Circulation Research

COMPENDIUM ON ATRIAL FIBRILLATION

Epidemiology of Atrial Fibrillation in the 21st Century

Novel Methods and New Insights

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ABSTRACT: Accompanying the aging of populations worldwide, and increased survival with chronic diseases, the incidence and prevalence of atrial fibrillation (AF) are rising, justifying the term global epidemic. This multifactorial arrhythmia is intertwined with common concomitant cardiovascular diseases, which share classical cardiovascular risk factors. Targeted prevention programs are largely missing. Prevention needs to start at an early age with primordial interventions at the population level. The public health dimension of AF motivates research in modifiable AF risk factors and improved precision in AF prediction and management. In this review, we summarize current knowledge in an attempt to untangle these multifaceted associations from an epidemiological perspective. We discuss disease trends, preventive opportunities offered by underlying risk factors and concomitant disorders, current developments in diagnosis and risk prediction, and prognostic implications of AF and its complications. Finally, we review current technological (eg, eHealth) and methodological (artificial intelligence) advances and their relevance for future prevention and disease management.

Key Words: artificial intelligence ■ atrial fibrillation ■ incidence ■ prevalence ■ risk factors

With increased average global life expectancy and longer survival with chronic conditions, incidence and prevalence of atrial fibrillation (AF) has reached the dimension of a 21st-century cardiovascular disease (CVD) epidemic.[1–4] Despite multifaceted research efforts, the prevention of AF and its related complications remains challenging.[5]

EPIDEMIOLOGY

The incidence and prevalence of AF are increasing globally. Based on data from the FHS (Framingham Heart Study), the prevalence of AF increased 3-fold over the last 50 years.[1] The Global Burden of Disease project estimated a worldwide prevalence of AF around 46.3 million individuals in 2016.[6] The lifetime risk of AF was estimated about 1 in 4 in white men and women older than 40 years in 2004[7]; a decade later, lifetime risk estimates reached about 1 in 3 in white individuals and 1 in 5 for black individuals (Figure 1).[8]

In the United States alone, at least 3 to 6 million people have AF, and the numbers are projected to reach ≈6 to 16 million by 2050.[9,10] In Europe, prevalent AF in 2010 was ≈9 million among individuals older than 55 years and is expected to reach 14 million by 2060.[11,12] It was estimated that by 2050 AF will be diagnosed at least in 72 million individuals in Asia, ≈3 million with AF-related strokes.[13]

Awareness and enhanced detection of AF have improved over the past decade, which is important since about one-third of the total AF population is asymptomatic.[14] Therefore, the global AF burden is certainly underestimated (Figure 1). Facilitated and broadly applied rhythm monitoring by portable devices, including smartphones and wearables, initiated by consumers will further increase the prevalence of known AF.[15] Precision medicine approaches are needed to identify individuals

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AI	artificial intelligence
ARIC	Atherosclerosis Risk in Communities
CHS	Cardiovascular Health Study
CKD	chronic kidney disease
CVD	cardiovascular disease
DM	diabetes mellitus
FHS	Framingham Heart Study
HF	heart failure
LA	left atrial
LV	left ventricular
MESA	Multi-Ethnic Study of Atherosclerosis
eHealth	electronic health
MI	myocardial infarction
ML	machine learning
PA	physical activity
RAS	renin-angiotensin system
TGF	transforming growth factor
VTE	venous thromboembolism

at higher risk for AF and its sequelae, as well as to implement the most resource-efficient strategies to determine which subgroups of patients to screen and to target for preventive and therapeutic management.

In this review, we summarize the role of common AF risk factors, biomarkers, and omics for prediction of incident AF and their value for risk stratification of AF onset and perpetuation. Furthermore, we review comorbidities with important prognostic aspects and highlight future directions towards precision AF risk assessment and prevention using increasingly available artificial intelligence (AI) methods.

PRIMORDIAL AND PRIMARY PREVENTION OF AF

Nonmodifiable Factors

Advancing Age

Age is the most important risk factor for AF. It is associated with increased AF burden, with a sharp incline after age 65 years. It is expected that the population of >65-year-old adults will double from 12% in 2010 to 22% in 2040.[16]

In AF, many risk factors act over decades. For example, chronic subclinical inflammation, defined as continuous low-grade activation of the systemic immune response, is a hallmark of biological aging across multiple organ systems. Both AF and age are associated with elevated concentrations of reactive oxygen species. Furthermore, inflammation is related to endothelial dysfunction, collagen catabolism, consequent increase of TGF (transforming growth factor)-ß1 activity, and changes in the extracellular matrix.[17] Myocardial and vascular aging comprise changes at structural, functional, cellular, and molecular levels. Therefore, healthy aging could be considered as a goal in primordial and primary AF prevention. Controlling known AF risk factors would slow these degenerative processes and promote fit longevity.

Racial/Ethnic Differences in Epidemiology of AF

The overall prevalence of AF in United States is 1% to 2%.[10] AF prevalence and incidence in Asians and blacks are lower than in individuals with European ancestry, despite a higher burden of comorbidities in blacks. Possible explanations comprise genetic, socioeconomic, and environmental determinants of health, which have not been completely evaluated.[18,19] In the MESA (Multi-Ethnic Study of Atherosclerosis), the AF incidence was 46% to 65% lower in Hispanics, Asians, and blacks >65 years compared with non-Hispanic whites.[19] In a study of over 600 000 Veteran Affairs patients, the age-adjusted prevalence of AF in whites was almost 2-fold higher than in other ethnicities.[18]

Although a lower AF incidence has been explained by underdetection caused by worse access to healthcare[20] and more frequent paroxysmal AF,[21] there is evidence that blacks have up to 2 mm smaller left atria (LA) on average compared with whites.[22] Genetic studies have shown a single-nucleotide polymorphism mediating part of the increased risk of AF in European ancestry Americans compared with blacks.[23] Also, using ancestry informative markers, the CHS (Cardiovascular Health Study) and ARIC (Atherosclerosis Risk in Communities) study reported that European ancestry was associated with higher risk of AF.[24]

The same paradox has been found within the ethnic groups originating from India, Pakistan, Nepal, Sri Lanka, and Bangladesh, which represent about 20% of the world's population.[2,25] Similar to blacks, lower AF incidence could be explained by smaller LA size indexed to body dimensions[26] and ethnic variations in cardiac ion channels.[27–29] However, systematic data on electrophysiological parameters in different ethnic groups remain an unmet need.

