



# 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)  $\geq 20$  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 criteria 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,

**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

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], 7.2% of the population fulfilled both criteria 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  $\geq 25$  kg/m<sup>2</sup>)], 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  $\geq 25$  kg/m<sup>2</sup>].

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  $\geq 25$  kg/m<sup>2</sup>) 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<sup>2</sup> and 1.13 to 1.26 in those with BMI  $< 25$  kg/m<sup>2</sup>. 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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### **Footnote**

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## References

- Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;129:837-47.
- Bai Y, Wang YL, Shantsila A, et al. The global burden of atrial fibrillation and stroke. A systematic review of the clinical epidemiology of atrial fibrillation in Asia. *Chest* 2017;152:810-20.
- Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013;34:2746-51.
- Boriani G, Diemberger I, Martignani C, et al. The epidemiological burden of atrial fibrillation: a challenge for clinicians and health care systems. *Eur Heart J* 2006;27:893-4.
- Mahajan R, Lau DH, Brooks AG, et al. Electrophysiological, electroanatomical, and structural remodeling of the atria as consequences of sustained obesity. *J Am Coll Cardiol* 2015;66:1-11.
- Tung P, Levitzky YS, Wang R, et al. Obstructive and central sleep apnea and the risk of incident atrial fibrillation in a community cohort of men and women. *J Am Heart Assoc* 2017;6. pii: e004500.
- Johansen OE, Brustad E, Enger S, et al. Prevalence of abnormal glucose metabolism in atrial fibrillation - a case control study in 75-year old subjects. *Cardiovasc Diabetol* 2008;7:28.
- Grundvold I, Skretteberg PT, Liestøl K, et al. Upper normal blood pressures predict incident atrial fibrillation in healthy middle-aged men: a 35-year follow-up study. *Hypertension* 2012;59:198-204.
- Lavie CJ, O'Keefe JH, Sallis RE. Exercise and the heart--the harm of too little and too much. *Curr Sports Med Rep* 2015;14:104-9.
- Wolowacz SE, Samuel M, Brennan VK, et al. The cost of illness of atrial fibrillation: a systematic review of the recent literature. *Europace* 2011;13:1375-85.
- Lee SS, Ae Kong K, Kim D et al. Clinical implication of an impaired fasting glucose and prehypertension related to new onset atrial fibrillation in a healthy Asian population without underlying disease: a nationwide cohort study in Korea. *Eur Heart J* 2017;38:2599-607.
- Kato T, Yamashita T, Sekiguchi A, et al. AGEs-RAGE system mediates atrial structural remodeling in the diabetic rat. *J Cardiovasc Electrophysiol* 2008;19:415-20.
- Kim SJ, Choisy SC, Barman P, et al. Atrial remodeling and the substrate for atrial fibrillation in rat hearts with elevated afterload. *Circ Arrhythm Electrophysiol* 2011;4:761-9.
- Lau DH, Shipp NJ, Kelly DJ, et al. Atrial arrhythmia in ageing spontaneously hypertensive rats: unraveling the substrate in hypertension and ageing. *PLoS One* 2013;8:e72416.
- Lau DH, Mackenzie L, Kelly DJ, et al. Hypertension and atrial fibrillation: evidence of progressive atrial remodeling with electrostructural correlate in a conscious chronically instrumented ovine model. *Heart Rhythm* 2010;7:1282-90.
- Tuomilehto J, Lindström J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344:1343-50.
- Jamaly S, Carlsson L, Peltonen M, et al. Bariatric surgery and the risk of new-onset atrial fibrillation in Swedish obese subjects. *J Am Coll Cardiol* 2016;68:2497-504.
- Alonso A, Bahnson JL, Gaussoin SA, et al. Effect of an intensive lifestyle intervention on atrial fibrillation risk in individuals with type 2 diabetes: the Look AHEAD randomized trial. *Am Heart J* 2015;170:770-7.e5
- Pathak RK, Middeldorp ME, Meredith M, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). *J Am Coll Cardiol* 2015;65:2159-69.
- Fein AS, Shvilkin A, Shah D, et al. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. *J Am Coll Cardiol* 2013;62:300-5.
- Liu T, Li G. Thiazolidinediones as novel upstream therapy for atrial fibrillation in diabetic patients: a review of current evidence. *Int J Cardiol* 2012;156:215-6.
- Thacker EL, Jensen PN, Psaty BM, et al. Use of statins and antihypertensive medications in relation to risk of long-standing persistent atrial fibrillation. *Ann Pharmacother* 2015;49:378-86.
- Rienstra M, Hobbelt AH, Alings M, et al. The routine versus aggressive upstream rhythm control for prevention of early persistent atrial fibrillation in heart failure study. ESC 2017 presentation. Available online: [http://www.clinicaltrialresults.org/Slides/ESC2017/RACE%203\\_Van%20Gelder.pdf](http://www.clinicaltrialresults.org/Slides/ESC2017/RACE%203_Van%20Gelder.pdf)

24. Freedman B, Camm J, Calkins H, et al. Screening for Atrial Fibrillation: A Report of the AF-SCREEN International Collaboration. *Circulation* 2017;135:1851-67.
25. Berge T, Brynildsen J, Larssen HKN, et al. Systematic

screening for atrial fibrillation in a 65-year-old population with risk factors for stroke: data from the Akershus Cardiac Examination 1950 study. *Europace* 2017. [Epub ahead of print].

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