Editorial

Understanding modifiable risk factors for new onset atrial fibrillation: the knowledge gap is closing

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There is a steady increase in the global prevalence of atrial fibrillation (AF) in all regions of the world (1,2) and in the European Union an increase from 8.8 million adults over 55 years in 2010, to 17.9 million in 2060, is estimated (3). Part of this increase can be explained by the changing demographics with increasing longevity and thus an ageing population (4), but also due to an increasing prevalence of risk factors for AF (*Table 1*), in particular obesity (5), but also obstructive sleep apnea (OSA) (6), type 2 diabetes mellitus (T2DM) (7), hypertension (8), and a sedate lifestyle (9), which all plays an important attributable role in the pathophysiology of AF.

AF is associated with a reduced quality of life, and is a strong risk factor for severe and devastating complications like heart failure (HF) and non-fatal stroke as well as for mortality, primary due to fatal stroke or HF. Thus, AF imposes a significant burden on the individual affected as well as a financial burden on the society (10). Estimation of direct cost of treatment of AF is estimated to range from $2,000 to $14,200 per patient-year in the USA and from €450 to €3,000 in Europe (10). Implementation of effective measures to combat this ever-increasing trend must therefore be implemented without further delay.

Lee and colleagues reported in *Eur Heart J* in 2017 (11) an important insight on the implications of early stages of the AF-risk factors T2DM, i.e., impaired fasting glucose (IFG), and hypertension, i.e., prehypertension, by assessing the relationship between IFG and prehypertension with new-onset AF and AF-related outcomes (HF, stroke, mortality).

IFG and prehypertension are conditions that affect millions of individuals across the globe, and in prevalence these early disease trajectory conditions exceed the conventional conditions T2DM and hypertension approximately two-fold. Lee and co-workers assessed long-term outcomes in 227,102 healthy individuals (51.1% females) ≥20 years of age, i.e., free from non-valvular AF, HF, hypertension, T2DM, stroke or vascular disease, from the Korean National Health Insurance Service (NHIS) Sample Cohort database. The population studied was recruited 2003–2008 and followed for outcomes until 2013 with a mean observation period of 7.7 years. The study-cohort underwent a biannual health check (including blood tests, chest X-ray, physical examinations, recording of medical history) with ~70% adherence rate. Causes of deaths were identified by linking the NHIS cohort database with the Korea National Statistical Office (KNSO).

Prehypertension was defined as systolic blood pressure (SBP) or diastolic BP (DBP) between 120–139 mmHg or 80–89 mmHg, respectively, and amongst the 227,102 individuals, 20.3% fulfilled both criterions whereas 48.6% fulfilled the SBP-only criterion and 35.2% the DBP-only criterion. IFG was defined according to contemporary cut-offs according to international accepted standards, and 5.2% of the cohort had a fasting glucose in the range 110–125 mg/dL [2006 World Health Organization (WHO) standard], whereas 17.8% in the range 100–125 mg/dL [2003 American Diabetes Association (ADA) standards],

Table 1 Modifiable and non-modifiable risk factors for atrial fibrillation

Modifiable risk factors
Obesity
Physical inactivity
Vigorous long-term endurance training
Hypertension
Prehypertension
Thyroid dysfunction
Type 2 diabetes mellitus
Prediabetes
Alcohol consumption
Smoking
Poor cardiorespiratory fitness
Intermediate modifiable risk factors
Heart failure
Valvular disease
Chronic obstructive pulmonary disease
Sleep apnea syndrome
Enlarged left atrial volume/size
Left ventricular hypertrophy
Type 1 diabetes mellitus
Inflammation and endothelial dysfunction
Non-modifiable risk factors
Age
Gender
Genetic background

7.2% of the population fulfilled both criterions for prehypertension and IFG (per ADA standard).

In total, 1,479 subjects (0.7%) developed new-onset AF during the period of observation. New-onset AF was associated with known risk factors [advancing age, male gender and obesity (BMI ≥25 kg/m^2)], with the strongest contributors being age [e.g., hazard ratio (HR), 22.26 (95% CI: 18.14–27.32) for age 65–74 years] and obesity [HR, 1.42 (95% CI: 1.24–1.62) for BMI ≥25 kg/m^2].

When adjusted for clinical variables, prehypertension, defined by fulfilling both the SBP/DBP criteria or the SBP-only criterion, was not associated with increased risk for new-onset AF, whereas prehypertension according to the DBP-only criterion was, with a 11% higher relative risk (HR, 1.11; P=0.045). Both categorizations of IFG (ADA and WHO) were also associated with a significant increased risk for new-onset AF, and in a dosage related manner, with the numerically highest risk found with the most conservative definition of IFG (WHO: HR, 1.21; P=0.040 *vs.* ADA: HR, 1.16; P=0.017). Amongst the 7.2% of the population with both IFG and prehypertension, also a higher risk of new-onset AF was observed [HR, 1.27 (95% CI: 1.05–1.54)] as compared to the majority population without these risk factors. Since obesity was identified as a strong risk factor in this cohort, the risk for new-onset AF was further accentuated when adding obesity at baseline (BMI ≥25 kg/m^2) to IFG and prehypertension, however not dramatically [HR, 1.50 (95% CI: 1.19–1.89)]. An interesting observation therefore was the influence of IFG and prehypertension on new-onset AF in the absence of obesity. Herein, depending on whether one of the conditions or both were considered, HR for AF ranged 1.09 to 1.47 in those with BMI <20 kg/m^2 and 1.13 to 1.26 in those with BMI <25 kg/m^2. Expectedly, risk for stroke, death or HF increased with increasing risk-factor burden, without indications of an obesity paradox.