Modern Lifestyle and Modifiable Risk Factors for AF

Age, body mass index, height, hypertension, diabetes mellitus (DM), obstructive sleep apnea, myocardial infarction (MI), heart failure (HF), smoking, and genetic predisposition are well-established risk factors for AF development and perpetuation.[30] There is evidence that psychosocial and lifestyle factors are important modulators of AF occurrence, in particular at younger age.[31] In this section, besides traditional risk factors such as hypertension and DM, we highlight the importance of

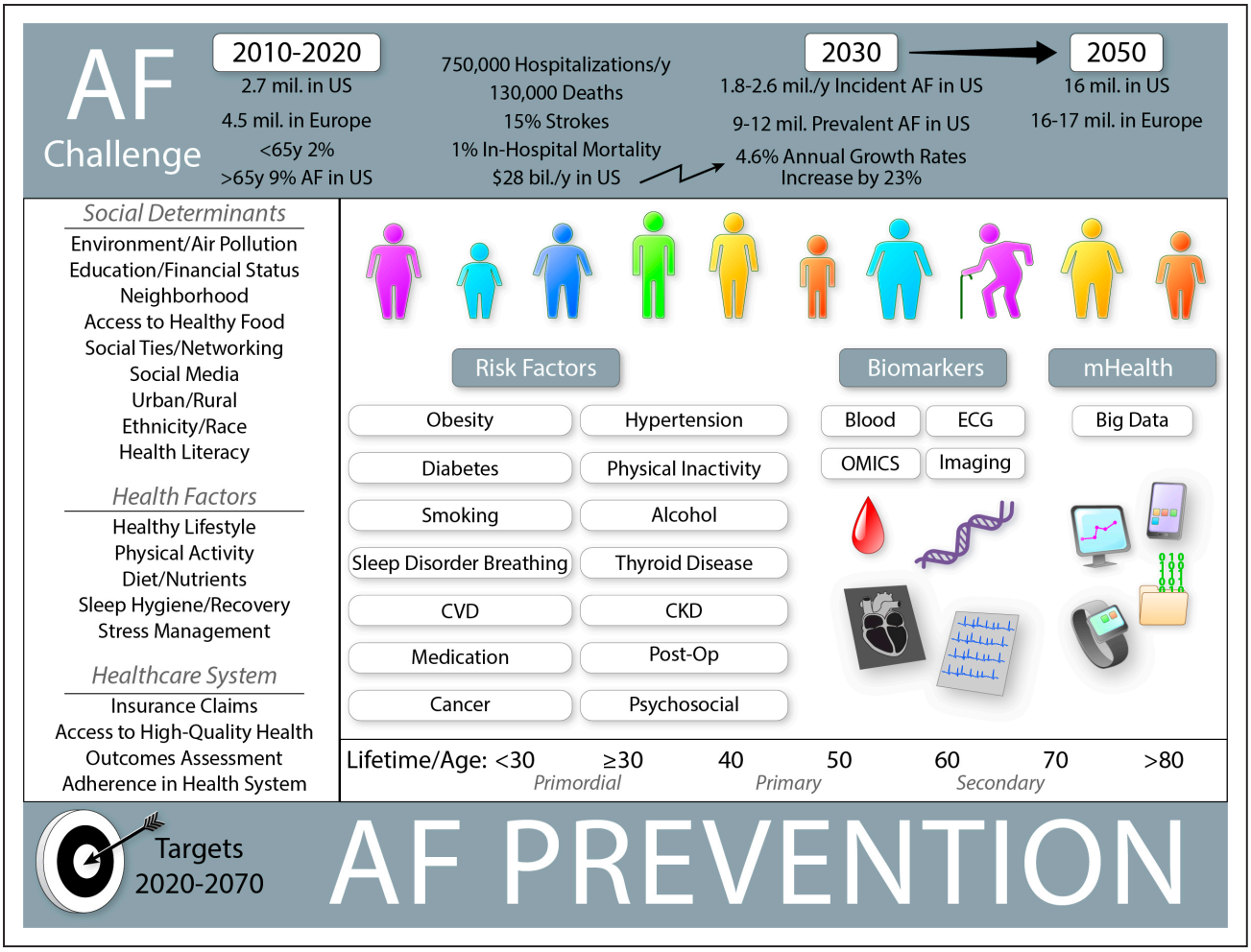

Figure 1. Challenges in atrial fibrillation (AF) epidemiology.
Prevention in AF becomes important because of epidemic character of disease development. While primary and secondary prevention play a crucial role in older individuals with cardiovascular diseases (CVD) and noncardiac diseases, primordial and primary prevention are fundamental in young adults and individuals without known comorbidities. Personal, lifestyle, and social factors as well as societal and health system interventions remain essential prevention targets. CKD indicates chronic kidney disease; OP, surgical operation; and QoL, quality of life. Illustration Credit: Ben Smith and Dr Jelena Kornej.

lifestyle factors, for example, smoking, alcohol, obesity, extreme sports, and psychological stress.

Hypertension

Up to one-third of US adults have hypertension, and its prevalence is expected to increase up to 46%.[6,32] The prevalence of hypertension reaches 80% in individuals >65 years and 26% in adults <45 years. Hypertension predisposes to cardiovascular complications, including coronary heart disease and HF, which contribute to AF initiation and mortality.[33] Hypertension carries the largest population attributable risk for AF development worldwide. In the ARIC study, the hypothetical elimination of borderline or elevated risk factors was predicted to avoid more than half of diagnosed AF cases.[34] Almost 25% of AF cases were attributed to elevated blood pressure.

Chronic elevated blood pressure leads to LA and left ventricular (LV) structural remodeling and contributes to cardiac profibrotic changes.[35] The main contributor to remodeling in hypertension remains the renin-angiotensin system (RAS) with upregulated TGF-ß1 expression, increased aldosterone production, activation of nicotinamide adenine dinucleotide phosphate oxidase, and apoptosis.[35] Some post hoc analyses suggested that inhibition of RAS could be considered an upstream therapy for AF prevention and management, but the observational and randomized data were inconsistent.[36,37] RAS activation is present also in individuals with chronic kidney disease (CKD), which is closely related to hypertension and AF. Importantly, all 3 diseases—AF, hypertension, CKD—share age and DM as the most important risk factors and stroke as a relevant complication.

Diabetes Mellitus

Glucose intolerance and insulin resistance are main components in DM and are modulators in AF substrate development.[38] Type 2 DM is increasingly diagnosed not only in older adults. During past decade, the prevalence of type 2

DM increased by 30% in young, usually obese, individuals aged <20 years.[39] DM has been associated with 1.6-fold increased risk of AF.[40,41] A meta-analysis reported a 40% increased risk for AF development in adults with compared with individuals without DM.[42] Human and animal studies revealed that oxidative stress and inflammation are central modulators for mitochondrial dysfunction and consequent DNA damage, generating a substrate for AF initiation in metabolically stressed hearts.[43,44] Also, there is evidence that TGF-β1, RhoA–Rho-associated protein kinase pathway, and advanced glycation end products and their receptor axis are activated in DM and contribute to AF initiation.[45] However, the association of DM with AF is not as strong as with other CVD.

