European Heart Rhythm Association (EHRA)/ European Association of Cardiovascular Prevention and Rehabilitation (EACPR) Position Paper on

How to Prevent Atrial Fibrillation

endorsed by the Heart Rhythm Society (HRS) and Asia Pacific Heart Rhythm Society (APHRS)

Task force: Bulent Gorenek (chair)[1], Antonio Pelliccia (co-chair)[2], Emelia J. Benjamin[3], Giuseppe Boriani[4], Harry J. Crijns[5], Richard I. Fogel[6], Isabelle C. Van Gelder[7], Martin Halle[8], Gulmira Kudaiberdieva[9], Deirdre A. Lane[10], Torben Bjerregaard Larsen[11], Gregory Y. H. Lip[12], Maja-Lisa Løchen[13], Francisco Marín[14], Josef Niebauer[15], Prashanthan Sanders[16], Lale Tokgozoglu[17], Marc A. Vos[18], David R. Van Wagoner[19]

1 Eskisehir Osmangazi University, Eskisehir, Turkey
2 Institute of Sport Medicine And Science, Rome, Italy
3 Framingham, (Massachusetts), United States of America
4 University of Modena and Reggio Emilia, Modena, Italy
5 Maastricht University Medical Centre, Maastricht, Netherlands
6 St Vincent Medical Group , Indiana, United States of America
7 University Medical Center Groningen, Netherlands
8 Technical University Munich, Prevention And Sports Medicine, Germany
9 Adana, Turkey
10 University Of Birmingham, United Kingdom
11 Aalborg University Hospital, Denmark
12 University Of Birmingham, United Kingdom
13 UiT The Arctic University of Norway, Tromso, Norway // Mary MacKillop Institute for Health Research, Centre for Research Excellence to Reduce Inequality in Heart Disease, Australian Catholic University, Melbourne, Australia
14 Hospital Universitario Virgen De La Arrixaca, Murcia, Spain
15 Paracelsus Medical University Salzburg, Austria
16 Royal Adelaide Hospital, Adelaide, South Australia
17 Hacettepe University, Ankara, Turkey
18 Umc Utrecht, Netherlands
19 Cleveland Clinic Foundation, United States of America

Document reviewers:

Laurent Fauchier[1], Irina Savelieva[2], Andreas Goette[3], Stefan Agewall[4], Chern-En Chiang[5], Márcio Figueiredo[6], Martin Stiles[7], Timm Dickfeld[8], Kristen Patton[9],

Massimo Piepoli[10], Ugo Corra[11], Pedro Manuel Marques-Vidal[12], Pompilio Faggiano[13], Jean-Paul Schmid[14], Ana Abreu[15]

1 Centre Hospitalier Universitaire Trousseau, Tours, France
2 St George's University Of London, United Kingdom
3 St. Vincenz-Krankenhaus Gmbh, Paderborn, Germany
4 Oslo Uni Hospital Ulleval, Norway
5 Taipei Veterans General Hospital, Taiwan
6 State University of Campinas, San Paolo, Brazil
7 Waikato Hospital, Hamilton, New Zealand
8 Baltimore, Maryland, United States of America
9 University of Washington, Seattle, United States of America
10 Polichirurgico Hospital G. Da Saliceto, Romagna, Italy
11 Irccs Rehabilitation Medical Center, Veruno, Italy
12 University Hospital of Lausanne, Switzerland
13 Unita' Operativa di Policardiografia, Brescia, Italy
14 Spital Tiefenau, Bern, Switzerland
15 Hospital de Santa Marta, Lisboa, Portugal

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Prof. Gregory Lip (chair), Prof. Bulent Gorenek (co-chair), Prof. Christian Sticherling, Prof. Laurent Fauchier, Prof. A. Goette, Prof. Werner Jung, Prof. Marc A Vos, Dr Michele Brignole, Dr. Christian Elsner, Prof. Gheorghe-Andrei Dan, Dr Francisco Marin, Prof. Giuseppe Boriani, Dr Deirdre Lane, Prof. Carina Blomstrom Lundqvist, Dr Irina Savelieva

Correspondence to: Prof. Bulent Gorenek MD FACC FESC
Department of Cardiology, Faculty of Medicine, Eskisehir Osmangazi University
Eskisehir-Turkey
Email: bulent@gorenek.com
Tel/Fax: +902222292266

Abstract

Atrial fibrillation (AF) is a common arrhythmia and major healthcare problem associated with increased morbidity and mortality. Several risk factors, triggers and medical disorders have been identified in the development of this arrhythmia.

To address this issue, a Task Force was convened by the European Heart Rhythm Association (EHRA) and the European Association of Cardiovascular Prevention and Rehabilitation (EACPR), endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS), with the remit to comprehensively review the published evidence available, to publish a joint consensus document on the prevention of AF, and to provide up-to-date consensus recommendations for use in clinical practice. In this document, our aim is to summarize the association of each modifiable risk factor associated with AF and the available data on the impact of possible interventions directed at these factors in preventing or reducing the burden of AF.

