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REVIEW TOPIC OF THE WEEK

Is Atrial Fibrillation a Preventable Disease?

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ABSTRACT

Atrial fibrillation (AF) is an increasing burden worldwide. However, AF prevention has not been emphasized enough in clinical practice or guidelines. In this paper, the authors review the associations of modifiable lifestyle factors, including alcohol abuse, smoking, physical inactivity, and unhealthy psychological stress, with the risk for AF development. The authors also review the associations of cardiovascular risk factors that can be better managed, including obesity and overweight, high blood pressure, diabetes, dyslipidemia, obstructive sleep apnea, and other cardiovascular diseases, with the risk for AF. The conclusion is that a high proportion of AF can be prevented by combining strategies, focusing on the high-risk population for better risk factor management, and emphasizing healthy lifestyle choices in the whole population. (J Am Coll Cardiol 2017;69:1968–82)

Atrial fibrillation (AF), the most common persistent cardiac arrhythmia, significantly influences health and health care. In the United States alone, 2.7 million to 6.7 million people have AF, and this is projected to reach 5.6 million to 15.9 million by 2050 (1,2). In the European Union, AF prevalence in 2010 was estimated at 8.8 million among adults older than 55 years and is expected to double by 2060 if age- and sex-specific prevalence remains stable (3). In Asia, it is estimated that by 2050, there will be 72 million patients with AF and 2.9 million AF-associated strokes (4). Beyond North America and Europe, epidemiological assessment is scarce, with estimated AF prevalence ranging widely from 0.1% in India and 3% in Israel to 4% in Australia (5,6). The global burden of AF in 2010 was estimated at about 33.5 million, with close to 5 million new cases diagnosed annually (7). Despite the increased awareness and enhanced detection of AF over the past few decades (8), one-third of the total AF population is asymptomatic, and a considerable proportion of patients with unknown AF can be detected by mass screening (9); therefore, AF burden worldwide should be considerably underestimated.

AF is associated with an increased risk for morbidity, with 5-, 3-, and 2-fold increased risk for stroke, heart failure, and dementia, respectively, and 40% to 90% increased risk for mortality (10,11). In the United States, AF-related Medicare expenses are approximately $16 billion annually (12). In Australia, the number of AF hospitalizations tripled between 1993 and 2007, with the rate of increase greatly surpassing those for heart failure or myocardial infarction (13). More recently, tremendous progress has been made in AF treatment and AF-related stroke prevention. Nevertheless, new technologies place even more remarkable economic demands on us. With increased life expectancy in both developing and developed countries, AF is expected to cause more harm and to be costlier. Dr. Eugene Braunwald (14) pointed to AF as a new cardiovascular disease epidemic of the 21st century. To reduce AF burden, it is essential to embrace prevention as a priority. However, cardiology practice has focused primarily on AF treatment and AF-related stroke prevention rather than preventing AF itself. It is estimated that at least 80% of coronary heart disease could be prevented if the major risk factors were eliminated (15,16). In this paper, we suggest that AF prevention deserves similar recognition by reviewing

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the impact of modifiable lifestyle and cardiovascular risk factors on the risk for AF development, and we conclude by calling for a multidisciplinary approach to AF prevention.

MODIFIABLE LIFESTYLE AND AF PREVENTION

ALCOHOL ABUSE. Drinking alcohol is a popular habit, with >50% of American adults reported to be regular drinkers and an additional 13% reported to be infrequent drinkers (17). The association between acute alcohol ingestion and AF was recognized several decades ago, and AF was termed the "holiday heart syndrome." Risk for AF increased with increased alcohol consumption. More than 21 drinks weekly increased AF risk by 39% (18,19), and >35 drinks increased AF risk by 45% in the Copenhagen City Heart Study (20) and by 1.90 times in a Japanese study (21). The relative AF risk of alcohol consumption is achieved at a relatively low dosage in women. In the WHS (Women's Health Study), ≥2 drinks/day was associated with a 60% increased risk for AF (22). Even light to moderate alcohol consumption may increase the risk for AF. The Danish Diet, Cancer, and Health study found that moderate alcohol intake (about 1.5 drinks daily) increased AF risk by 25% to 46% among men (23). Studies among patients at high risk for cardiovascular disease reported that moderate alcohol intake may cause a 14% increase in the relative risk for AF (24). A more recent meta-analysis that included prospective studies reported that each additional drink per day was associated with an estimated 8% increase in relative risk for AF in both men and women. The relationship between alcohol consumption and risk for AF appeared to be linear, and there was no drink threshold below which alcohol consumption was safe (19). **Table 1** summarizes the impact of different amounts of alcohol drinking.

In summary, current data consistently indicate that alcohol consumption increases the risk for AF. Given the popularity of unhealthy drinking, a non-negligible proportion of AF can be prevented if unhealthy drinking is avoided.

PHYSICAL ACTIVITY AND CARDIORESPIRATORY FITNESS. Evidence is accumulating that physical activity (PA) and cardiorespiratory fitness (CRF) are closely associated with the risk for AF development. However, the association varies among different populations and at different dosages.

Walking and bicycling are considered low- to moderate-intensity PA, whereas leisure-time exercise, such as running, soccer, and swimming, among others, is considered moderate- to high-intensity PA. In a Swedish male cohort, retrospectively reported leisure-time exercise for >5 h/week at 30 years of age was associated with a higher risk for AF (relative risk: 1.17; 95% confidence interval [CI]: 1.03 to 1.32) compared with those who reported exercising <1 h/week, whereas leisure-time exercise at 45 to 79 years of age was not associated with risk for AF. Walking and/or bicycling at 30 years of age was not associated with risk for AF. In contrast, walking or bicycling at 45 to 79 years of age was inversely associated with risk for AF (relative risk: 0.87; 95% CI: 0.77 to 0.97 for >1 h/day vs. almost never) (25). Another Swedish cohort reported that in women, there was no association between leisure-time exercise or walking and/or bicycling at 30 years of age and risk for AF, whereas both leisure-time exercise and walking and/or bicycling at 49 to 83 years of age were inversely associated with risk for AF (26). The differences between men and women, and between different ages, could be explained by differences in exercise intensity, atrial remodeling, and autonomic tone. The protective effect of PA was also observed in the Women's Health Initiative Observational Study, in which 93,676 post-menopausal women were followed for an average of 11.5 years. After adjustment for other risk factors, PA of >9 metabolic equivalent (MET)-hours was associated with a 10% lower risk for AF (hazard ratio [HR]: 0.90; 95% CI: 0.85 to 0.96) compared with those with no PA (27).