Interrelationship between hyperglycaemia and hypertension in promoting AF

Intermediate hyperglycaemia, like IFG, and prehypertension have some common pathophysiological features with relevance for AF incidence, like insulin resistance and inflammation, and the timing of their "peak activity" could be of importance for the risk for new-onset AF. On the other hand, IFG and prehypertension also have unique effects on the development of an abnormal atrial substrate. Hyperglycaemia for example is associated with advanced glycation end-product (AGE) formation, which could lead to atrial fibrosis (12) in turn associated with AF risk. Hypertension, on the other hand, has an influence on afterload and cardiac vascular hemodynamics, which in turn has implications for, e.g., left atrial enlargement, atrial fibrosis (13,14) and electrophysiological disturbances (15).

The study by Lee *et al.* (11) underscores the importance of assessing multiple risk factors in preventive medicine, and also reminds us that the interplay of risk factors can be different in different subpopulations. This study therefore adds to the literature that an increased risk for new-onset AF is present also in slimmer individuals being early in

their disease trajectories for T2DM and hypertension, can this therefore be used to argue for continued efforts for a healthy lifestyle and diet, potentially supplemented with pharmaceutical interventions, if needed?

Lifestyle interventions targeting hyperglycaemia or hypertension to prevent now-onset AF

Lifestyle modification to prevent T2DM or prediabetes (e.g., IFG) have been studied extensively and we know now that counselling aimed at reducing weight, total intake of fat, and intake of saturated fat and increasing intake of fibre and physical activity (16) can modify this risk, and similarly, we know that lifestyle interventions for hypertension is effective. The main question is however, would intervention target the risk factors identified by Lee and colleagues, and others (*Table 1*), lead to reduced risk for new-onset AF? Unfortunately, lifestyle-intervention in normal-weight individuals targeting prediabetes or prehypertension is lacking. However, since obesity, that significantly increase the risk for AF (5), is interlinked with prediabetes, T2DM, prehypertension and hypertension, effects of interventions targeting weight-loss is of relevance in this setting. Indeed, it is reported that large weight loss induced by bariatric surgery is associated with reduced risk for new onset AF (17), however, the evidence to support that weight loss induced by lifestyle intervention in obese individuals leads to a reduction in incident AF is less convincing (18), although in patients with established AF, long-term sustained weight loss by lifestyle intervention has been shown to be associated with significant reduction in AF-burden and maintenance of sinus rhythm (19). Of importance in this setting is also the emerging role of continuous positive airway pressure utilization for OSA to reduce AF risk, in particular following catheter ablation (20).

Some data suggest that reducing hyperglycaemia by certain pharmacological interventions, might reduce AF risk (21), but the body of evidence is weak, and no glucose lowering drug has such an indication. Similarly, drugs effective to treat (pre)hypertension, or other cardioprotective drugs, has not much evidence (22) for such prevention either. A holistic approach therefore seems warranted, and a recent study (23) looked at the effect on sinus rhythm maintenance at 12 months, in 250 patients with early symptomatic persistent AF and early mild to moderate HF by "upstream modulation" induced by cardiac rehabilitation, statins, mineralocorticoid receptor antagonists, and angiotensin-converting enzyme inhibitors. This trial ("RACE 3"), which was a multicentre, randomized, open-label study, observed at 1-year follow-up using continuous 7-day Holter that sinus rhythm was maintained in 75% of the upstream therapy group *vs.* 63% in the control group (P=0.021).

Screening for subclinical AF

Massive efforts are undertaken worldwide today to investigate different methods to detect subclinical AF with the aim of preventing stroke (24). Screening of the general population is very resource-demanding, and focusing on populations with increased risk of AF (and increased risk of stroke) will probably make screening more cost-effective. Thus, the increased risk of AF associated with IFG or prehypertension may be of relevance in the selection of candidates for screening. Interestingly, in a recent study on screening for subclinical AF in 65-year-olds, 7 out of 14 subjects with screen-detected, subclinical AF cases actually had diabetes (25). Those findings, alongside others (7,8) and the report from Lee and coworkers may indicate that subjects with diabetes or prediabetes are important candidates for AF screening.

Conclusions

Further research should be undertaken to assess which strategy is best to reduce new-onset AF in patients early in their comorbid-disease trajectories. It is the responsibility of all health-care providers and policy makers to step-up their efforts in preventive medicine to efficaciously combat the global challenge of AF.

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