Key Words: Arrhythmias, Atrial Fibrillation, Prevention, Risk Factors, Obesity, Hyperlipidemia, Diet, Caffeine, Alcohol, Obstructive Sleep Apnea, Diabetes, Hypertension, Smoking, Air Pollution, Recreational Drugs, Psychological Distress, Physical Activity, Genetic Predisposition, Hyperthyroidism, Supraventricular Arrhythmias, Post-Operative Atrial Fibrillation, Therapy, Stroke, Patient preferences, Health Economics, Medications

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Abbreviations and acronyms

ACEI –angiotensin converting enzyme inhibitors
AF - atrial fibrillation
ARB- angiotensin receptor blockers
AVNRT - atrioventricular nodal re-entry tachycardia
BMI – body mass index
$CHADS_2$ – cardiac failure, hypertension, age, diabetes, stroke (doubled)
CHA_2DS_2-VASc – Congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes, Stroke/Transient Ischaemic Attack (doubled)-Vascular Disease, Age 65-74, Sex category (female)
CI – confidence interval
FU – follow-up
HR – hazard ratio
HDL - high-density lipoprotein cholesterol
ICD - implantable cardioverter defibrillators
LA – left atrium
LDL -low-density lipoprotein cholesterol
LV – left ventricle
NOAC - non-VKA oral anticoagulant
OAC – oral anticoagulation
OR – odds ratio
OSA – obstructive sleep apnea
n3-PUFA -omega-3 polyunsaturated fatty acids
RAAS- renin-angiotensin-aldosterone system
RR-relative risk
SBP - systolic blood pressure
SAMe-TT_2R_2 - Sex (female), Age (<60 years), Medical history, Treatment (interacting drugs, e.g. amiodarone for rhythm control), Tobacco use (within 2 years) (doubled), Race (non-Caucasian) (doubled)
SVT - supraventricular tachyarrhythmia
VKA – vitamin K antagonist

Introduction

Atrial fibrillation (AF) is an important and highly prevalent arrhythmia, which is associated with significantly increased morbidity and mortality, including a 4- to 5-fold increased risk for stroke (1, 2), a 2-fold increased risk for dementia (3, 4), a 3-fold risk for heart failure (2), a 2-fold increased risk for myocardial infarction (5, 6), and a 40% to 90% increased risk for overall mortality (2, 7). The constantly increasing number of AF patients and recognition of increased morbidity, mortality, impaired quality of life, safety issues and side effects of rhythm control strategies with antiarrhythmic drugs, and high health care costs associated with AF have spurred numerous investigations to develop more effective treatments for AF and its complications (8). Although AF treatment has been studied extensively, AF prevention has received relatively little attention, while it has paramount importance in prevention of morbidity and mortality, and complications associated with arrhythmia and its treatment. Current evidence shows a clear association between the presence of modifiable risk factors and the risk of developing AF.

By implementing AF risk reduction strategies aiming at risk factors such as obesity, hypertension, diabetes and obstructive sleep apnea, which are interrelated, we impact upon the escalating incidence of AF in the population and ultimately decrease the healthcare burden of associated co-morbidities of AF.

To address this issue, a Task Force was convened by the European Heart Rhythm Association (EHRA) and the European Association of Cardiovascular Prevention and Rehabilitation (EACPR), endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS), with the remit to comprehensively review the published evidence available, to publish a joint consensus document on the prevention of AF, and to provide up-to-date consensus recommendations for use in clinical practice. In this document, our aim is to summarize the current evidence on the association of each modifiable risk factor with AF and the available data on the impact of possible interventions directed at these factors in preventing or reducing the burden of AF. While the evidence on AF prevention is still emerging, the topic is not fully covered in current guidelines and some aspects are still controversial. Therefore, there is a need to provide expert recommendations for professionals participating in the care of at-risk patients and populations, with respect to addressing risk factors and lifestyle modifications.

Health economic considerations

Atrial fibrillation is a costly disease, both in terms of direct, and indirect costs, the former being reported by cost of illness studies as per-patient annual costs in the range of US $2000 to 14 200 in North America and of €450 to 3000 in Europe (9).

In individuals with AF or at risk of developing AF, any effective preventive measure, intervention on modifiable risk factors or co-morbidities, as well as any effective pharmacological or non-pharmacological treatment has the aim to reduce AF occurrence, thromboembolic events and stroke, morbidity and, possibly, mortality related to this arrhythmia. Apart from the clinical endpoints, achievement of these goals has economic significance, in terms of positive impact on direct and indirect costs and favorable cost-effectiveness at mid or long term, in the perspective of health care systems (10-12).

In view of the epidemiological profile of AF and progressive aging of the population (13), an impressive increase of patients at risk of AF or affected by AF (14), also in an asymptomatic stage, is expected in the next decades, inducing a growing financial burden on health care systems, not only in Europe and North America, but also worldwide (15, 16).

In consideration of this emerging epidemiological threat due to AF, it is worth considering a paradigm shift, going beyond the conventional approach of primary prevention based on treatment of AF risk factors, but, instead, considering the potential for "primordial" prevention, defined as prevention of the development of risk factors predisposing to AF in the first place (17). This approach, aimed at avoiding the emergence and penetration of risk factors into the population, has been proposed in general terms for the prevention of cardiovascular diseases (17) and should imply combined efforts of policymakers, regulatory and social service agencies, providers, physicians, community leaders, and consumers, in an attempt to improve social and environmental conditions, as well as individual behaviors, in the pursuit of adopting healthy lifestyle choices (16). Since a substantial proportion of incident AF events can be attributable to

elevated or borderline levels of risk factors for AF (18), this approach could be an effective way to reduce the financial burden linked to AF epidemiology. In terms of individual behavior and adoption of a "healthy lifestyle", it is worth considering that availability of full healthcare coverage (through health insurance or the health care system) may in some cases facilitate the unwanted risk of reducing, at an individual level, the motivation to adopt all the preventive measures that are advisable, in line with the complex concept of "moral hazard effect" (19). Patient education and patient empowerment are the correct strategies for avoiding this undesirable effect.

Obesity

Obesity is associated with the development of AF and has an important impact on AF-related clinical outcomes (Table 1) (20-25). A strategy of weight control may reduce the increasing incidence of AF making it an important subject in the prevention of AF (20, 26, 27) and long-term benefit for patients at risk for developing AF (28). The strongest evidence for adverse clinical outcomes comes from various large cohort studies (Table 1). The Framingham Heart Study (21) revealed that obesity is an important predictor of development of AF in adults and demonstrated via echocardiographic data, that the relationship between body size and AF is mediated by left atrial enlargement and inflammation (29) . A recent community-based study in the Netherlands confirmed that, in addition to the conventional risk factors for AF, body mass index (BMI) was strongly associated with AF with a 45% increased risk of AF with every 5 points of BMI increase (22). This study supports the notion that BMI should be regarded as a validated risk factor for incident AF (22). Indeed, obesity was the strongest contributor to incident AF in a number of studies, worldwide (22-24, 30). In the Guangzhou Biobank Cohort Study, for example, both general and central obesity were associated with increased risk of AF in an Asian population with generally much lower levels of obesity compared to Western countries (24).