Vigorous exercise might be associated with a higher risk for developing AF, but different studies have had conflicting results. An early study found that middle-age veterans who undertook long-term vigorous exercise had a 5.5-fold higher risk for developing lone AF than those who did not (28). Among participants in a cross-country skiing event, those who had faster finishing times and large numbers of completed races had a 20% to 29% higher risk for AF (29). However, in the Physicians' Health Study, in which 1,661 of 16,921 apparently healthy men developed AF during 12 years of follow-up, the risk for developing AF was not significantly associated with vigorous exercise after adjusting for other variables that may influence AF risk (30).

CRF is an index of health status, unlike PA. The association of CRF with risk for AF was consistent and was not reversed at higher levels of CRF. The FIT (Henry Ford Exercise Testing) Project retrospectively studied 64,561 patients who underwent treadmill stress testing. Over a 5.4-year follow-up period, the risk for incident AF was reduced by 7% with every MET achieved, after adjusting for potential

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme
AF = atrial fibrillation
ARB = angiotensin receptor blocker
BMI = body mass index
CI = confidence interval
CPAP = continuous positive airway pressure
CRF = cardiorespiratory fitness
DM = diabetes mellitus
HR = hazard ratio
MET = metabolic equivalent
OSA = obstructive sleep apnea
PA = physical activity

TABLE 1 Impact of Alcohol Drinking on Risk for Atrial Fibrillation

Study (Ref. #)	Study Type	Study Time	Sample Size (n)	AF Cases (n)	Reference Compared	Adjusted HR
Cohort of Swedish Men and Swedish Mammography Cohort (19)	Cohort study	Late 1997, follow-up 12 yrs	68,848	6,019	<1 drink/week	1.13 (95% CI: 1.05–1.22) for binge drinking, 1.01 (95% CI: 0.94–1.09) for 1–6 drinks/week, 1.07 (95% CI: 0.98–1.17) for 7–14 drinks/week, 1.14 (95% CI: 1.01–1.28) for 15–21 drinks/week, 1.39 (95% CI: 1.22–1.58) for >21 drinks/week
Copenhagen City Heart Study (20)	Cohort study	1976	16,415	1,071	<1 drink/week (spirits)	1.06 (95% CI: 0.86–1.31), 0.92 (95% CI: 0.67–1.28), 1.19 (95% CI: 0.76–1.87), and 1.47 (95% CI: 0.85–2.56) for 1–6, 7–13, 14–20, and ≥21 drinks/week for men; 0.85 (95% CI: 0.65–1.09), 1.11 (95% CI: 0.75–1.65), and 1.19 (95% CI: 0.55–2.57) for 1–6, 7–13, and ≥14 drinks/week for women
Circulatory Risk in Communities Study (21)	Cohort study	1991–1995, follow-up 6.4 yrs	8,602	296	Nondrinkers	0.89 (95% CI: 0.60–1.32), 1.19 (95% CI: 0.73–1.95), 1.36 (95% CI: 0.79–2.35), and 2.90 (95% CI: 1.61–5.23) for <23, 23–46, 46–69, and >69 g/day
WHS (22)	Cohort study	1993–2006, follow-up 12.4 yrs	34,715	653	Nondrinkers	1.05 (95% CI: 0.88–1.25), 0.84 (95% CI: 0.58–1.22), and 1.60 (95% CI: 1.13–2.25) for >0 and <1, ≥1 and <2, and ≥2 drinks/day
Danish Diet, Cancer, and Health Study (23)	Cohort study, prospective	1993–1997, follow-up 5.7 yrs	47,949	556	Lowest quintile	1.04 (95% CI: 0.73–1.49), 1.44 (95% CI: 1.04–2.01), 1.25 (95% CI: 0.89–1.76), and 1.46 (95% CI: 1.05–2.04) for quintiles 2, 3, 4, and 5 for men; 1.09 (95% CI: 0.68–1.75), 1.27 (95% CI: 0.80–2.04), 1.23 (95% CI: 0.77–1.98), and 1.14 (95% CI: 0.70–1.85) for quintiles 2, 3, 4, and 5 for women
ONTARGET and TRANSCEND (24)	2 antihypertensive drug treatment trials	2001–2004	30,433	2,093	<1 drink/week	1.14 (95% CI: 1.04–1.26) for 1–21 drinks/week for men and 1–14 drinks/week for women; 1.32 (95% CI: 0.97–1.80) for >3 drinks/d for men and >2 drinks/day for women
Meta-analysis (19)	7 prospective studies	–	180,652	12,554	Nondrinkers	1.08 (95% CI: 1.06–1.10) per 1 drink/day increment in alcohol consumption

AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio; ONTARGET = Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; TRANSCEND = Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease; WHS = Women's Health Study.

confounders (HR: 0.93; 95% CI: 0.92 to 0.94) (31). The inverse association between CRF and incident AF was also reported in another study (32). Compared with the first CRF quartile, HRs for the risk for AF were 0.88 (95% CI: 0.65 to 1.19), 0.70 (95% CI: 0.49 to 0.99), and 0.98 (95% CI: 0.66 to 1.43) for the second to fourth quartiles, after adjustment for other risk factors (32). An exercise program to enhance CRF proved effective in reducing the burden of AF in obese patients with paroxysmal or persistent AF. Patients who gained ≥2 METs after the training program had a significantly lower recurrence rate: AF recurrence decreased by 10% for each MET gained, after adjustment for baseline CRF and weight loss (HR: 0.90; 95% CI: 0.83 to 1.00) (33). **Table 2** summarizes the impact of exercise and CRF on AF risk.

In summary, current data suggest that although vigorous exercise might be associated with increased AF risk, moderate PA is protective. Avoiding a sedentary lifestyle should be considered an important way to avoid the hazards of AF.

