to be one of the most common types of tobacco among the youth, and e-cigarettes have also gained a lot of popularity among the youth

especially in high-income countries. Whether switching to such products alters CVD risks is not well understood yet and remains another research priority.

Chronic venous insufficiency (CVI) refers to a spectrum of entities, which are related to both structural and functional pathologies of the venous system. The pathophysiology of CVI displays a complex interplay of venous valve dysfunction and venous hypertension, with subsequent macro- and microcirculatory haemodynamic and vascular alterations. Telangiectasia, reticular venectasia, varicose veins, and CVI ranging from oedema to active skin ulcers represent the most common clinically visible manifestations of chronic venous disease. Evidence regarding the health burden of CVI, its clinical determinants, and impact on outcome is scarce. In a Clinical Research article entitled '**Chronic venous insufficiency, cardiovascular disease, and mortality: a population study**' Jürgen H. Prochaska from the University Medical Center of the Johannes Gutenberg University Mainz in Germany, and colleagues looked into this issue further.[13] Systematic phenotyping of CVI according to the established CEAP (Clinical–Etiologic–Anatomic–Pathophysiologic) classification was performed in >12 000 participants (age range: 40–80 years) of the Gutenberg Health Study from April 2012 to April 2017. Replication of findings was done in an independent cohort study (MyoVasc, NCT04064450). The prevalence of telangiectasia/reticular veins, varicose veins, and CVI was 36, 13, and 41%, respectively. Age, female sex, arterial hypertension, obesity, smoking, and clinically overt CVD were identified as clinical determinants of CVI. During a mean follow-up of 6.4 years, CVI was a strong predictor of all-cause death independent of the concomitant clinical profile and medication (HR 1.46, $P = 0.0003$). The association of CVI with an increased risk of all-cause death was externally validated in the MyoVasc cohort (HR 1.51, $P = 0.009$).

The authors conclude that CVI is highly prevalent in the population and is associated with the presence of cardiovascular risk factors and disease. Individuals with CVI experience an elevated risk of death, which is independent of age and sex, and present cardiovascular risk factors and comorbidities. This manuscript is accompanied by an **Editorial** by Naomi Hamburg from the Boston University School of Medicine in the USA.[14] Hamburg concludes that the study by Prochaska *et al.* provides another reason to examine our patients' legs for signs of chronic venous disease as a window to the heart. Hamburg points out that she will still explain to patients with chronic venous disease that varicose veins are not the same as blocked arteries. But, she will also be sure to comprehensively evaluate for the presence of cardiovascular risk factors, encourage exercise and risk factor modification, and await future research to identify the impact of venous targeted therapies on cardiovascular disease.

Heart failure (HF) is an ongoing epidemic and a serious clinical and public health issue.[15–17] Currently, little is known about prospective associations between insomnia symptoms and HF incidence. In a clinical research article entitled '**Insomnia symptoms and incident heart failure: a population-based cohort study**', Asos Mahmood from the The University of Memphis School of Public Health in Memphis, TN, USA, and colleagues investigated the longitudinal associations between time-varying insomnia symptoms (difficulty initiating sleep, difficulty maintaining sleep, early-morning awakening, non-restorative sleep) and incident HF.[18] Data were obtained from the Health and Retirement Study in the USA for a population-representative sample of 12 761 middle-aged and older adults who were free from HF at baseline in 2002. Respondents were followed for 16 years for incident HF. We employed marginal structural discrete-time survival analyses to adjust for potential time-varying biological, psycho-cognitive, and behavioural factors and to account for bias due to differential loss to follow-up. At baseline, 38% of the respondents reported experiencing at least one insomnia symptom. During the 16-year follow-up, 1730 respondents developed incident HF. Respondents experiencing one (HR = 1.22), two (HR = 1.45), three (HR = 1.66), or four (HR = 1.80) insomnia symptoms had a significantly higher hazard of incident HF than asymptomatic respondents as well as respondents that had trouble initiating sleep (HR = 1.17), maintaining sleep (HR = 1.14), early-morning awakening (HR = 1.20), or non-restorative sleep (HR = 1.25).