A large Danish prospective population-based cohort study (25), among 55,273 men and women aged 50-64 years of age at recruitment, also confirmed the association between obesity and incident AF. In

addition, bioelectrical impedance derived measures of body composition and combinations of anthropometric measures of body fat distribution were associated with the increased risk of developing AF (25). Also, diabetes at baseline increased proportionally from 6.9% with a BMI <25 kg/m^2 to 26% in those with a BMI >30 kg/m^2 (25). This is probably important since a meta-analysis has shown that patients with diabetes had an approximately 40% greater risk of AF compared to those without diabetes (31).

The potential implications of these findings are amplified by the fact that obesity has reached epidemic proportions worldwide (32). As both AF and obesity are increasing in low and middle income countries, the results should have significant public health implications. Importantly, obesity may contribute to the risk of AF-related complications. For example, another large cohort study from Denmark has shown that the combination of overweight and AF can increase the risk of stroke and death (33), demonstrating that being either overweight or obese increases the risk for ischemic stroke, thromboembolism and death in patients with AF, even after adjustment for the $CHADS_2$ and CHA_2DS_2-VASc risk scores. However, an obesity paradox exists. As an example, The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, one of the largest multicenter trials of AF including 4,060 patients, found that obese patients with AF appear to have better long-term outcomes than non-obese patients (34).

A logical consequence of these studies is that overweight/obese patients should be informed that there is not only a risk for the commonly known consequences such as diabetes, hypertension, coronary artery disease and heart failure, but also that there is a greater risk of developing AF and a subsequent risk of stroke and death.

Table 1. Obesity and risk of AF in population cohorts. Incidences per total duration of follow-up.

Study	Design	Subjects	FU	BMI groups (kg/m^2)	AF,%	Risk* (95%CI)
Dublin et al.[23]	Population based, case-control design	1,410 cases 2,203 controls	N/A	Obese: (BMI ≥30)	N/A	OR: 1.40 (1.15-1.71)
Long et al.[24]	Nested case-control study	5,882 men 14,548 women	N/A	Overweight (BMI 23-<25) Obese (BMI ≥25)	0.8	Overweight: 1.18 (0.78–1.79), Obese: 1.47 (1.01–2.13)
Tedrow et al.[20] Women's Health Study	Prospective cohort study	34,309	12.9±1.9 yrs	Overweight (BMI 25-<30) Obese (BMI ≥30)	2.4	Overweight: HR 1.22(1.02 1.45) Obese: HR: 1.65(1.36 - 2.00)
Wang et al.[21] Framingham Heart Study	Prospective cohort study	5,282	13.7 yrs	Normal (BMI 18.5-<25) Overweight (BMI 25-<30) Obese (BMI≥30)	10.0	Obese: men 1.52 (1.09-2.13) women 1.46 (1.03-2.07)
Frost et al.[25]	Prospective cohort study	55,273	13.5 yrs	Underweight (BMI< 18.5) Normal (BMI 18.5-<25) Overweight (BMI 25-<30) Obese (BMI ≥30)	Men 3% (1,669) Women 1.6% (912)	1.29 (1.24-1.33)
Vermond et al[22]	Dutch community based cohort study	8,265	9.7 yrs	Continuous BMI	AF incidence 3.3 per 1000 person-year	BMI, per 5 kg/m^2 HR: 1.45 (1.21–1.74)

*HR per 1 sex-specific standard deviation (SD) or the adjusted HR for 1 sex-specific SD increment
AF – atrial fibrillation, BMI – body mass index, CI – confidence interval, FU – follow-up, HR – hazard ratio, N/A – not available, OR- odds ratio, pts- patients, SD – standard deviation, yrs-years

General dietary considerations

There is currently a paucity of evidence on the effect of unhealthy or extreme weight-loss diets on the development of AF (Table 2) (35-40), and therefore the association between specific dietary factors and AF is tenuous at this time. Only one study falls under this topic, by Al Suwaidi et al. (41) which enrolled 465 outpatients who were fasting during the month of Ramadan. Of the approximately 5% who had AF at enrollment, only one had to be hospital admitted. There were no reports on conversion to or from AF in other patients. All other studies refer to specific dietary habits or interventions (42), rather than to extreme diets. Other data are limited by virtue of selective reporting, multiple testing, and positive publication bias. Also, many studies are small, some are retrospective and the effect sizes of dietary exposures are modest

leading to potential residual confounding, especially since diet is inextricably linked with age, race, sex, socioeconomic status, etc.