PSYCHOSOCIAL FACTORS. Emotional stress was only recently identified as a risk factor for AF development. In the Framingham Offspring Study, trait anger, hostility, and symptoms of anger increased AF risk in men by 10%, 30%, and 20%, respectively. However, this relationship was not found among women, possibly because of the low event rate (34). The study also found that tension was associated with a higher risk for AF (relative risk: 1.24; 95% CI: 1.04 to 1.48) (35). Similar results were reported in several other studies. Panic disorder was also reported to be associated with a 73% higher risk for AF development during 7 years of follow-up (36). In a longitudinal Swedish general population, high job strain was associated with an increased risk for AF (HR: 1.23; 95% CI: 0.84 to 1.82) (37). A survey of 100 patients with idiopathic paroxysmal AF showed that

TABLE 2 Impact of Exercise and Cardiorespiratory Fitness on Development of Atrial Fibrillation

Study (Ref. #)	Study Type	Study Time	Sample Size (n)	AF Cases (n)	Reference Compared	Adjusted HR
Drca et al. (25)	Prospective cohort study, male study population	1997–2009, mean follow-up 12 yrs	44,410	4,568	<1 h/week leisure-time exercise and almost never walking/bicycling at 30 yrs of age and at 45–79 yrs of age	1.17 (95% CI: 1.03–1.32) and 1.00 (95% CI: 0.90–1.12) for leisure-time exercise for >5 h/week at age 30 and at ages 45–79; 1.04 (95% CI: 0.90–1.20) and 0.87 (95% CI: 0.77–0.97) for walking and/or bicycling >1 h/day at age 30 and at ages 45–79
Swedish Mammography Cohort (26)	Prospective cohort study, female study population	1998–2009, mean follow-up 12 yrs	36,513	2,915	<1 h/week leisure-time exercise and almost never walking/bicycling at age 30 and at ages 49–83 yrs	1.00 (95% CI: 0.86–1.16) and 0.85 (95% CI: 0.75–0.95) for exercise ≥4 h/week at age 30 and at ages 49–83; 0.97 (95% CI: 0.78–1.21) and 0.81 (95% CI: 0.72–0.92) for walking and/or bicycling >40 min/day at ages 30 and 49–83
Women's Health Initiative Observational Study (27)	Prospective cohort study	1994–1998, follow-up 11.5 yrs	93,676	9,792	No activity	0.98 (95% CI: 0.91–1.06), 0.94 (95% CI: 0.88–1.01), and 0.90 (0.85–0.96) for >0 to 3, >3 to 9, and >9 MET-h/week
Andersen et al. (29)	Prospective cohort study	1989–2005, follow-up 9.7 yrs	52,755	681	Slowest group in race or completed only 1 race during 10 yrs	1.20 (95% CI: 0.93–1.55) in fastest group; 1.29 (95% CI: 1.04–1.61) in those who finished ≥5 races
Physicians' Health Study (30)	Prospective cohort study	1982–2001, follow-up 12 yrs	16,921	1,661	0 day/week of vigorous exercise	1.14 (95% CI: 0.86–1.51), 1.06 (95% CI: 0.91–1.23), 1.01 (95% CI: 0.89–1.16), and 1.16 (95% CI: 0.99–1.36) for <1, 1–2, 3–4, 5–7 days of vigorous exercise/week
FIT Project (31)	Follow-up data of adults who underwent exercise treadmill testing	1991–2009, median follow-up 5.4 yrs	64,561	4,616	1 higher MET achieved during treadmill testing	0.93 (95% CI: 0.92–0.94)
KIHD (32)	Cohort study of men with mean age 52.6 yrs	Average follow-up 19.5 yrs	1,950	305	First quartile	0.88 (95% CI: 0.65–1.19), 0.70 (95% CI: 0.49–0.99), and 0.98 (95% CI: 0.66–1.43) for second to fourth quartiles
CARDIO-FIT (33)	Cohort study	–	308	AF recurrent	Each MET gain	0.90 (95% CI: 0.83–1.00)

CARDIO-FIT = Impact of Cardiorespiratory Fitness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation; CRF = cardiorespiratory fitness; FIT = Henry Ford Exercise Testing; KIHD = Kuopio Ischaemic Heart Disease Risk Factor Study; MET = metabolic equivalent; other abbreviations as in Table 1.

psychological stress triggered 54% of AF episodes (38). Negative emotions (anger, stress, impatience, anxiety) were associated with 3- to 6-fold higher risk for AF occurrence among patients with paroxysmal AF, whereas happiness had a protective effect (HR: 0.12 after adjustment for other variables) (39). Another study also reported that "feeling happy some and/or a good bit of the time" was associated with a 30% lower risk for AF (40). **Table 3** summarizes the impact of unhealthy psychosocial factors on risk for AF.

In summary, data indicate a strong link between negative emotions and an increased risk for AF. These studies offer new clues for interventions that could reduce the risk for AF.

SMOKING. More recent studies have found an independent association between smoking and AF development (41–43). The Rotterdam study reported a 51% higher risk for AF development among current and former smokers (43). Even exposure to secondhand smoke during gestational development and childhood was associated with higher AF risk later in life (44). A smoker's excess risk for AF reduces after quitting (41). In the ARIC (Atherosclerosis Risk In Communities) study, current smokers, compared with never smokers, had a 2-fold higher risk for developing AF after adjusting for other variables, and the risk was lower in those who quit (HR: 1.32; 95% CI: 1.10 to 1.57). Therefore, as many as 12% of cases of AF could be avoided if current smokers were to quit (42). The impact of smoking on AF risk is summarized in **Table 4**.

In summary, although smoking is well known to be the leading cause of preventable death worldwide, it is important to realize that smoking also is a major risk factor for AF.

TABLE 3 Impact of Unhealthy Psychosocial Factors on Risk for Atrial Fibrillation

Study (Ref. #)	Study Type	Study Time	Sample Size (n)	AF Cases	Reference Compared	Adjusted HR
Framingham Offspring Study (34)	Prospective cohort study	1984–1997, follow-up 10 yrs	3,873	194	Men without trait anger, hostility, symptoms of anger	1.1 (95% CI: 1.0–1.4) for trait anger; 1.3 (95% CI: 1.1–1.5) for hostility; 1.2 (95% CI: 1.0–1.4) for symptoms of anger
Framingham Offspring Study (35)	Prospective cohort study	1984–1997, follow-up 10 yrs	3,682	194	Men without tension	1.24 (95% CI: 1.04–1.48) for tension
National Health Insurance program in Taiwan (36)	Prospective cohort study	1995–2007, follow-up 7 yrs	42,788	406	No panic disorder	1.73 (95% CI: 1.26–2.37) for panic disorder
Swedish national registry data (37)	Prospective cohort study	1974–1977, followed until death, hospital discharge, or age 75 yrs	6,035	436	Low job strain	1.23 (95% CI: 0.84–1.82) for high job strain
WHS (40)	Randomized trial post hoc analysis	1993–2010, median follow-up 125 months	30,746	771	Felt happy none or little of the time	0.69 (95% CI: 0.49–0.99) for those who felt happy some or a good bit of the time

WHS = Women's Health Study; other abbreviations as in Table 1.