Smoking

In the United States, up to 38 million people are current smokers.[6] Compared with nonsmokers, the risk for AF in current smokers was significantly higher in the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) AF Consortium,[46] although the association is not as strong as with other CVD. A meta-analysis of 29 prospective studies reported a dose-dependent association between smoking and increased AF risk.[47]

The main components in tobacco products are nicotine besides tar and carbon monoxide. Nicotine activates profibrotic mechanisms and blocks potassium channels and may thus be directly involved in the development of an electroanatomic substrate for AF.[48,49] Indirectly, smoking increases systemic catecholamine release and promote coronary vasospasm leading to myocardial ischemia and, secondarily, to AF.[50] Furthermore, smoking is associated with inflammation, oxidative stress, endothelial dysfunction, and prothrombotic conditions, which facilitate atherosclerotic changes and contribute to atrial ischemic processes.[51] Similarly, it has been suggested that vaping leads to proinflammatory changes and endothelial dysfunction. Although data on e-cigarettes' adverse cardiovascular effects are sparse, a recent retrospective study reported that e-cigarette use was associated with an almost 2-fold risk for MI.[52] Whether vaping is associated with AF risk needs to be examined.

Alcohol

Alcohol consumption is common in Western countries, with almost 50% of the American population regularly consuming alcohol. The American Heart Association recommends to limit alcoholic beverages to a maximum of 2 drinks daily for men and 1 drink for women, ideally consumed with meals.[53] A meta-analysis found that low alcohol consumption defined as one drink/day was not associated with increased AF incidence.[54]

In United States over 17% of adult drinkers (≈37 million) are binge drinkers.[55] A recent meta-analysis found almost 8% increased AF risk with each additional daily alcoholic drink suggesting a linear dose-response relation.[56] The results of ARIC cohort indicate a duration- and dose-dependent association with a higher risk of developing AF.[57] Lower AF incidence was associated with longer duration of alcohol abstinence among former heavy drinkers, and every decade of alcohol abstinence—with almost 20% decreased risk of incident AF (≈2%/y).

Long-term alcohol consumption promotes supraventricular and ventricular arrhythmias, particularly after periods of heavy drinking. Chronic ethanol exposure is associated with longer HV interval, QRS duration, and atrial myocyte action potentials, explaining predisposition to arrhythmias in animal and human models.[58] High alcohol consumption has direct toxic, inflammatory, and oxidative effects on LA myocardium. In the FHS, alcohol consumption predicted LA size enlargement and incident AF.[59] Alcohol promotes LV remodeling and increases LV pressures facilitating diastolic dysfunction.[60] A recent study demonstrated that abstinence or substantial reduction of alcohol intake was associated with fewer AF recurrences in regular drinkers.[61] Besides the elimination of direct proarrhythmic effects, the results could be explained by weight reduction. Due to its high energy content (7 kcal/g), unrestricted alcohol intake may lead to weight gain and hypertension, contributing further to AF initiation.

Therefore, alcohol restriction or abstinence should be considered as one of the potentially effective strategies for AF prevention.

Obesity

The prevalence of overweight and obesity has increased significantly over the last decades worldwide with significant impact on public health with reduced quality of life and high medical costs.[62] It is expected that by 2030 ≈38% of the world's adult population will be obese.[63] However, not only measurements of weight at a single point in time but also dynamic weight changes are associated with higher AF risk compared with stable body weight.[64] Interestingly, body mass index gain in later life posed higher AF risk than that during younger years.

A causal role of obesity for AF has been supported by a Mendelian randomization study, which demonstrated that a genetic risk score comprised of 39 polymorphisms associated with body mass index were associated with AF.[65] Sustained obesity is associated with hypertension, DM, metabolic syndrome, coronary heart disease, and obstructive sleep apnea, which provide the substrate for atrial remodeling and contribute to AF initiation and perpetuation (Figure 2).[63] There are robust associations between weight gain and electroanatomic remodeling,[66] enhanced neurohormonal activation modulating LA enlargement, and electrical instability.[67] Furthermore, obesity is related to low-grade inflammation and greater epicardial fat thickness, which impair atrial electrophysiology.[68] Some studies indicate that obesity may have a direct influence on myocardial structure via increased oxidative stress.[69]

Weight variability >5% is another factor associated with an almost 2-fold risk of AF recurrence.[70] Importantly, weight regain during weight cycling leads to rapid adipose tissue growth and metabolic shifts facilitating lipid storage,[71] which are associated with AF risk.