Table 2. Relation between diet and AF

Study	Design	Subjects	FU	Intervention	AF risk (95%CI)	Comment
(a) Population cohorts						
Shen et al.[35] Framingham Heart Study	Prospective	4,526 from original and off-spring cohort; participants without AF	4 yrs	None	No association with alcohol, caffeine, fiber and fish-derived polyunsaturated fatty acids; limited attributable risk of AF>4 servings of dark fish/wk had HR 6.53 (2.65-16.06) vs. <1 serving	Alcohol, caffeine, fiber, and fish-derived polyunsaturated fatty acids were not associated with AF risk
Khawaja et al.[36] Physicians' Health Study	Prospective	21,054 men	20 yrs (median 24 yrs)	None	-	No association between nut consumption and incident AF
Fretts et al[37] Cardiovascular Health Study	Prospective	4,337 >65 yrs; no prevalent CHD or AF	up to 19 yrs	None	-	No association between plasma phospholipid or dietary alpha linoleic acid and incident AF
Costanzo et al.[38]	Prospective	217; cardiac surgery	ICU stay + 1 wk post surgery unit	None	Highest tertile of dietary total antioxidant capacity vs. 2 lowest tertiles: OR 0.46 (0.22-0.95)	Antioxidant-rich foods are associated with reduced incidence of postoperative AF
Mattioli et al.[39]	Case-control	800; 400 first detected AF episode	-	None	a) OR 1.9 (1.58-2.81) b) OR 1.8 (1.56-2.99)	a) Lower adherence to Mediterranean diet and lower antioxidant intake in patients with AF compared to control population; b) Patients with arrhythmia who had higher Mediterranean score had higher probability of spontaneous conversion from AF to sinus rhythm
Pastori et al.[40]	Prospective	709 anticoagula-ted pts with AF	39.9 months	None	-	Reduction in CV events; antioxidant effects such as down-regulation of NOX2 and decreased excretion of F2-isoprostanes
(b)Intervention studies						
Martínez-González et al.[42] PREDIMED-Prevención con Dieta Mediterránea	Randomized primary prevention trial; post-hoc analysis	6,705	Median 4.7 yrs	3 diets: Mediterranean diet enriched with extra virgin olive oil or mixed nuts; control group	Mediterranean diet enriched with extra virgin olive oil vs mixed nuts; HR 0.89 (0.65-1.2) Mediterranean diet enriched with extra virgin olive oil vs control group: HR 0.62 (0.45-0.85)	Mediterranean diet with olive oil reduced AF risk compared with control group, however with no effect in a group with nuts Reduced incidence of stroke, myocardial infarction, and CV mortality; consumption of extra virgin olive oil but not nuts was associated with a lower risk of AF

AF – atrial fibrillation, CHD – coronary heart disease, CI – confidence interval, CV- cardiovascular, FU – follow-up, HR – hazard ratio, ICU – intensive care unit, OR- odds ratio, pts-patients, wk-week, yrs-years

Blood lipids and fish consumption

Among the modifiable risk factors that can be targeted for AF prevention, caloric intake and physical activity are critical factors that significantly impact weight, blood pressure, risk of diabetes mellitus and atherosclerosis, and atrial structure/function (43).

What is the impact of blood lipids on risk of AF?

Table 3A summarizes two recent cohort-based studies that evaluated the association of blood lipid components with the development of AF during follow-up (44, 45). In both, with adjustments for age, sex, and race, but no adjustment for BMI, low levels of HDL cholesterol and high levels of plasma triglycerides were associated with increased risk of AF. Low-density lipoprotein cholesterol levels (LDL) were not associated with AF risk in either study; elevated total cholesterol was associated with risk of AF in one study (44). Both studies note the impact of comorbid conditions confounding the association of blood lipid levels with AF risk. Thus, evidence for selectively targeting lower plasma LDL or total cholesterol as a means of reducing AF risk is weak.

Despite the uncertain association of lipids with incident AF, there is evidence that statins protect against AF in patients with chronic stable coronary artery disease, independently of reductions in plasma total cholesterol level (46). In experimental studies, statin use protected against electrical remodeling associated with atrial tachycardia pacing (47) and decreased AF inducibility in a canine model of sterile pericarditis (48). Recent meta-analyses suggest that statins reduce new onset AF following cardiac surgery, a setting in which inflammatory processes are strongly implicated in AF onset (49, 50). In contrast to the post-surgical setting, large meta-analyses have not demonstrated the efficacy of statins for primary prevention of AF, whilst a heterogeneous benefit is reported for secondary AF prevention (51, 52). Statins, which impact oxidant and inflammatory mechanisms in addition to lowering plasma LDL levels, most likely attenuate AF risk primarily due to effects independent of LDL reduction.

In recognition of this “uncoupling,” recent ACC/AHA guidelines for prevention of coronary heart disease have changed from a primary focus on specific LDL target levels to one that focuses on the overall risk factor profile of the patient (53). A similar logic may apply to AF prevention as well.

Dietary fish consumption vs. studies with fish oil supplements

Older epidemiologic studies have suggested that consumption of fatty fish is associated with significant health benefits, including reduced risk of AF (54). One recent study in the USA (Table 3B) noted a non-significant trend for a lower incidence of AF with higher intake of fatty fish (p=0.09) (55). Fish oil is enriched in omega-3 polyunsaturated fatty acids (ω3-PUFA), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA). The Kuopio Study found a trend for the highest vs. lowest quartile of plasma EPA+DHA+DPA to be associated with lower risk of AF (p=0.07). This relationship was modestly significant for DHA (p=0.02) (56). A retrospective analysis of a large Danish cohort (n=55,246), which was a population with high fish consumption, suggests that the relationship between fish consumption and AF risk is more complex and U-shaped, with both low- and high-levels of either fatty fish consumption or consumption of the individual omega-3-fatty acids associated with increased risk of AF (57). Also, in the Danish population (Table 3B), analysis of adipose DHA and EPA content identified non-significant trends for benefit with elevated levels of both DHA and EPA (58). An obvious and important confounding factor is the individual burden of adiposity.

While fish oil extracts have demonstrated significant effects on the development of atrial fibrosis in the setting of experimental heart failure (59), and on the inducibility of AF after experimental cardiac surgery (60), highly purified n3-PUFA supplements, often formulated as ethyl esters, have demonstrated either poor or no efficacy in randomized clinical trials for the prevention of new onset AF following cardiac surgery (61), or for prevention of AF recurrence (62, 63) It remains unclear if the lack of efficacy is related to differences in bioavailability (64), to loss of other components in fish that are functionally important, or to intrinsic differences between studies in younger experimental animals and those in older patients at greatest risk of AF. At present, there is no compelling argument for the use of commercially available fish oil supplements for either primary or secondary AF prevention (65, 66).