CARDIOVASCULAR RISK FACTORS AND AF PREVENTION

OBESITY OR OVERWEIGHT. Roughly 14% of men and 10% of women worldwide were obese in 2013 (45). A meta-analysis of cohort studies revealed that in the general population, obesity increased the risk for AF by 49% (46). There was no significant heterogeneity among the different studies. The WHS, which was not included in the meta-analysis, reported similar results (47). In all studies, body mass index (BMI) had a linear association with AF risk: with each unit increase in BMI, AF risk increased by 4% to 8% (48). The influence of obesity on the risk for AF starts very early; even birth weight was significantly associated with AF risk later in life (49). Weight gain from age 20 to midlife is also a risk factor for AF, independent of BMI: with 16% to 35% and >35% weight gain, AF risk increased by 34% and 61%, respectively (50). It is estimated that about 18% of cases of AF could be prevented by achieving an optimal body weight (1). The impact of obesity or overweight and birth weight is summarized in Table 5.

Interventional studies have investigated the effect of weight management on AF burden and reverse remodeling of cardiac structure. By achieving a mean 14.3-kg weight reduction, AF symptom burden and severity scores and the cumulative duration and number of AF episodes all significantly improved in the intervention group (51). The same investigators reported that management of weight and other risk factors also proved effective in preventing AF recurrence after ablation therapy (52). For patients who had a 10% or greater weight loss, 3% to 9% weight loss, and those with <3% weight loss or weight gain, the probability of freedom from AF in the absence of antiarrhythmic drug or ablation therapy was 45.5%, 22.2%, and 13.4%, respectively (53). A more recently

TABLE 4 Impact of Smoking on Risk for Atrial Fibrillation

Study (Ref. #)	Study Type	Study Time	Sample Size (n)	AF Cases	Reference Compared	Adjusted HR
FHS (109)	Prospective cohort study	1968–1971, 1981–1984, 1971–1975, 1984–1987, follow-up 10 yrs	4,764	457	Nonsmokers	1.08 (95% CI: 0.88–1.33) for current smokers
Shinken Database (41)	Prospective cohort study	2004–2012, follow-up 2 yrs	15,221	190	Nonsmokers	1.81 (95% CI: 1.17–2.79) for current smokers; 1.33 (95% CI: 0.94–1.89) for those who quit smoking
ARIC (42)	Prospective cohort study	1987–2002, follow-up 13.1 yrs	15,329	876	Nonsmokers	1.32 (95% CI: 1.10–1.57) for former smokers; 2.05 (95% CI: 1.71–2.47) for current smokers
Rotterdam Study (43)	Prospective cohort study	Follow-up 7.2 yrs	5,668	371	Nonsmokers	1.51 (95% CI: 1.07–2.12) for current smokers; 1.49 (95% CI: 1.14–1.97) for former smokers

ARIC = Atherosclerosis Risk in Communities; FHS = Framingham Heart Study; other abbreviations as in Table 1.

TABLE 5 Impact of Obesity or Overweight and Birth Weight on Risk for Atrial Fibrillation

Study (Ref. #)	Study Type	Study Time	Sample Size (n)	AF Cases	Reference Compared	Adjusted HR
Meta-analysis (46)	Meta-analysis of 5 cohort studies and 11 post-cardiac surgery studies	1966–2007	123,249		Nonobese individuals	1.49 (95% CI: 1.36–1.64) for obese individuals in the general population; 1.02 (95% CI: 0.99–1.06) for obese surgery patients
WHS (47)	Randomized trial post hoc analysis	1993–2004, follow-up 12.9 yrs	34,309	834	BMI <25 kg/m^2	1.22 (95% CI: 1.02–1.45) for BMI 25–30 kg/m^2; 1.65 (95% CI: 1.36–2.00) for BMI ≥30 kg/m^2
FHS and Framingham Offspring Study (48)	Prospective cohort study	Follow-up 13.7 yrs	5,282	526	Individual with normal BMI	1.52 (95% CI: 1.09–2.13) for obese men; 1.46 (95% CI: 1.03–2.07) for obese women; 1.04 (95% CI: 1.01–1.07) per unit increase in BMI in men and in women
WHS (49)	Randomized trial post hoc analysis	1993–2004, follow-up 14.5 yrs	27,982	735	Birth weight <2.5 kg	1.27 (95% CI: 0.94–1.71), 1.10 (95% CI: 0.83–1.46), 1.41 (95% CI: 1.01–1.96), and 1.29 (95% CI: 0.84–1.98) for birth weight 2.5–3.2, 3.2–3.9, 3.9 to 4.5, and >4.5 kg, respectively
Swedish Primary Prevention Study (50)	Prospective cohort study	1970–2004	6,903	1253	No weight change from age 20 yrs to midlife (±4%)	1.11 (95% CI: 0.92–1.33) for 5%–15% gain; 1.34 (95% CI: 1.12–1.61) for 16%–35% gain; 1.61 (95% CI: 1.26–2.06) for >35% gain, respectively

BMI = body mass index; other abbreviations as in Tables 1, 3, and 4.

published study reported that weight loss through bariatric surgery may reduce the risk for incident AF by approximately one-third among persons being treated for severe obesity (54).

In summary, data have repeatedly demonstrated that overweight and obesity are independent risk factors for AF. Weight reduction would reduce the risk for AF development among overweight and obese subjects.

HIGH BLOOD PRESSURE AND INCREASED PULSE PRESSURE. Between 1980 and 2008, the number of subjects with uncontrolled blood pressure was estimated to have increased from 605 million to 978 million (55). Blood pressure is a strong and independent predictor of new-onset AF and appears to be linearly related to the incidence of AF. Cohort studies repeatedly proved that even pre-hypertensive blood pressure was associated with higher risk for AF (56–58). For every 10 mm Hg increase in systolic blood pressure, the risk for AF increased 1.11 times (59). Consequently, elevated blood pressure is the most important contributor to the burden of AF. The population-attributable risk for hypertension for AF has been estimated at 14% to 20% and at nearly one-fourth if borderline hypertension was also included (60,61).