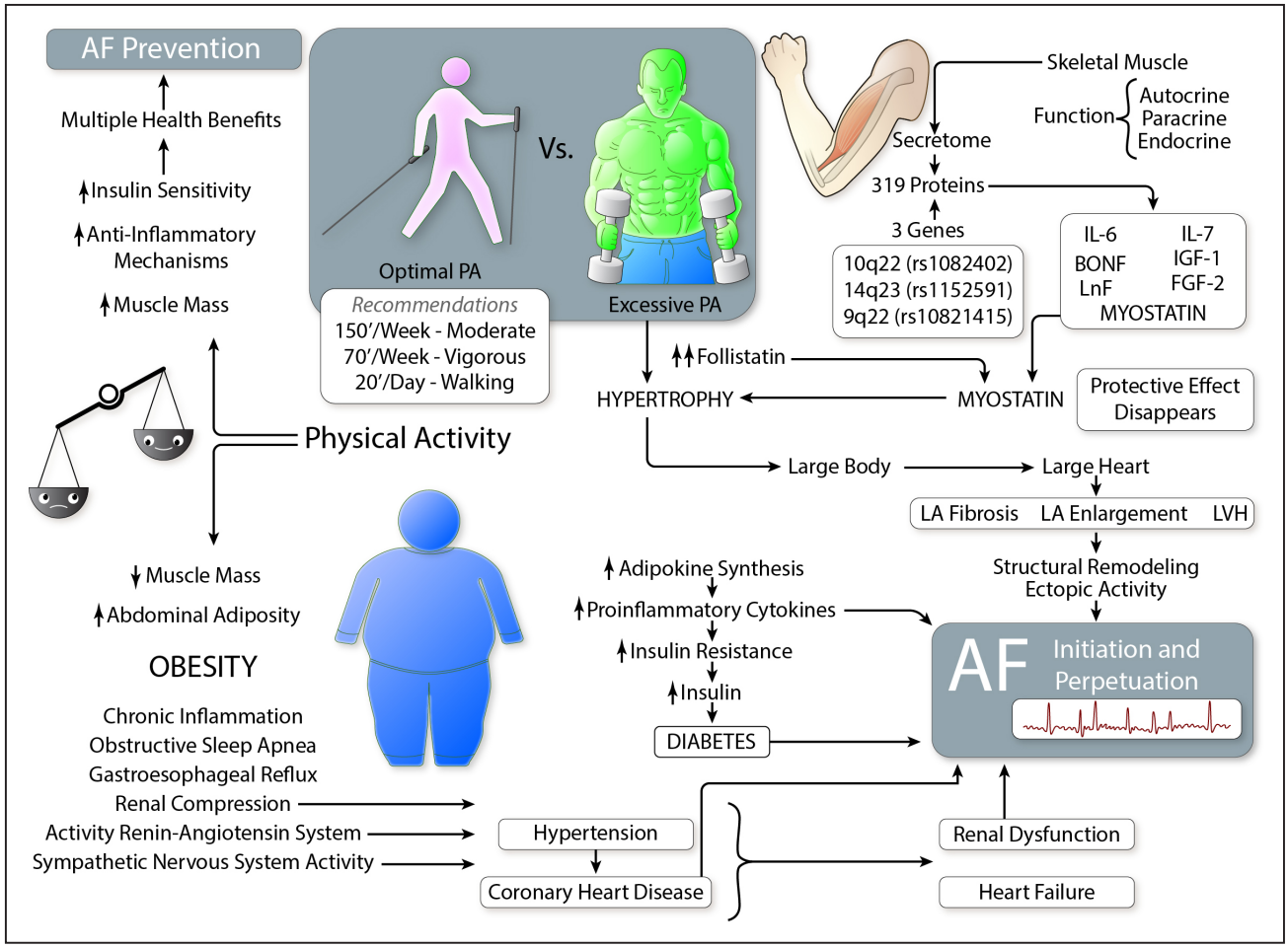

Figure 2. Relationship between physical activity, obesity, and lean body mass in atrial fibrillation (AF).
Moderate physical activity (PA) should be recommended for all AF prevention levels – primordial, primary, and secondary. Low and extreme PA predisposes to obesity (fat) or excessive muscle (lean body) mass, respectively. Through complex pathophysiological mechanisms, both are risk factors for AF. BDNF indicates brain-derived neurotrophic factor; FGF, fibroblast growth factor; IGF, insulin-like growth factor; IL, interleukins; LA, left atrial; LIF, leukemia inhibitory factor; and LVH, left ventricular hypertrophy. Illustration Credit: Ben Smith and Dr Jelena Kornej.

Finally, there are intriguing findings indicating that AF risk is primarily associated with high lean body mass (eg, fat-free mass) and that fat tissue itself contributes remotely to AF development[72,73] (Figure 2). One possible explanation is skeletal muscles, which are a secretory organ distinguished by production and release of diverse cytokines and peptides with endocrine effects.[74] Muscle activity promotes liver synthesis of follistatin. Follistatin is an inhibitor of myostatin, which is involved in metabolic homeostasis, influencing adipose tissue function, and cardiac hypertrophy.[74,75] Thus, inhibition of myostatin was associated with LV hypertrophy, LA enlargement, atrial fibrosis, and spontaneous AF.[75]

Physical Activity

Regular, moderate physical activity (PA) is a cornerstone of a healthy lifestyle (Figure 2). It is inversely and independently associated with clinical AF incidence and progression, and several studies indicate beneficial effects for AF prevention in individuals pursuing regular PA.[76,77] Among the multifactorial beneficial effects of moderate PA are attenuation of many of the cardiovascular consequences related to obesity as insulin resistance, dyslipidemia, endothelial dysfunction, and reduced blood pressure.[78] In overweight and obese individuals, moderate PA reduces systemic inflammation independently of weight loss, minimizing atrial arrhythmogenesis.[79]

Some investigators reported an association between moderate PA and decreased[80,81] AF risk, whereas vigorous PA increased AF risk.[82] Although a meta-analysis found that intermediate and high-level PA was associated with lower risk for AF,[83] there is a J-shaped relationship between exercise intensity and incident AF.[84] In the Tromsø Study, compared with individuals without regular exercise history, individuals with moderate PA had a 28% lower AF risk.[85]

In contrast to moderate PA, a high volume of endurance exercise increases the risk of AF in elite athletes.[86] The risk of AF development in athletes is 5× higher than in referents.[87] Some athletes may be more aware of their body and AF symptoms, possibly resulting in earlier diagnosis of AF. However, there are several underlying

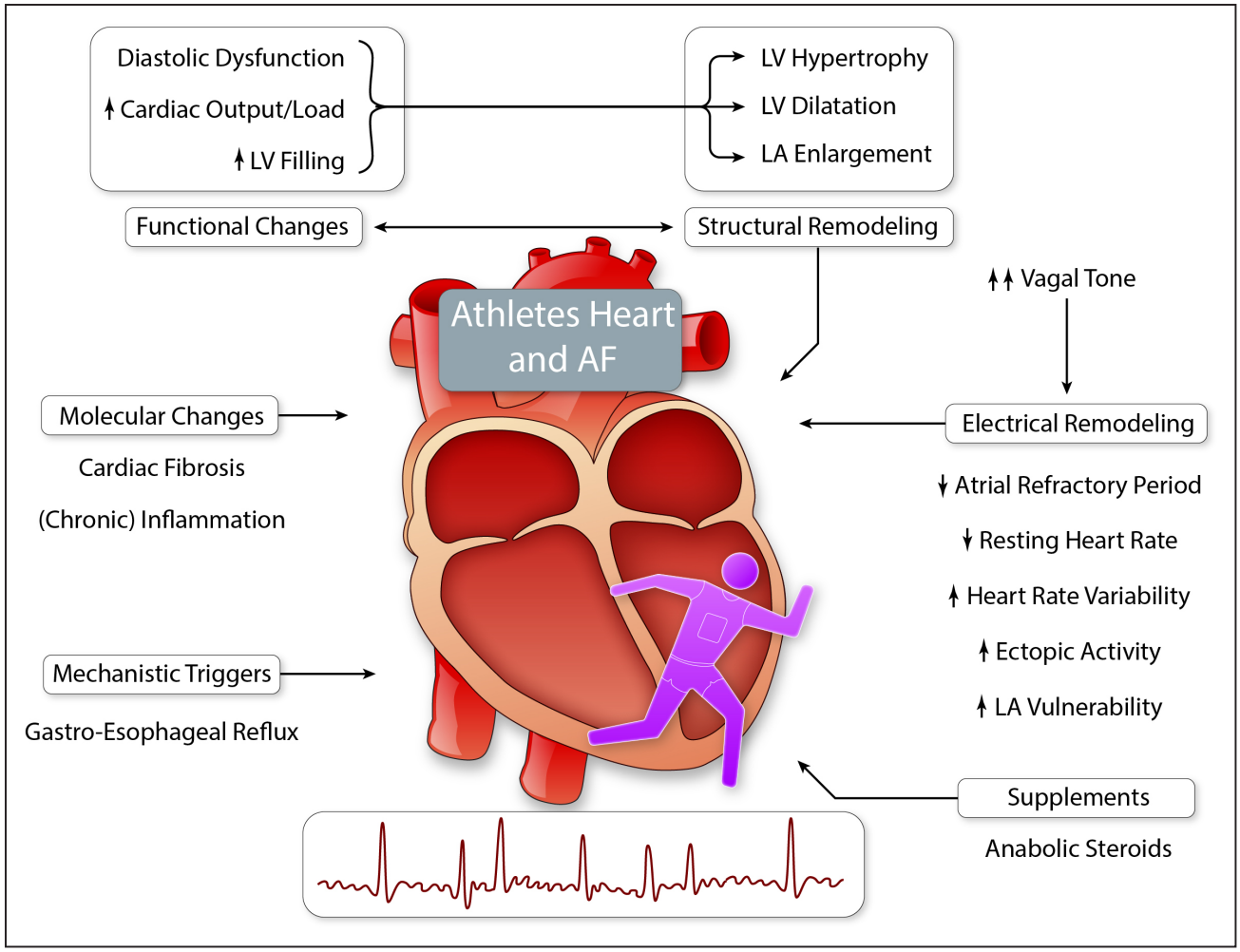

Figure 3. Athletes' heart and atrial fibrillation (AF).
Cardiac adaptations to exercise are considered as beneficial, although vigorous physical activity and prolonged endurance exercise, may lead to cardiac overadaptation or even maladaptation and (patho)-physiological changes, which facilitate AF initiation and perpetuation. LA indicates left atrial; and LV, left ventricular. Illustration Credit: Ben Smith and Dr Jelena Kornej.