On the basis of the available epidemiologic studies, the current AHA/ACC guidelines for individuals with elevated blood LDL levels now recommends consumption of a diet "that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils, and nuts; and limits intake of sweets, sugar-sweetened beverages, and red meats" (66).

While quite reasonable, this and other similar guidelines do not specifically address diet in relation to AF risk. Lacking direct evidence, the above dietary suggestions coupled with an emphasis on physical activity and maintenance of a healthy lifestyle and weight seem reasonable as interim guidance for AF patients, and for those with significant risk of AF.

Table 3. Relationship of blood lipids, fish and n-3 polyunsaturated fatty acids to incident AF risk per total duration of follow-up.

Study	Design	Subjects	FU, yrs	LDL/ HDL, TG, TC levels	AF, n(%)	Risk HR (95% CI), p-value
(a) Blood lipids						
Lopez et al.[44] ARIC	Community cohort study; baseline age – 45-64 yrs	13,969	18.7	HDL ≥60 mg/dL, vs. ≤40 mg/dL TC >240 mg/dL vs. <200 mg/dL TGs ≥200 mg/dL vs. ≤150 mg/dL LDL (not significant)	1,433 (10.25)	0.63 (0.53-0.74),* p<0.0001 0.89 (0.77-1.02), p=0.03 1.4 (1.21-1.62), p<0.0001
Alonso et al.[45] MESA Framingham Heart Study	Community cohorts; average baseline age 60.5 yrs (10)	7,142	9.6	HDL ≥60 mg/dL, vs. ≤40 mg/dL TGs ≥200 mg/dL vs. ≤150 mg/dL TC, LDL not significant	480 (6.7)	0.64 (0.48-0.87) 1.6 (1.25, 2.05)
(b) Fish intake and plasma n-3 fatty acid levels						
Gronroos et al.[55] ARIC	Community cohort study, baseline age 45-64 yrs	14,222	17.6	Intake of canned tuna/oily fish > 2/week, vs. none Dietary DHA+EPA (Q4 vs. Q1) Plasma DHA+EPA (Q4 vs. Q1) Plasma DHA (Q4 vs. Q1) Plasma EPA (Q4 vs. Q1)	1,604 (11.3)	0.86 (0.72-1.03), p=0.09 0.95 (0.82-1.10)*, p=0.42 0.79 (0.60, 1.03), p=0.18 0.74 (0.57, 0.97), p=0.10 1.12 (0.85, 1.49), p=0.33
Rix et al.[57] Danish Diet, Cancer and Health cohort study	Cohort study, baseline ages 50-64 yrs	57,053	13.6	Dietary intake: Q1 (<0.39 g/day) Q2 vs. Q1 Q3 vs. Q1 Q4 vs. Q1 Q5 vs. Q1	3,345 (5.9)	 1 0.92 (0.82-1.03), p=0.16 0.87 (0.78-0.98), p=0.02 0.96 (0.86-1.08), p=0.49 1.05 (0.93-1.18), p=0.42
Rix et al.[58] Danish Diet, Cancer and Health cohort study	Cohort study, baseline ages 50-64 yrs	3,440 with adipose tissue specimens	13.6	Total adipose n3-PUFA T2 vs. T1 T3 vs. T1 Adipose DHA T2 vs. T1 T3 vs. T1 Adipose EPA T2 vs. T1 T3 vs. T1	179 (5.2)	 0.87 (0.60-1.24) 0.77 (0.53-1.1) 1.03 (0.73-1.46) 0.73 (0.5-1.06) 0.67 (0.46-0.99) 0.86 (0.61-1.22)
Virtanen et al.[56] Kuopio Ischemic Heart Disease Risk Factor Study	Cohort study, baseline ages 42-60 years	1,941 with serum specimens	17.7	Plasma DHA+EPA+DPA Q2 vs. Q1 Q3 vs. Q1 Q4 vs. Q1 Plasma DHA (Q4 vs. Q1) Plasma EPA (Q4 vs. Q1)	240 (11.0)	 0.65 (0.46-0.93) 0.82 (0.58-1.14) 0.65 (0.46-0.93) 0.64 (0.45-0.92) 0.93 (0.0.65-1.33)

*corrected only for age, sex, race
AF – atrial fibrillation, CI – confidence interval, DHA - docosahexaenoic acid, FU – follow-up, HDL – high-density lipoprotein cholesterol, HR – hazard ratio, EPA - eicosapentaenoic acid, LDL – low-density lipoprotein cholesterol, n3-PUFA -omega-3 polyunsaturated fatty acids, Q-quartile, T- tertile, TC- total cholesterol, TG-

triglyceride, yrs- years

Obstructive sleep apnea

Sleep related breathing disorders are common and approximately 25% of adults are at risk for sleep apnea of some degree (67), with obstructive sleep apnea (OSA) commonly seen in patients with cardiovascular diseases, especially in obese patients and those with type 2 diabetes mellitus (68). Various studies have established that patients with OSA, particularly those with more severe disease, are significantly more likely to develop AF, and patients with AF have about twice the risk for developing OSA (Table 4) (69, 70).

Patients with AF and those with OSA share several similar characteristics. For example, hypertension is common (one third of OSA) in both conditions, and both occur more frequently in men and increase with advancing age (68). Furthermore, increasing BMI plays an important role in development of both obstructive sleep apnea and AF (28, 71).

The mechanisms for this may be multifactorial, but autonomic dysregulation may connect sleep apnea and AF, independent of other known risk factors. This has been confirmed experimentally in dogs (72) and clinically (73). In a prospective cohort study (73), a relationship among the severity of sleep apnea syndrome, cardiac arrhythmias, and autonomic imbalance was demonstrated.