Optimal blood pressure control significantly reduces AF occurrence in patients with hypertension. In a prospective observational study, poor blood pressure control was associated with a 7-fold higher risk for developing new-onset AF during 2 years of follow-up (62). The Cardio-Sis (Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica) study provided the most robust evidence that intensive blood pressure control reduces the risk for AF by randomly assigning patients with hypertension to either a usual blood pressure control group with a target of systolic blood pressure ≤140 mm Hg or a tight control group with target systolic blood pressure ≤130 mm Hg (63). After a median follow-up period of 2 years, the prespecified secondary outcome of new-onset AF occurred in 1.8% of participants in the tight-control group, compared with 3.8% in the usual-control group (HR: 0.46; 95% CI: 0.22 to 0.98).

Pulse pressure, a marker of aortic stiffness, is also a strong predictor of future AF. Each 20 mm Hg increase in pulse pressure was associated with a 26% increase in the risk for developing AF (64). Other studies reported similar results (65,66). The impact of blood pressure and pulse pressure increment on AF risk is summarized in **Table 6**.

Results are inconsistent as to whether angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) lower AF risk beyond their effect on blood pressure. None of the studies recruiting hypertension-only patients found any significant differences in AF incidence among the randomized treatment groups (67–71). In contrast, the

TABLE 6 Relative Risk of High Blood Pressure and Increased Pulse Pressure on Risk for Atrial Fibrillation

Study (Ref. #)	Study Type	Study Time	Sample Size (n)	AF Cases	Reference Compared	Adjusted HR
Multi-Ethnic Study of Atherosclerosis (56)	Prospective cohort study	Follow-up 5.3 yrs	5,311	182	BP <120/80 mm Hg	1.8 (95% CI: 1.004–3.2) and 2.6 (95% CI: 1.6–4.4) for BP 120–139/80–89 mm Hg and BP ≥140/90 mm Hg or antihypertensive medication use, respectively
WHS (57)	Prospective cohort study	1993–2006, follow-up 12.4 yrs	34,221	644	SBP, per 10 mm Hg increment	1.16 (95% CI: 1.09–1.23)
					DBP, per 10 mm Hg increment	1.17 (95% CI: 1.05–1.29)
					SBP <120 mm Hg	1.28 (95% CI: 1.00–1.63) for SBP 130–139 mm Hg
					DBP <65 mm Hg	1.53 (95% CI: 1.05–2.23) for DBP 85–89 mm Hg
Cohort of healthy Norwegian men (58)	Prospective cohort study	1972–2010, follow-up 35 yrs	2,014	270	Lowest quartile of SBP (88–116 mm Hg), lowest quartile of DBP (54–78 mm Hg)	1.98 (95% CI: 1.22–3.27) for SBP 128–138 mm Hg; 1.67 (95% CI: 1.00–2.85) for DBP 80–86 mm Hg
Cardiovascular Health Study (59)	Prospective cohort study	1989–1993, follow-up 3.28 yrs	4,884	304	SBP, per 10 mm Hg increment	1.11 (95% CI: 1.05–1.18)
Cardio-Sis (63)	Open-label randomized trial, nondiabetic patients with SBP ≥150 mm Hg	Median follow-up 2.0 yrs	1,111	137	Usual BP control (target SBP <140 mm Hg)	0.50 (95% CI: 0.31–0.79) for tight BP control (target SBP <130 mm Hg) group
FHS (64)	Prospective cohort study	Median follow-up 12 yrs	5,331	698	Pulse pressure, per 20 mm Hg increment	1.26 (95% CI: 1.12–1.43)
LIFE study (65)	Randomized trial	1995–2001, follow-up 4.9 yrs	8,810	353	Pulse pressure, per 15.5 mm Hg increment	1.39 (95% CI: 1.22–1.58)
Multi-Ethnic Study of Atherosclerosis (66)	Prospective cohort study	2000–2012, follow-up 4.9 yrs	3,441	307	Pulse pressure, per 17.2 mm Hg increment	1.29 (95% CI: 1.05–1.59)

BP = blood pressure; Cardio-Sis = Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica; DBP = diastolic blood pressure; LIFE = Losartan Intervention for Endpoint Reduction in Hypertension; SBP = systolic blood pressure; other abbreviations as in Tables 1, 3, and 4.

VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) study (72), which included hypertensive patients ≥50 years of age with at least 1 pre-defined cardiovascular risk or disease factor, reported a significantly lower rate of new-onset AF in the valsartan group, even though the valsartan group had a higher mean blood pressure than the amlodipine group. The LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) study also showed that losartan significantly reduced the frequency of new-onset AF in hypertensive patients with left ventricular hypertrophy compared with atenolol (73). In contrast, all randomized trials comparing ACE inhibitors or ARBs among patients with myocardial infarction or heart failure consistently identified a significant beneficial effect of ACE inhibitors or ARBs on the incidence of AF, despite the heterogeneity in their effect sizes. Patients with myocardial infarction with reduced left ventricular function who were treated with trandolapril showed a 55% lower risk for new-onset AF compared with those on placebo (74). Treatment with a combination of lisinopril and nitrates was associated with a significant 24% reduction in AF incidence among patients with myocardial infarction (75). Meta-analyses of trials comparing effects of ACE inhibitors or ARBs and placebo on AF in patients with heart failure showed that almost one-half of cases of AF could be prevented if ACE inhibitors or ARBs were consistently used in patients with heart failure (odds ratio: 0.52; 95% CI: 0.31 to 0.87) (76–79). The heterogeneity in results may be partially explained by the differences in AF risk in the clinical trial participants. **Table 7** summarizes the impact of blood pressure–lowering agents on AF risk.

In summary, data suggest that elevated blood pressure is the most important modifiable AF risk factor. ACE inhibitors and ARBs significantly reduce AF risk among those with structural and functional heart disease.

DIABETES. Diabetes mellitus (DM) is among the fastest growing public health problems. It is predicted that the number of adults with diabetes will increase worldwide from 366 million in 2011 to 552 million by 2030 (80). The association between diabetes and the risk for AF has been proved by many studies, although a causal relationship has not been established.