pathomechanisms explaining higher AF risk in athletes (Figure 3). Cardiac adaptation to vigorous exercise involves increased vagal tone, lower resting heart rate, and increased stroke volume, chamber dilatation, and hypertrophy, all of which may predispose to AF.[88,89]

Psychological Stress and Psychosocial Factors

The prevalence of chronic stress is ≈8% in United States, but in certain populations, its exposure is ≈40% (eg, military deployment, sexual assault, natural disaster, gun violence).[90] In a nationwide study with >1 million young veterans (median age 27 years), posttraumatic stress disorder was associated with 13% higher risk of incident AF.[31] Pathophysiologically, psychosocial stress might lead to dysregulations in autonomic tone, hormonal imbalance, and catecholamine overload resulting in the alteration of LA electrophysiology[91] and facilitating atrial fibrosis formation.[92,93] Furthermore, there is evidence that chronic changes in autonomic tone impair atrial electrophysiological pattern and facilitate AF initiation.[94] Chronic psychological stress, including work-related stress as well as depression, anger, anxiety, and sleep deprivation, are linked to the metabolic syndrome and its components[95–98] and associated with unhealthy behavior. The prevalence is higher in individuals with lower employment category or socioeconomic level, and in those with continuous stress at work.[96,99] Also, psychological stress leads to sleep disorders, including disturbances in sleep-wake cycle and sleep patterns with consequent malfunction of the hypothalamic-pituitary-adrenal axis.[100,101] Sleep deprivation impairs the physiological balance in circadian cortisol concentrations, which results in increased sympathetic nervous system activity[102] and decreased vagal activity.[91]

The role of stress reduction for AF prevention has been incompletely studied, partly because of the potential for residual confounding. There is evidence that relaxation strategies, including prayer, yoga, and meditation, transiently modify indices of autonomic activation,[103] and improve quality of life in patients with AF.[104] The role of stress reduction to prevent incident AF is less certain. Since stress is an exposure that may change over time,

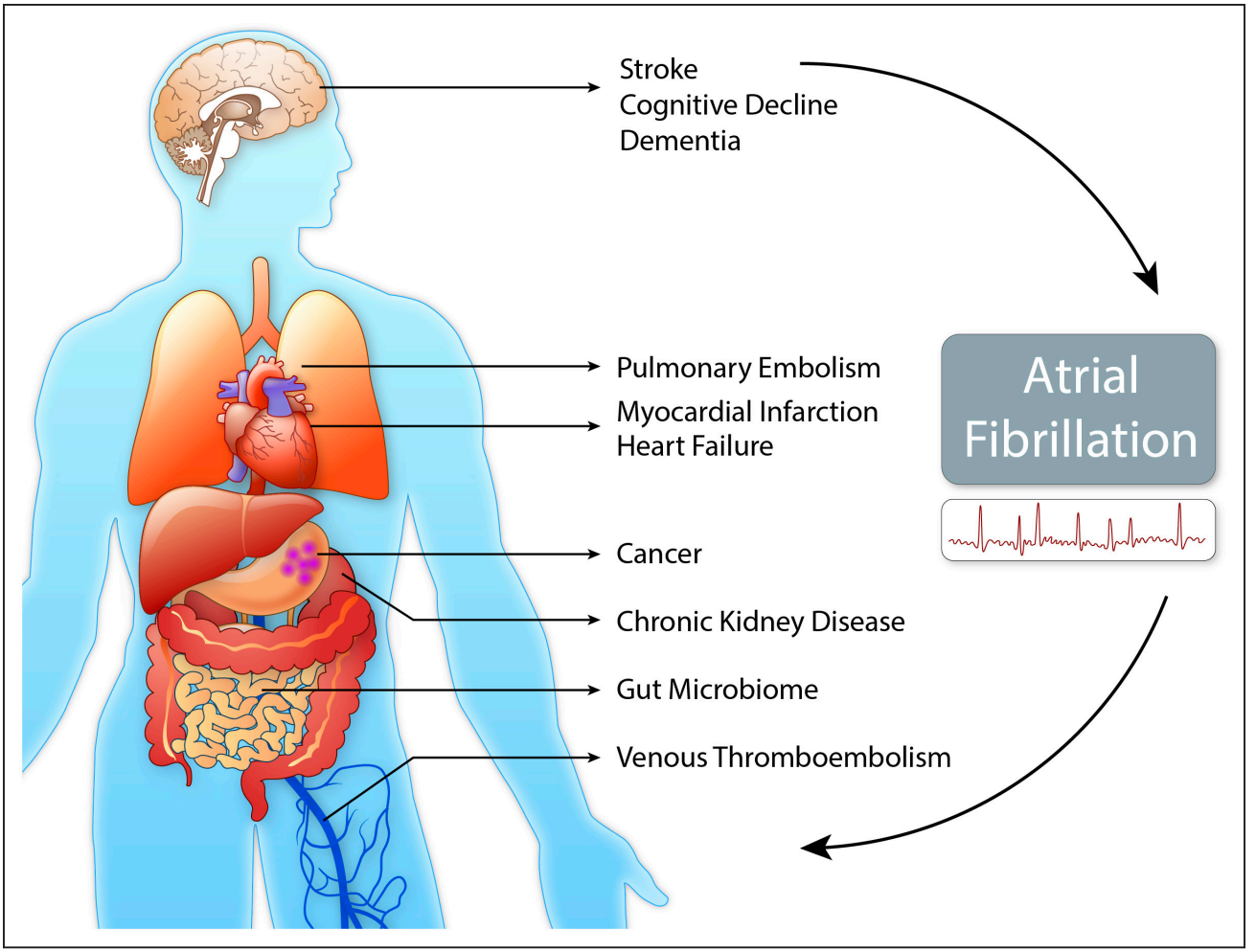

Figure 4. Association between atrial fibrillation (AF) and system diseases.
AF is a multisystem disorder with complex relations to associated diseases, risk factors and the environment. An improved comprehension of this interplay may help improve risk assessment and management of AF and its comorbidities in the future. Illustration Credit: Ben Smith and Dr Jelena Kornej.

repeated measurements in longitudinal studies with extended follow-up would advance the field.