These observations may have important clinical implications, and large observational studies suggest that OSA may be a modifiable risk factor for recurrent AF after cardioversion or ablation (74, 75). Furthermore, some data support a role for continued positive airway pressure (CPAP) therapy in abolishing nocturnal ventricular asystole and improving other arrhythmias in patients with obstructive sleep apnea (76-78, 79). CPAP therapy was effective in several other studies (80-83), but not in heart failure patients (84).

Based on the evidence, routine screening for OSA and other sleep related breathing disorders in general practice and in cardiac rehabilitation programs may be considered if clinically indicated. More data

are needed to show the benefit of prevention and treatment of OSA and associated improvement of AF incidence, recurrence rate and outcomes in patients with new onset or recurrent AF.

Table 4. Incident risk of AF in obstructive sleep apnea per total duration of follow-up.

Study	Design	Subjects	FU, yrs	OSA, n (%)	AF,%	Risk (95%CI)
Gami et al.[69]	Olmsted County cohort study	3,542	4.7	2626 (74)	14.0	HR 2.18 (1.34- 3.54)
Cadby et al.[70]	Sleep-clinic cohort study	6,841	11.9	100%	6.7	HR 1.55 (1.21- 2.00)

AF – atrial fibrillation, CI – confidence interval, FU – follow-up, HR – hazard ratio, OSA- obstructive sleep apnea, pts- patients, yrs – years

Hypertension

Hypertension is a major risk factor for AF (Table 5). In the Framingham Heart Study (85) the odds ratios for the development of AF in men and women with hypertension were 1.5 and 1.4, respectively. Data from the Atherosclerotic Risk in Communities Study (18) show that approximately one fifth of the risk of developing AF was attributable to hypertension. The optimal systolic blood pressure appears to be 120-130 mm Hg with both higher and lower blood pressures associated with an increased incidence of AF (22, 86, 87).

Proposed mechanisms include sympathetic activation, activation of the renin-angiotensin-aldosterone system, atrial dilation, fibrosis and left ventricular remodeling including diastolic dysfunction and left ventricular hypertrophy (43). Hypertension may also lead to coronary disease and myocardial infarction, subsequently increasing the risk for AF. Alcohol consumption is also a common predisposing factor to both AF and hypertension.

For the primary prevention of AF in a hypertensive population, the optimal on-treatment systolic BP goal appears to be <130 mmHg (88). Nevertheless, it remains unclear whether different antihypertensive medications affect the development of AF independent of blood pressure reduction. In the Losartan

Intervention for End Point Reduction in Hypertension Study (89), for example, new onset AF occurred less frequently in patients treated with losartan compared to patients treated with atenolol, although blood pressure reduction was similar in both groups. In another study (90), ACE inhibitors and angiotensin II-receptor blocker (ARB) were superior to beta-blockers and diuretics for the primary prevention of AF. These two studies suggest that the inhibition of the renin-angiotensin system may be associated with a decreased risk of new onset AF, incremental to the effect of BP reduction alone.

ARB therapy has also been studied for the secondary prevention of AF. For example, the GISSI-AF study (91) evaluated the secondary prevention of AF using valsartan, but was not superior to placebo. Follow-up was only for one year and it remains possible that the beneficial effects of ARBs on atrial remodeling might be seen with a longer study duration (92). In the ANTIPAF trial (93), olmesartan did not decrease AF burden compared to placebo in patients without structural heart disease.

Additionally, Lip and colleagues (94), retrospectively analyzing data from the SPORTIF III and SPORTIF V trials, found that ACEI and ARBs did not result in any difference in stroke or systemic embolism in a controlled, anticoagulated AF population. Mortality was lower in the AF population over 75 years of age treated with ACEI or ARBs.

The role of aldosterone antagonists in the treatment of AF has been evaluated in the setting of heart failure (95), but not in its absence. Given the increasing incidence of AF, additional well-conducted studies are needed to clarify the impact of renin-angiotensin-aldosterone system (RAAS) inhibitors on both the primary and secondary prevention of AF (8, 96).

Table 5. Hypertension and risk of AF

Study	Design	Subjects	FU	BP levels, mmHg/ Treatment	AF	Risk (95% CI)
AF Incidence Trials						
Benjamin et al.[85] Framingham Heart Study	Cohort	2,090 men 2,641 women	38 yrs	SBP > 160 DBP > 95		OR for AF Men 1.5 (1.2-2.0) Women 1.4 (1.1-1.8)
Huxley et al.[18] ARIC Study	Cohort	14,598	17.1 yrs	SBP > 140 DBP > 90		21.6% (16.8-26.7) of risk of AF is attributable to HT
Thomas et al.[86]	Case - Control	433 pts with AF 899	20 yrs (median)	SBP < 120 120-129 130-139		OR 1.99 (1.10-3.62) Reference 1.19 (0.78-1.81)