The authors conclude that insomnia symptoms, both cumulatively and individually, are associated with incident HF. Public health awareness and screening for insomnia symptoms in at-risk populations should be encouraged to reduce HF incidence. The contribution is accompanied by an **Editorial** by Mathieu Berger from the Lausanne University Hospital (CHUV) and University of Lausanne in Switzerland, and colleagues.[19] The authors conclude that overall, the study of Mahmood *et al.* provides robust evidence that insomnia complaints are not minor symptoms in a middle- to older-age population but may also have severe long-term cardiovascular consequences. Insomnia symptoms are easily recognizable and modifiable, but many individuals with insomnia remain untreated despite the effectiveness of available treatment options. Although the ability of insomnia treatments to prevent HF remains unproven, they advise general practitioners and cardiologists to consider sleep complaints when conducting clinical cardiovascular risk assessment. Where significant issues are identified, patients should be referred to sleep specialists for investigation of the sleep complaints, to rule out another sleep disorder and, if necessary, manage insomnia disorder with appropriate treatments such as cognitive behavioural therapy (CBT-I). At the very least, this should improve health-related quality of life. Sleep is essential to health. It is time to put sleep back at the heart of our concerns.

With the intensification of social production pressure and the refinement of the division of labour, shift work is gradually becoming common among employees in modern society. According to the 6th European Working Conditions Survey, nearly 21% of the working population engaged in shift work, which is identified as an irregular working schedule outside the conventional daytime. Growing evidence indicates that shift work, particularly night shift work, has an adverse impact on individual health and organ function. In a Clinical Research article entitled **'Long-term night shift work is associated with the risk of atrial fibrillation and coronary heart disease'**, Ningjian Wang from the Shanghai JiaoTong University School of Medicine in China, and colleagues sought to test whether current and past night shift work was associated with incident AF and whether this association was modified by genetic vulnerability.[20] Its associations with coronary heart disease (CHD), stroke, and HF were measured as a secondary aim. This cohort study included >283 000 participants in paid employment or self-employed without AF and >276 000 participants free of CHD, stroke, and HF at baseline in

the UK Biobank. The weighted genetic risk score for AF was calculated. During a median follow-up of 10.4 years, 5777 incident AF cases were documented. From 'day workers', 'shift but never/rarely night shifts', and 'some night shifts' to 'usual/permanent night shifts', there was a significant increasing trend in the risk of incident AF (*P* for trend 0.013). Usual or permanent night shifts were associated with the highest risk (HR 1.16). These associations were not modified by genetic predisposition to AF. Usual/permanent current night shifts, ≥10 years and 3–8 nights/month of lifetime night shifts were significantly associated with a higher risk of incident CHD (HR 1.22, HR 1.37, and HR 1.35, respectively).

The authors conclude that night shift exposures are associated with increased AF risk, regardless of genetic AF risk. Night shift exposure also increases the risk of CHD but not of stroke or HF. Whether decreasing night shift work frequency and duration might represent another avenue to improve heart health during working life and beyond warrants further study. The manuscript is accompanied by an **Editorial** by Dominik Linz from the Maastricht University Medical Centre and Cardiovascular Research Institute Maastricht in the Netherlands, and colleagues.[21] The authors conclude that lifestyle and behavioural interventions have become increasingly recognized as important tools for risk factor modification for primary and secondary CVD prevention. Whether environmental and lifestyle modifications of circadian rhythm and clock-based therapeutic strategies, including chronotherapy, and pharmacological agents that target core clock components and proximal regulators, are likely to alter CVD outcomes remains unclear. It appears that limiting night shifts to a minimum and allowing recreational recovery periods after each night shift block, and coordinating the work schedule with family or social time is the best advice a clinician can provide in this regard. To implement this strategy, discussions with all stakeholders are needed, and governmental countermeasures need to be implemented.

The issue is also complemented by two Discussion Forum contributions. In a commentary entitled '**Air pollution and cardiovascular diseases in young adults**', Yanguo Xin from the Beijing Friendship Hospital and Junli Li from Sichuan University in China comment on the recent publication '**Association of the combined effects of air pollution and changes in physical activity with cardiovascular disease in young adults**' by Seong Rae Kim from the Seoul National University College of Medicine in South Korea.[22,23] Kim *et al.* respond in a separate comment.[24]

The editors hope that readers of this issue of the *European Heart Journal* will find it of interest.

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