After correcting for publication bias, a meta-analysis of 7 prospective cohort studies and 4

TABLE 7 Impact of Blood Pressure–Lowering Agents on Risk for Atrial Fibrillation

Study (Ref. #)	Study Type	Patients	Sample Size (n)	Agents Compared	Incidence of New-Onset AF	HR
CAPPP (67)	Randomized trial, secondary endpoint	Hypertension patients ages 25–66 yrs	10,915	Captopril vs. diuretic agents or beta-blockers	11.1/1,000 patient-yrs in captopril group vs. 10.2/1,000 patient-yrs in control group	1.05 (95% CI: 0.90–1.22)
HOPE (68)	Randomized trial, post hoc analysis	Stable vascular disease, age ≥55 yrs, without heart failure or left ventricular systolic dysfunction	8,335	Ramipril vs. placebo	2.0% in ramipril group vs. 2.2% in placebo group	0.92 (95% CI: 0.68–1.24)
STOP-2 (69)	Randomized trial, secondary endpoint	Hypertensive patients ages 70–84 yrs	6,303	Enalapril/lisinopril vs. diuretic agents/ beta- blockers or calcium antagonist	9.58% in enalapril/ lisinopril group vs. 8.47% in control group	1.14 (95% CI: 0.95–1.37)
TRANSCEND (70)	Randomized trial, secondary endpoint	High-risk hypertension patients age ≥55 yrs	5,926	Telmisartan 80 mg/d or placebo	6.4% in telmisartan group vs. 6.3% in placebo group	1.02 (95% CI: 0.82–1.26)
ALLHAT (71)	Randomized trial, post hoc analysis	Hypertensive patients age ≥55 yrs with ≥1 additional CVD risk factor	25,332	12.5–25 mg/d chlorthalidone; 2.5–10 mg/d amlodipine; 10–40 mg/d lisinopril	20.9, 22.4, and 20.6/ 1,000 participants in chlorthalidone, amlodipine, and lisinopril groups, respectively	1.083 for the amlodipine and 0.939 for the lisinopril groups vs. chlorthalidone group
VALUE (72)	Randomized trial, pre-specified analysis	Hypertensive patients at high cardiovascular risk	15,245	Valsartan 80–160 mg/d vs. amlodipine 5–10 mg/d	3.67% in valsartan group; 4.34% in amlodipine group	0.843 (95% CI: 0.713–0.997)
LIFE (73)	Randomized trial, post hoc analysis	Hypertensive patients with left ventricular hypertrophy	9,193	50–100 mg/d losartan vs. 50–100 mg/d atenolol	6.8 vs. 10.1/1,000 person-yrs in losartan and atenolol groups, respectively	0.67 (95% CI: 0.55–0.83)
TRACE (74)	Randomized trial post hoc analysis	Patients with reduced left ventricular function secondary to AMI	1,577	1–2 mg/d trandolapril vs. placebo	5.3% in trandolapril group vs. 2.8% in placebo group	0.45 (95% CI: 0.26–0.76)
GISSI-3 (75)	Randomized trial post hoc analysis	Patients within 24 h of AMI	17,749	Lisinopril + nitrates; lisinopril; nitrates; double-placebo control	6.8% in lisinopril + nitrates group; 8.2% in lisinopril group; 7.6% in nitrates group; 8.7% in double-control group	0.76 (95% CI: 0.65–0.89) for lisinopril + nitrates group vs. double-placebo group
SOLVD (77)	Randomized trial post hoc analysis	LVEF <35% or overt heart failure	374	5–20 mg/d enalapril vs. placebo	5.4% in enalapril group; 24% in placebo group	0.22 (95% CI: 0.11–0.44)
Val-HeFT (78)	Randomized trial post hoc analysis	Heart failure patients	4,395	Valsartan or placebo	5.12% in valsartan group; 7.95% in placebo group	0.63 (95% CI: 0.49–0.81)
CHARM (79)	Randomized trial, secondary endpoint	Symptomatic heart failure with reduced or preserved left ventricular systolic function	6,379	Candesartan with a target dose of 32 mg/d vs. placebo	5.55% in candesartan group; 6.74% in placebo group	0.812 (95% CI: 0.662–0.998)

ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; AMI = acute myocardial infarction; CAPPP = Captopril Prevention Project; CHARM = Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CVD = cardiovascular disease; GISSI-3 = Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico 3; HOPE = Heart Outcomes Prevention Evaluation; LIFE = Losartan Intervention for Endpoint Reduction in Hypertension; LVEF = left ventricular ejection fraction; SOLVD = Studies of Left Ventricular Dysfunction; STOP-2 = Swedish Trial in Old Patients With Hypertension-2; TRACE = Trandolapril Cardiac Evaluation; Val-HeFT = Valsartan Heart Failure Trial; VALUE = Valsartan Antihypertensive Long-Term Use Evaluation; other abbreviations as in Table 1.

case-control studies showed diabetes to be associated with a 34% increased risk for AF (81). This association was supported by analysis of the impact of cumulative exposure to DM on the risk for AF. In a population-based case-control study, the risk for developing AF was 3% higher for each additional year of diabetes duration (82). Further support for a possible causal role of diabetes in AF comes from studies showing a positive linear association between glycated hemoglobin and AF risk. With each 1% increase in glycated hemoglobin, the risk for AF increased by 13% and 5% in patients with and without diabetes, respectively (83). Another study also reported a 33% increase in AF risk for each 1 mmol/l increment of fasting blood glucose (84).

However, a causal relationship between diabetes and AF was challenged by other investigators, who argued that adjustment for other AF risk factors may have been inadequate (85). Aggressive treatment with a target glycated hemoglobin level <6.0% failed to

TABLE 8 Impact of Diabetes on Risk for Atrial Fibrillation

Study (Ref. #)	Study Type	Study Time	Sample Size (n)	AF Cases (n)	Reference Compared	Adjusted HR
Group Health in United States (82)	Population-based case-control study	10/1/2001–12/31/2004	1,410 newly recognized AF cases and 2,203 controls	1,410 cases	No history of diabetes	1.07 (95% CI: 0.75–1.51) for treated diabetes <5 yrs; 1.51 (95% CI: 1.05–2.16) for >5 but ≤10 yrs; 1.64 (95% CI: 1.22–2.20) for >10 yrs; 1.03 (95% CI: 1.01–1.06) for each year treated diabetes duration
ARIC (83)	Prospective cohort study	1990–2007, follow-up 14.5 yrs	13,025; 51.4% pre-diabetes and 14.9% diabetes	1,311	HbA_{1c}, 1% increment	1.13 (95% CI: 1.07–1.20) in those with diabetes; 1.05 (95% CI: 0.96–1.15) in those without diabetes
NAVIGATOR (84)	Randomized clinical trial	Follow-up 6.5 yrs	8,943 patients with impaired glucose tolerance but not overt diabetes	613	Fasting glucose, 1 mmol/l increment	1.33 (95% CI: 1.11–1.59)
WHS (85)	Randomized clinical trial	1993–2011, follow-up 16.4 yrs	34,720	1,079	Without DM	1.95 (95% CI: 1.49–2.56) for DM in age-adjusted model; 1.37 (95% CI: 1.03–1.83) for DM in multivariate-adjusted model; 1.14 (95% CI: 0.93–1.40) for DM in time-updated model adjusted for changes in risk factors and cardiovascular events
ACCORD (86)	Randomized clinical trial intensive vs. standard glucose control	Median follow-up 4.68 yrs	10,082	159	Targeting HbA_{1c} 7.0%–7.9%	Incident rate of AF: 5.9/1,000 person-yrs in the intensive-therapy group, 6.37/1,000 person-yrs in the standard-therapy group (p = 0.52)