		Controls		140-149 150-159 160-169 >170		1.40 (0.93-2.09) 2.02 (1.30-3.15) 2.27 (1.31-3.93) 1.84 (0.89-3.80)
Vermond et al.[22]	Dutch community based cohort study	8,265	9.7 yrs	Per 10 mm SBP	AF incidence 3.3 per 1000 person-year	SBP, per 10 mm Hg HR 1.11 (1.01–1.22)
Intervention Trials						
Primary Prevention						
Wachtell et al.[89] LIFE Study	Randomized, double blind comparison of losartan vs. atenolol	Losartan 4,298 Atenolol 4,182	4.8 yrs (mean)	Losartan Atenolol	New AF 150 New AF 221	RR 0.67 (0.55-0.83)
Marott er al.[90]	Registry analysis: Comparison of AF incidence in pts with HT treated with ACEI and ARB compared to BB, diuretics and CCB	725,680 Danish pts treated with anti-HT monotherapy	5.9 – 6.8 yrs depending on comparison	ACEI vs BB ARB vs BB ACEI vs diuretic ARB vs diuretic ACEI vs CCB ARB vs CCB		0.12 (0.10-0.15) 0.10 (0.07- 0.14) 0.51 (0.44-0.59) 0.43 (0.32- 0.58) 0.97(0.81- 1.16) 0.78 (0.56- 1.08)
Okin et al.[88]	Analysis of the effect of BP reduction using losartan or atenolol (randomly assigned) on the risk of new AF	8831patients with HT, ECG evidence of LVH and no history of AF	4.6 yrs	SBP < 130 SBP 131-141 SBP > 142	Overall new AF in 701 pts (7.9%)	Compared to SBP > 142, SBP < 130 is associated with 40% lower risk of AF (18%-55%). Compared to SBP > 131-141, SBP < 130 is associated with 24% lower risk of AF (7%-38%).
Secondary Prevention						
GISSI-AF[91]	Randomized double blind comparison of valsartan vs placebo for prevention of recurrent AF	1,442 pts Valsartan 722 Placebo 720	1 year	Valsartan Placebo	Recurrent AF 371 (51.4%) Recurrent AF 375 (52.1%)	HR 0.97 (0.83-1.14)
ANTIPAF[93]	Randomized double blind comparison of olmesartan vs placebo for prevention of recurrent AF burden	425 pts w/o structural heart disease. Approx. 49% with htn	12 months	Olmesartan Placebo	% of AF days 15.1% % of AF days 14.7%	No difference (p=0.77)

Lip et al.[94]	Retrospective longitudinal analysis of participants in SPORTIF III and V trials. Comparison of clinical event rates and mortality in ACEI and ARB users compared to non-users in an anti-coagulated AF population	4,760 ACEI or ARB users 2,569 ACEI or ARB non-users	18.7 months ACEI ARB users 18.4 months ACEI ARB non-users	ACEI-ARB users ACEI-ARB non-users		No difference in stroke, systemic embolic event, or mortality in ACEI, ARB users compared to non-users in the entire cohort For age > 75 years lower mortality in ACEI or ARB users compared to non-users: HR 0.71 (0.52-0.95)

ACEI – angiotensin-converting enzyme inhibitor, AF – atrial fibrillation, ARB – angiotensin receptor blocker, BB – beta-blocker, BP – blood pressure, CCB- calcium channel blocker, CI – confidence interval, DBP – diastolic blood pressure, FU – follow-up, HR – hazard ratio, HT – hypertension, OR – odds ratio, pts- patients, RR – relative risk, SBP – systolic blood pressure, yrs – years

Diabetes Mellitus

Diabetes and elevated blood glucose have been recognized for several years as potential risk factors for AF, although there are conflicting results (97) (Table 6). Multiple studies (31, 85, 98-104) report an increased incidence of AF in patients with diabetes. However, there are methodological differences that make comparisons among studies difficult. In particular, some studies adjusted the results for confounding variables including obesity and hypertension, while others did not. When these other risk factors were considered, the risk attributable to the development of AF from diabetes was limited. In a meta-analysis of seven cohort studies and 4 case control studies including more than 1,600,000 subjects, Huxley et al. (31) found that patients with diabetes had a 39% greater risk of developing AF compared to individuals without diabetes. In studies that adjusted the risk for confounding variables, the relative risk decreased to 1.24 (95% CI 1.06 to 1.44).

Using a population based, case-control design, Dublin et al. (104) found that patients with longer durations of diabetes had a greater risk of AF development. Specifically, the risk of AF was 3% higher for each year of diabetes treatment, and the risk of AF correlated with worsened glycemic control. Hence, better glycemic control (as measured by hemoglobin A_{1c}) was associated with a lower risk of AF development.

High basal hemoglobin A_{1c} level, increased body mass index and advanced age were also associated with higher recurrence of AF after catheter ablation in patients with diabetes (105).

Recently, investigators using the Taiwan National Health Insurance Research Database developed a time-dependent Cox proportional hazard model to study the effects of metformin on the development of AF (106). The study population included 645,710 patients with diabetes taking metformin but not other diabetic medications. Over a 13-year follow-up, fewer patients taking metformin developed AF, suggesting that metformin had a protective effect on the development of AF in diabetic patients.

Additionally, the duration of diabetes appears to be related to a higher risk of thromboembolic events in patients with AF. Using data from multiple Danish registries, Overvad et al. (107) identified 13,722 patients with AF, 12.4% of whom had diabetes. Compared to AF patients without diabetes, thromboembolism was more prevalent and this relationship was time-dependent with longer diabetes duration being associated with higher rates of thromboembolism and death. A longer diabetes duration was not associated with an increased risk of bleeding among AF patients treated with vitamin K antagonists.

In summary, diabetes appears to confer an increased risk for the development of AF, but this risk seems less than for other factors including hypertension, obesity and smoking (18). Furthermore, a longer diabetes duration and worse glycemic control increases the risk for AF and its complications, and in one retrospective study (106), treatment with metformin appeared to reduce this risk.

Table 6. Diabetes and risk of AF

Study	Design	Subjects	FU	FBG or HbA1c levels/DM duration	AF	Risk (95% CI)
Incidence						
Benjamin et al.[85] Framingham Heart Study	Cohort	2,090 men 2,641 women	38 yrs	FBG >140 mg/dl Non-fasting BG >200 mg/dl		OR for AF Men 1.4 (1.0-2.0) Women 1.6 (1.1- 2.2) After adjustment for valve disease Men 1.1 (0.8- 1.7) Women 1.5 (1.0- 2.3)
Alonso et al.[98]	Meta-analysis of 3 cohorts: ARIC, CVH and FHS	18,556 pts				HR 1.27 (1.10, 1.46) for 5- year AF risk in pts with DM