Future Directions in Primary AF Prevention

- Further research needs to characterize optimal primordial AF prevention measures (PA, body composition, nutrition) and test implementation strategies targeted to specific populations.
- For this aim improvement of AF study populations (eg, inclusion of young individuals, large multiethnic/racial cohorts, long follow-up for lifetime risk analyses) is required to close the remaining, significant knowledge gaps.
- Understudied external exposures with many unanswered questions are social determinants, geographic residential environment (rural versus urban), neighborhood, and neighborhood-specific factors (as pollution, socioeconomic status). Also, the role of health literacy remains a challenging condition in vulnerable groups and should be addressed in future epidemiological research.

COMORBIDITIES OF AF AND THEIR IMPACT ON PROGNOSIS

AF is associated with increased mortality. Patients generally do not die from the arrhythmia but of accompanying comorbidities and complications, for example, HF, MI, CKD, venous thromboembolism (VTE), stroke, dementia, and cancer. Beyond shared risk factors, there are multiple direct causal interactions between AF and its comorbidities,[105] resulting in an interdependence in disease development (Figure 4).

Heart Failure

HF is closely related to AF, and their coexistence is associated with substantially increased morbidity and mortality.[106,107] Both AF and HF are associated with increased incidence of the other disease suggesting a bidirectional relationship. In a subset of FHS participants who developed new AF, 37% had previously diagnosed HF. Vice versa, 57% of participants developing HF had prevalent

AF.[107] Incidence of both diseases increases steeply after age of 60 years.[16,108]

In contrast to the general population, AF development is 4× to 6× higher in patients with HF.[40] The most important underlying pathological feature seems to be LA vulnerability caused by structural and electrical remodeling, as shown by electrophysiological mapping in patients with HF.[109] Also, the RAS, which is upregulated compensatorily in patients with HF, contributes to the development of AF in patients with HF. The prevalence of AF in patients with HF is related to the severity of HF and rises from <10% in New York Heart Association class I of >50% in New York Heart Association class IV.[108] Individuals with HF with preserved ejection fraction are particularly at risk.[107,110] Up to two-thirds of patients with HF with preserved ejection fraction develop AF simultaneously or close after the diagnosis, and in HF with preserved ejection fraction, AF is associated with a particularly adverse prognosis.[110]

HF becomes manifest in ≈50% of patients with AF.[106] Modifiable cardiovascular risk factors strongly influence the risk of developing HF, and their optimized management may decrease risk,[111] but a strong evidence base to prevent HF in AF remains to be defined. Direct effects of AF, such as irregular heart rate, shortened diastole, and loss of atrial contraction, directly result in declines in cardiac output contributing to the development of HF.[112] However, there are also long-term effects of AF, also referred to as AF-mediated cardiomyopathy.[113] The resulting LV dysfunction is largely reversible after heart rate is controlled.[114] However, an increased presence of diffuse fibrosis and cardiomyocyte apoptosis was described,[115] which may explain the strong association between previous AF and HF with preserved ejection fraction.[116]

Myocardial Infarction

In patients with AF, the risk of MI is ≈2-fold increased.[117] Conversely, MI is associated with increased incidence of AF, especially in the acute phase.[118] Considering the frequent occurrence of asymptomatic AF, real incidence rates may be much higher. The 12-month incidence rate of AF in a post-MI trial monitoring patients with implantable cardiac devices was 32%.[119]

Not only common cardiovascular risk factors but also several direct interactions explain the bidirectional relationship between both diseases. Tachyarrhythmic episodes may directly result in type 2 MI due to insufficient coronary artery perfusion.[120] Furthermore, AF may induce MI by coronary thromboembolism, which accounts for ≈3% of MI cases.[121] Likewise, there are several mechanisms of how MI promotes the development of AF. In the acute phase after MI, risk factors for AF development include LV dysfunction, LV hypertrophy, and elevated heart rate.[122] Atrial ischemia may cause early-onset AF after MI.[123] Also, atrial stretching as a result of acute HF after MI may increase atrial excitability,[124] and infarction-related pericarditis has been described as direct cause of AF.[125] Further pathophysiologic links between AF and MI are systemic inflammation and endothelial dysfunction, which predispose both diseases. Otherwise, there is evidence that both AF and MI further aggravate cytokine release and systemic inflammation, eventually facilitating development of the other disease.[126,127]

The co-occurrence of MI and AF is associated with increased mortality of ≈40%.[128] Particularly at risk are patients with new-onset AF after MI, which is associated with an 87% higher mortality compared with permanent AF.[129] An increased vulnerability for ventricular arrhythmias and an aggravation of ischemia by hemodynamic alterations have been discussed as possible explanations.[130]

Chronic Kidney Disease

Albuminuria, mild renal impairment, and declining renal function are associated with higher AF incidence.[131,132] In a Japanese cohort, patients with glomerular filtration rate of 30 to 59 mL/min had 32% higher risk AF compared with individuals with normal renal function. For those with glomerular filtration rate <30 mL/min, the risk was 57% higher.[132]

AF and CKD share similar risk factors, but their association remains significant in individuals without hypertension or DM.[132] A common pathophysiologic pathway is the activation of the RAS. In patients with CKD, RAS activation eventually results in fibrogenesis, oxidative stress, and a downward spiral of kidney function. In AF, similar mechanisms have been described, leading to atrial fibrosis, increased atrial pressure, and modulation of ion channels.[133] Likewise, an association with systemic inflammation has been described for both diseases.[127] However, AF may also directly contribute to development of CKD by reduced cardiac output or thromboembolism.

The co-occurrence of AF and CKD is associated with an adverse prognosis. In patients with renal impairment, AF is associated with higher risk for HF, MI, and all-cause mortality.[134] In a single-center study, patients with end-stage renal disease and AF had a 4-year mortality rate of 81%, compared with 29% in patients without AF.[135]

Venous Thromboembolism

VTE and AF appear as distinct diseases but are closely related to each other, often co-occur, and share multiple pathophysiological features. Both, incidence of AF after the diagnosis of VTE and incidence of VTE after the diagnosis of AF are ≥70% higher compared with the general population. Within first 6 months after diagnosis of AF or VTE, individuals are susceptible to the other diseases.[136]

In patients with pulmonary embolism development of AF may partly be caused by increased right cardiac pressure and dilation, resulting in atrial structural remodeling.[137] In addition, neurohormonal mechanisms, like the release of 5-hydroxytryptamine by activated platelets, have been proposed.[138] More recently, hypercoagulability has been linked to induction of atrial fibrosis.[139]

As one possible cause of pulmonary embolism in patients with AF, right-sided cardiac thrombus formation is assumed. This hypothesis is further supported by the fact that mortality by pulmonary embolism is increased in patients with right heart thrombi.[140] In addition, pulmonary embolism is more frequent in patients with AF than deep vein thrombosis.[141] AF itself has not only been associated with increased risk of pulmonary embolism but also of deep vein thrombosis,[141] which implies more complex pathophysiological interactions of AF and VTE. The most important common denominators seem to be shared risk factors and comorbidities. Both AF and VTE incidence are strongly age-dependent.[142] As further risk factors of both diseases HF, obesity, sepsis, and autoimmune diseases have been identified.[40,143–145] AF and VTE further have in common systemic inflammation with increased platelet activation, endothelial dysfunction, and resulting in a prothrombotic state.