ACCORD = Action to Control Cardiovascular Risk in Diabetes; DM = diabetes mellitus; HbA_{1c} = glycated hemoglobin; NAVIGATOR = Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; other abbreviations as in Tables 1 and 4.

reduce the incidence of new-onset AF compared with a target of 7.0% to 7.9% (86). These results suggest that diabetes appears to be a biomarker of increased risk for AF rather than a suitable target for AF prevention. **Table 8** summarizes the impact of diabetes on AF risk.

In summary, data indicate that DM is associated with increased risk for AF, regardless of whether it is in the pathway of AF development. DM prevention may help eliminate AF risk, either directly or indirectly.

DYSLIPIDEMIA AND STATIN THERAPY. Limited and inconsistent data exist on the association of blood lipid levels with incident AF. The ARIC study reported that total cholesterol and low-density lipoprotein cholesterol, but not triglycerides and high-density lipoprotein cholesterol, were associated with the risk for AF. For each 1-SD increase in low-density lipoprotein cholesterol, AF risk was reduced by 10% (HR: 0.90; 95% CI: 0.85 to 0.96) (87). However, other studies did not find any association between blood lipids and risk for AF (88).

Statins have been extensively studied as to whether their pleiotropic effects could potentially influence the incidence of AF. Although observational studies suggested a positive association between statin use and the incidence of AF in patients with coronary heart disease or at high risk for cardiovascular disease (89–94), findings from randomized controlled trials were highly heterogeneous (71,95). A meta-analysis of published and unpublished evidence from these trials did not support the suggested beneficial effect of statins on AF (96).

In summary, data suggest that the association between blood lipid level and risk for AF, as well as the preventive effect of statins, is uncertain.

OBSTRUCTIVE SLEEP APNEA. Obstructive sleep apnea (OSA) is a common form of sleep-disordered breathing, defined as ≥5 episodes of apnea or hypopnea per hour of sleep. A survey conducted between 2007 and 2010 reported a 26% prevalence of OSA among subjects 30 to 70 years of age (97). OSA has been associated with cardiovascular diseases, including AF.

OSA was first observed to be more prevalent among patients with AF referred for cardioversion than in patients in a general cardiology practice (49% vs. 32%). After adjusting for possible confounders, the odds ratio for the association between AF and OSA was 2.19 (95% CI: 1.40 to 3.42) (98). A cause-effect

relationship between OSA and AF was established recently in a cohort study. Residents of Olmsted County, Minnesota, who underwent initial diagnostic polysomnography were followed for a mean of 4.7 years. Nocturnal oxygen desaturation, a consequence of OSA, was found to be an independent risk factor for incident AF in subjects <65 years of age (HR: 3.29; 95% CI: 1.35 to 8.04 per 0.5-U log decrease) (99). Using a case-crossover design, respiratory disturbance was observed to trigger AF episodes. The odds of AF's occurring within the 90-second hazard period following a respiratory disturbance were 17.9-fold greater than the odds of AF's occurring during normal breathing (100).

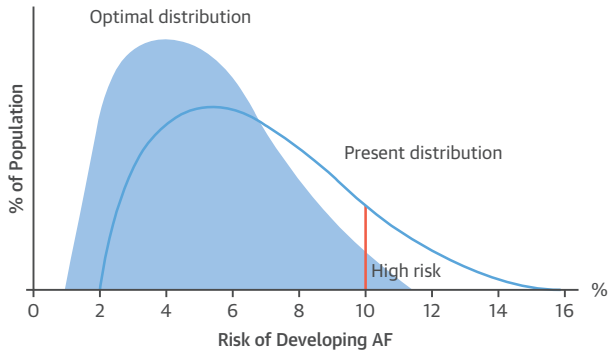
Treatment with continuous positive airway pressure (CPAP) among patients with OSA and paroxysmal AF may reduce AF recurrence. An early small study reported that at 12 months after cardioversion, AF recurrence rates were 82%, 42%, and 53% in untreated patients, CPAP-treated patients, and those without OSA, respectively (101). A recent study reported a significantly lower success rate of ablation therapy among patients with AF with OSA (36.7% vs. 66.7%), which dramatically increased to 71.9% in those treated with CPAP (102). However, both were small, observational studies. Solid evidence is still scarce.

In summary, data suggest that OSA is an important AF risk factor. However, solid evidence is lacking as to whether CPAP treatment is effective in AF prevention.

CARDIOVASCULAR DISEASES. AF frequently complicates coronary heart disease, particularly acute myocardial infarction. A 6.8% to 21% incidence of new-onset AF was reported in the reperfusion therapy era among patients hospitalized with acute myocardial infarction (103). The incidence of AF is always underestimated in patients after myocardial infarction because silent AF occurs more frequently than symptomatic AF (16% vs. 5%) (104). AF incidence after acute myocardial infarction has markedly decreased as a result of improved therapy.

Heart failure and AF are also closely related. Elevated filling pressure, atrial stretch, atrial remodeling, and an active neurohormonal system predispose heart failure patients to AF. About one-third of patients with heart failure will develop AF; conversely, one-third of patients with AF will develop heart failure (105). Heart failure is associated with a 4.5-fold increased risk for AF in men and a 5.9-fold increased risk in women (60). The risk for AF is also high in heart failure with preserved ejection fraction. A community-based study reported that AF occurred in 32% of patients who had heart failure with preserved ejection fraction over a median follow-up period of 3.7 years (106).

FIGURE 1 Population Distribution of Atrial Fibrillation Risk



Population-wide interventions could shift the distribution curve to lower risk. AF = atrial fibrillation.

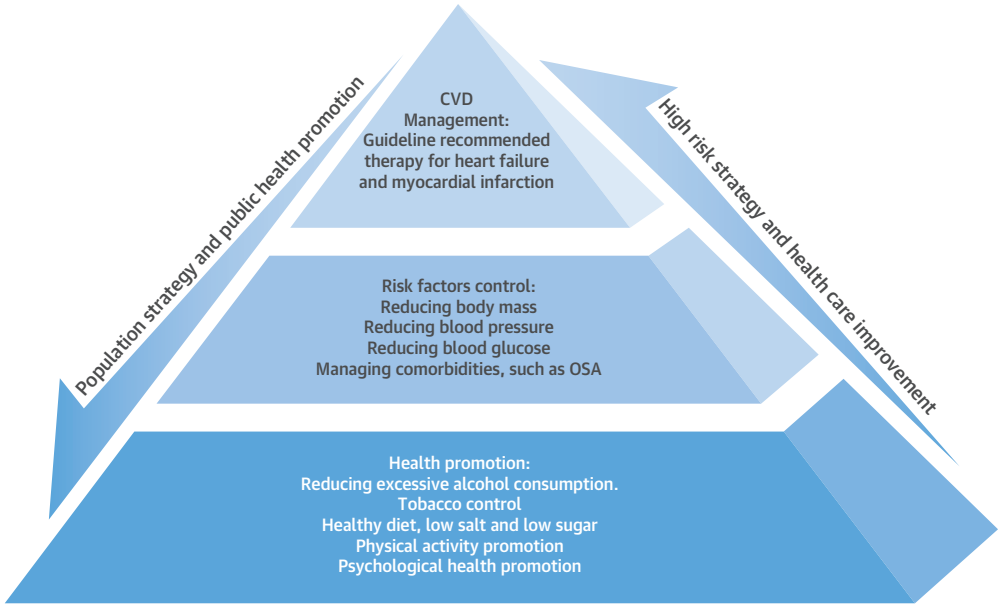
In summary, data indicate that cardiovascular diseases are closely related to AF. Prevention and proper management of cardiovascular diseases are of great importance in AF prevention.

LONE AF, FAMILIAL AF, AND AF PREVENTION

Lone AF, known as AF in younger adults with no evidence of concomitant cardiovascular diseases, accounts for 2% to 16% of all cases (107). Family history has been established as a risk factor for AF, and familial forms of AF have been described, indicating that genetic factors contribute to the risk for AF. The heritability of AF is even stronger in patients with lone AF. Mutations have been identified in ion-channel proteins and signaling molecules that are related to AF development; however, these genes are rare causes of AF, and the genetic determinants of AF in the majority of patients need to be better defined. Subjects with inherent risk factors are not destined to develop AF, and there is no doubt that genetic and environmental factors jointly influence its risk.

Although inherent risk factors are not changeable, identifying subjects with high-risk profiles enables them to minimize the overall risk by controlling their modifiable risk factors. How genetic risk may be attenuated by a favorable lifestyle in AF prevention is unknown. However, it has recently been proved that adherence to a healthy lifestyle was associated with a 50% decreased risk for incident coronary events in subjects at high genetic risk (108), suggesting that

CENTRAL ILLUSTRATION **Possible Preventability of Atrial Fibrillation**



Du, X. et al. J Am Coll Cardiol. 2017;69(15):1968–82.

The maximum possible atrial fibrillation (AF) prevention effect can be achieved by implementing interventions targeted at each level of the AF prevention pyramid. Interventions focusing on the lower level of the pyramid have a greater potential impact because they reach a broader population. CVD = cardiovascular disease; OSA = obstructive sleep apnea.

inherent high risk can be modified by adherence to healthy habits.

HIGH-RISK PREVENTION AND POPULATION PREVENTION

RISK PREDICTION AND HIGH-RISK PREVENTION. Identification of patients at high risk for AF and targeting them for preventive intervention is proposed as a more cost-effective approach to prevention that may offer substantial benefits for those high-risk subjects but will not benefit those at low risk. The motivation to change is high for high-risk subjects, whereas those at low risk need not be troubled with preventive measures. This conception can be easily accepted and adopted by doctors and patients.

However, it is difficult to predict the risk for developing AF for any subject. Although the relative risk for AF increases steeply with rising blood pressure, body weight, and other risk factors, the absolute risk is low for any subject with a known risk factor. Risk prediction models for the development of AF had been developed by integrating the known clinical risk factors (109,110). However, even the most comprehensive model, including both genetic factors and clinical AF risk factors, offers only moderate discriminatory ability (111). Even supposing that we can accurately identify all high-risk subjects, the majority of cases of AF will arise from the low-risk population, and these cases will be ignored if we focus interventions only on high-risk subjects.

POPULATION PREVENTION. As mentioned previously, many risk factors, such as blood pressure, BMI, and alcohol consumption, have linear relationships with AF risk. The risk increases progressively over the normal range, which means that those who are borderline overweight or with high normal blood pressure are already at high risk for developing AF. Small reductions in blood pressure or body weight by population-wide lifestyle modification will shift the population AF risk distribution curve to the left. This will make a big difference by shifting high-risk subjects out of the danger zone (e.g., >10% risk), and each subject will benefit from a small reduction in risk, as illustrated in **Figure 1**. In contrast, tiny increases in the mean values of blood pressure, BMI, and alcohol consumption in the whole population will increase the population risk for developing AF disproportionately.

Unfortunately, unhealthy lifestyle choices are common worldwide. According to the most up-to-date data, almost no adults in the United States meet all of the criteria for cardiovascular health metrics at ideal levels (112). The same result was also reported in the Chinese population (113).

CONCLUSIONS

Many modifiable lifestyle risk factors and concomitant cardiovascular diseases increase the risk for developing AF. The identification, prevention, and proper management of such conditions and the promotion of healthy lifestyle choices are important for the prevention of AF and its disease burden (**Central Illustration**).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: AF shares many of the same causes as atherosclerotic cardiovascular diseases. Reinforcement of healthy behaviors and improvement in cardiovascular disease and risk factor management can effectively address the increasing burden of AF.

COMPETENCY IN PATIENT CARE: Primary and secondary prevention of AF should be added to the 3 classical pillars of AF management: anticoagulation, rhythm control, and rate control.

COMPETENCY IN INTERPERSONAL AND COMMUNICATION SKILLS: It is important to discuss lifestyle modification and risk factor control for patients at high risk for developing AF.

TRANSLATIONAL OUTLOOK: Additional research is needed to understand the effectiveness of different interventions in AF prevention.

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