The co-occurrence of VTE and AF has serious prognostic implications, and mortality is significantly elevated.[146] This seems to account for both prevalent AF and subsequent AF.[147] However, it is unclear whether AF is the cause of the increased mortality or only indicates a subset of patients with more comorbidities or more severe embolism.

Stroke

AF is associated with 4- to 5-fold increased risk of stroke, which also accounts for subclinical AF.[36,148] Persistent forms of AF carry higher stroke risk compared with paroxysmal AF.[149] Currently, the CHA_2DS_2-VASc score is the most widely used stroke risk score.[150] However, there are several predictors, including obstructive sleep apnea[151] and renal failure,[152] which are not included in the score. Biomarkers such as high-sensitivity troponin T, N-terminal B-type natriuretic peptide, and growth differentiation factor-15 may improve performance of the current scoring systems.[153]

The underlying pathophysiological mechanisms of thrombus formation and stroke in AF include atrial fibrosis,[154,155] atrial enlargement,[156] and alterations of blood flow. Interestingly, new-onset AF is also increased after hemorrhagic stroke, which is not a direct result of AF.[157] Pathophysiological mechanisms may include dysregulation of autonomous nervous system and inflammation.[158] Investigations on patients with implantable cardiac devices did not show a strong correlation between episodes of AF and onset of stroke, suggesting an association beyond thrombus formation.[159] Both AF and stroke may indicate progressive CVD and represent risk factors for each other. A bidirectional temporal relationship of AF and stroke was confirmed in prospective community cohort studies.[160]

Dementia

Stroke in the setting of AF predisposes to dementia. Within 5 years, new-onset dementia was described in about one-third of all stroke patients.[161] In patients with AF, a meta-analysis revealed a 2.7-fold risk of dementia after first or recurrent stroke.[162]

However, there is an association between AF and dementia independent of stroke. Two meta-analyses revealed ≈30% increased risk of dementia in AF after adjustment for cerebrovascular events.[162,163] Furthermore, AF is related to cognitive impairment or dementia in younger ages.[164] In these studies, no brain imaging was performed to rule out clinically silent strokes as the underlying pathophysiology. In a case-referent study, which included magnetic resonance imaging brain imaging, stroke-free individuals with AF showed difficulties in learning, memory, attention, and executive function compared with healthy referents.[165]

Nonischemic mechanisms include cerebral hypoperfusion, vascular inflammation, and genetic factors. Cerebral hypoperfusion and hypoxia are mainly induced by AF-related HF, which appears in ≈50% of patients with AF.[106] In the FHS, a relation between cardiac output and lower cognitive performance was described.[166] In the Rotterdam Study, diastolic dysfunction was linked to stroke and dementia.[167] Inflammatory markers such as C-reactive protein and interleukin-6 are elevated in AF and correlate with AF duration, success of cardioversion, and thrombogenesis.[127,168] Inflammation itself is associated with cerebral microstructural changes and cerebral dysfunction and may be part of the common ground of atrial and cerebral disease.

Cancer

Although cancer and AF frequently co-occur, their relation is understudied. The risk of newly diagnosed cancer in the first three months after new-onset AF is almost 3-fold increased. Similarly, newly diagnosed cancer is accompanied by a significantly increased risk of incident AF.[169]

Similar to the other AF comorbidities, shared risk factors may contribute to the co-occurrence of AF and cancer.[170] The high incidence rate of cancer directly after diagnosis of AF may reflect improved detection of asymptomatic disease due to intensified medical examination. Furthermore, initiation of anticoagulation may trigger bleeding and consecutively lead to a cancer diagnosis.[171]

Conversely, there are multiple conceivable mechanisms of how cancer might predispose to the development of AF. Thoracic cancer manifestations and surgery may induce AF by cardiac infiltration, inflammation, or mechanical

disturbance.[172] Likewise, radiotherapy, cytotoxic chemotherapy, targeted therapies, and high-dose corticosteroids have been associated with AF onset.[173] The most notable chemotherapeutics associated with AF are alkylating agents, for example, the incidence of AF with cisplatin is 15% to 32% and with anthracyclines is 10%. More recent developments in oncology like targeted therapies share similar problems. A prominent example is ibrutinib, a Bruton tyrosine kinase inhibitor, which is associated with LA remodeling. In patients treated with ibrutinib, AF incidence rates may reach 38%.[174] Further pathophysiological links between cancer and AF include complications of cancer, such as VTE, organ dysfunction, metabolic disorders, hypoxia, and systemic inflammation.[93]

The incidence of AF in patients with cancer may predict unfavorable outcomes similar to the substantially increased risk of HF.[175,176] However, the impact on overall mortality is uncertain. Although in a large retrospective cohort of patients with cancer with AF, overall mortality was not increased,[175] a smaller prospective cohort of patients with lymphoma with new AF had nearly 5× higher mortality rate.[176] In patients with cancer with AF, disease management remains challenging, and CVD is the primary cause of death not related to cancer.[177] A predisposition to bleeding in patients with cancer with AF has been reported.[178]

Future Directions in Secondary AF Prevention

- A key research need in the understanding of AF and its frequent comorbidities is the disentangling of common and distinct pathophysiological pathways, their interactions, and the identification of specific mechanisms that could be addressed for disease prevention in patients in whom comorbidities are prevalent.

SUBCLINICAL MARKERS AND RISK PREDICTION FOR INCIDENT AF

Many research groups have analyzed the prediction of incident AF using diverse clinical scores based on different combinations and weighting of classical risk factors (Table I in the Data Supplement). Biomarkers have been shown to increase accuracy of risk prediction. Biomarkers are objectively measurable and quantifiable markers of health and disease states. They include protein-based blood markers, cardiac imaging, or electrocardiographic markers, which can provide additional refinement to clinical risk stratification for identification of high-risk individuals for AF onset and complications. Electrocardiographic parameters, such as PR interval and its indices, represent atrial and atrioventricular conduction; therefore, association between pathological PR interval and AF seems to be appropriate.[179] Multiple blood biomarkers—especially associated with cardiac damage and stress, cardiac proinflammatory and profibrotic changes in particularly in the atria—have been analyzed in multiple observational and clinical studies to refine prediction of AF incidence and progression (Table II in the Data Supplement). Finally, recent developments and increasing availability of imaging tools, including advanced echocardiography, computed tomography, and cardiac magnetic resonance imaging, have become a standard to assess risk profiles in AF but may also contribute to risk prediction for imminent AF. The easily quantifiable echocardiographic anteroposterior LA diameter is a known indicator of AF progression[180]; cardiac magnetic resonance imaging studies indicated the importance of anatomic and functional LA changes in AF.[181,182]

NEXT STEPS TOWARD PRECISION AF MANAGEMENT AND PREVENTION

Omics

Recent advances in high-throughput technologies will accelerate our understanding of AF. Integrated approaches combining genomic, epigenomic, transcriptomic, proteomic, metabolomic, and microbiome data offer the opportunity to further define the molecular framework of AF and have already brought new insights.

Genetics and genomics have come closest to clinical practice. In familial or early-onset forms of AF, several single rare genetic variants with large effect sizes in AF development have been reported over the past decades. These variants often encode ion channel or sarcomere protein components and provide a substrate for reentry or early and delayed after-depolarization leading to AF.[183,184] The reported mutations appear to be infrequent and rare variants appear to account for a relatively small proportion of genetically determined AF in the general population. The genetic variants associated with AF in individuals of non-European ancestry also are largely unknown.

Over the past few years, genome-wide association studies have revealed a polygenic basis with common genetic variations in over 100 loci associated with a modification of AF risk.[185,186] Polygenic scores based on common genetic variation may improve risk stratification beyond cardiovascular risk factors.[187] The majority of these common genetic variants are located in regulatory, noncoding-regions of genes enriched within the transcriptional regulation, development, and signaling pathways of electrophysiological, contractile, and structural characteristics of cardiomyocytes. Many of these genes have previously been associated with other medical conditions, such as cardiovascular or musculoskeletal diseases. These massive genotyping efforts provide many candidate loci for AF and lay the ground for further mechanistic investigation and therapeutic targets.

Other 'omics analyses also revealed new insights. Proteomic profiling recently identified 8 proteins associated with incident AF, whereas their causal relation to AF development remains unclear.[188] On the epigenetic

level, a methylome-wide association study of AF revealed 7 methylation signatures associated with prevalent or incident AF.[189] By combining phenomic, metabolic, and genomic data, potassium, sodium ion, chitin, benzo[a]pyrene-7,8-dihydrodiol-9,10-oxide, and celebrex were found to be the five most important AF-related metabolites.[190] Moreover, proton nuclear magnetic resonance spectroscopy revealed ketone body metabolism as a central step in persistent AF supported by proteomic analyses.[191] In this study, metabolic profiles correctly predicted postoperative AF in >80% of patients undergoing cardiac surgery. Yet to be discovered is the role of the microbiome, its composition, and quantity in predicting AF. First evidence suggests an association of the gut microbiome in the AF development.[192] Another aspect that has to be taken into account in a holistic approach is the so-called exposome, including environmental influences, living circumstances, and biopsychological aspects.

Until now, most 'omic studies have been small and remained without external validation. The step towards clinical implementation still must be taken. The hope is that better understanding of the triggers and mechanisms underlying AF may help define targets for prevention and treatment.

Future Directions for Translational Research

- In the future, 'omics-analyses may represent an important step towards AF precision medicine if ways for translational implementation of genetics and omics findings in clinical care with sufficient precision and justifiable costs can be defined.

eHealth and AI

Health promotion and maintenance takes part largely outside the clinical setting. Significant advances are expected from technological developments known as electronic or mobile health (eHealth). A dynamic increase in the availability of mobile devices, wearable sensors, and software applications (apps) allows close health and disease monitoring.[193] Following a general trend, eHealth has gained attention in cardiovascular prevention and diagnostics of AF.[194,195] eHealth can be helpful to control and modify diverse risk factors associated with AF (eg, PA, weight management, blood pressure, DM control, medication adherence). Also, it can help with AF detection (arrhythmic pulse, electrocardiograms). In patients with asymptomatic or paroxysmal AF with short episodes, eHealth gives the opportunity to improve early diagnosis of AF, with the potential to reduce future hospitalizations, morbidity, and mortality. However, overdiagnosis (and consequently overtreatment) is becoming a growing problem in contemporary medicine, partly due to rising influence of technical improvements. False-positive AF detection or ascertainment of very short self-limited AF may precipitate a testing and treatment cascade, which may significantly affect individuals' lives.[196] The risks of overdiagnosis are balanced against the thousands of patients with undiagnosed cerebrovascular complications related to AF that are associated with significant health care costs.[197]

Alternatives for rhythm monitoring are smartphones and smartwatches, which have become popular across all population groups. These devices and wearable fitness trackers recognize arrhythmia pattern using AI systems.[198] Deep learning algorithms monitor digital pulse waveforms and detect nonuniform and irregular heartbeats. Notifications permit timely medical consultation, further testing, and potential diagnosis of AF. Many evidence gaps remain, including whether high-risk individuals use such applications, whether wearable-detected AF carries a high enough risk to require anticoagulation, in particular, if only short episodes are present, whether anxiety and overuse of medical care are consequences of false positives, resulting in questions regarding whether the use of such devices for AF screening is efficient at the population level.

In the era of rapid advances of AI in cardiovascular medicine, new methods of almost hypothesis-free interrogation of big data sets for the identification of AF predictors carry the potential to render AF screening and targeted treatment more efficient. AI structures large amounts of data, often instantaneously, improves algorithms autonomously, and may facilitate processes along the public health continuum from primordial to primary and secondary prevention of AF by increasing effectiveness and efficiency of diagnosis, screening, and treatment. Using automated learning algorithms machine learning (ML) represents an approach to generate unique prediction tools in primary care, to recognize high-risk individuals for AF, as well as guide physicians and patients managing AF.[199]

More comprehensive use of available information from multiple distinct sources, for example, electronic health records, imaging, genetics, eHealth, etc, may promote understanding of disease patterns and permit the definition of clinically relevant AF subtypes. In initially healthy individuals in the deep-phenotyped MESA cohort, ML was able to improve predictive accuracy for AF.[200] ML can select clinical and biomarker variables indicating prevalent AF.[201] Recently, an ML data-driven approach assisted identification of multilevel interactions between clinical and ECG variables without predefined theoretical connections.[202] ML was able to predict incident AF with high accuracy using ECG analysis with documented sinus rhythm. Nevertheless, external validation of these findings and demonstration of clinical relevance is necessary. Also, there is a risk of a significant amount of data with little or no clinical relevance. As recently reported, although ML diagnosed subclinical AF more accurately than clinicians, predicted AF was neither associated with prolonged hospital stay nor with mortality.[203] In fact, there is a risk of an unnecessary (over)-treatment and treatment-related complications.[204] A further cautionary note

about the use of ML in AF research and clinical care is awareness that ML may amplify biases inherent in previously collected data.[205]

Future Directions for Digital Health

- Major research needs are the assessment of the effectiveness of eHealth, definition of the best-suited target population, and adaption of eHealth tools and requirements for AF screening, detection, monitoring, and treatment.
- Major knowledge gaps and research needs comprise the expansion of AI multilevel application to AF risk prediction, AF subtype classification, and management guidance, for example, decision support tools, and demonstrate generalizability outside the derivation samples.

CONCLUSIONS

The significantly increasing incidence, prevalence, and high lifetime risk render AF a relevant disease in the population with high morbidity, mortality, and significant health care costs. Identification and targeting modifiable risk factors might be considered as the most relevant investment for AF risk modulation, number of lives saved, and healthcare resources freed. Primordial, primary, and secondary AF prevention include interventions at personal, healthcare, and societal levels. Recent achievements in biomarker, omics, eHealth, and AI research will be essential to refine AF risk prediction and communication and will help modify AF prevention and management.

ARTICLE INFORMATION

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