Huxley et al.[99] ARIC Study	Cohort	13,025	14.5 yrs	FBG > 126 mg/dl or HbA1c > 6.5% or use of diabetic meds		Diabetes is associated with increased incidence of AF: HR 1.35 (1.14-1.60) HbA1c levels are independently associated with AF: HR 1.13(1.01-1.20) per 1% increase in HbA1c level
Ostgren et al.[100]	Cohort	171 HT + DM 147 DM only 597 HT only 825 no HT or DM		FBG > 6.6 mmol/l or 2hr glucose after oral glucose tolerance test > 11.0 mmol/l		HT + DM: OR 3.3 (1.6-6.7) DM only: OR 2.0 (0.9-4.7) HT only: OR 0.7 (0.3-1.5) Reference no HT or DM: ORR 1.0
Pfister et al.[101]	Analysis of development of new AF in the PROactive trial	5233 pt with DM	36 months			Incidence of new AF at: 12 months - 0.8% 24 months - 1.5% 36months – 2.4%
Schoen et al.[102] Womens Health Study	Cohort	34,720 women health professionals	16.4 years		At baseline 937 (2.75%) had DM	Compared to women without DM, women with DM had HR for new AF of 1.95 (1.49-2.56). In models that adjusted for HT, obesity (BMI) and inter-current cardiovascular events, HR for new AF decreased to 1.14 (0.93-1.40)
Dublin et al.[104]	Case-control	1,410 new AF pts 2,203 control pts	21 yrs - AF pts 20 yrs - control pts	 HbA1c <7% HbA1c 7-8% HbA1c 8-9% HbA1c > 9%	252 (17.9%) AF pts had DM 311 (14.1%) control pts had DM	OR for AF 1.40 (1.15-1.71) for pts with DM compared to those without DM Compared to pts without DM risk (OR): 1.06 (0.74-1.51) 1.48 (1.09-2.01) 1.46 (1.02-2.08) 1.96 (1.22-3.14)
Aksnes et al. [103] VALUE Trial	Prospective randomized trial comparing valsartan and amlodipine for treatment of htn	15,245 total pts with htn 5,250 diabetes at baseline 1,298 developed diabetes during FU	4.2 yrs	FBG >140 mg/dl	551 pts developed AF during the trial	HR 1.49 (1.14, 1.94) new onset diabetes for development of AF HR 1.19 (0.99, 1.42) baseline diabetes for development of AF
Huxley et al. [31]	Meta-analysis of cohort (7) and case control (4) studies.	1,686,097 subjects combined allstudies				RR of pts with DM for AF: 1.39 (1.10 – 1.75) Studies with adjustment for other risk factors, RR of pts with DM for AF: 1.24 (1.06 – 1.44)
Intervention Trials						
Chang et al.[106]	Registry	645,710 pts with diabetes	13 yrs		9983 pts developed AF, incidence rate 1.5% (287/100000 person/yrs)	Metformin use protected against the development of AF, HR 0.81 (0.76- 0.86)

Overvad et al.[107]	Registry	137,222 pts with AF		No DM 120204 DM 0-4 yrs 7922 DM 5-9 yrs 4781 DM 10-14 yrs 2435 DM > 15 yrs 1880		Risk of thromboembolism or death No DM Reference 1.0 HR 1.24 (1.20-1.29) HR 1.42 (1.37-1.48) HR 1.45 (1.37-1.53) HR 1.72 (1.62-1.82)
ARIC - Atherosclerotic Risk in Communities, CVH -Cardiovascular Health Study, FHS - Framingham Heart Study, VALUE -Valsartan Anti-hypertensive Long-term Use Evaluation Trial AF – atrial fibrillation, BG- blood glucose, BMI – body mass index, DM – diabetes mellitus, FBG – fasting blood glucose, FU – follow-up, HbA1c – glycated hemoglobin, HR – hazard ratio, HT – hypertension, OR – odds ratio, pts- patients, yrs- years						

Smoking

Smoking is reported to predict incident AF in individuals of European (98, 108-111), African, (108, 112) and Japanese (113) ancestry (Table 7). Risks of developing incident AF with smoking are similar in men and women (98, 108-114), and in blacks and whites (108). Multivariable risk prediction models for AF indicate that compared to nonsmokers, both current (109, 110) and ever smokers (110) have a higher risk of incident AF. Current smoking was responsible for about 10% of the variability in AF risk (18). Some data also suggest a dose response relationship, with the highest risk of AF observed in individuals with the greatest cigarette-years of smoking (108) and current smokers with increasing number of cigarettes per day (114). However, not all studies have reported an adjusted association between smoking and AF (2, 30, 115-119), but the lack of association has been ascribed to several factors including modest numbers of cases of AF, combining current and former smokers (120), adjusting for factors along the causal pathway such as myocardial infarction, heart failure, and lung disease (114) and competing risks of death among smokers (108, 120).

Whether other forms of tobacco exposure are associated with AF is more equivocal. One case report of an elderly woman with several comorbidities, suggests a possible temporal relation between electronic cigarettes and paroxysms of AF (121). To our knowledge, there is no published research linking electronic cigarettes with AF. Similarly, there are no prospective data regarding the relation of secondhand smoke to AF. However, one recent retrospective study suggested that being exposed to second hand smoke gestationally or living with a smoker during childhood were associated with an increased risk of AF as an adult (122). There have also been case reports of AF associated with chewing nicotine gum (123-125). In contrast, a pooled analysis of Swedish studies found current use of snus, a powdered smokeless tobacco

product, was not significantly associated with incident AF (RR, 1.07; 0.97-1.19) (126). Whether nicotine per se, or other chemicals associated with smoking are responsible for the increased risk of tobacco is uncertain.

Both experimental and human studies support multiple mechanisms linking smoking to AF. Nicotine and cigarettes predispose to inflammation (127), atrial electrical alterations (128, 129), atrial fibrosis (130-132), reduced lung function (133, 134), myocardial infarction (108), and heart failure (108), all of which predispose to AF. Smoking also may be a marker of deprivation and unhealthy lifestyle (135, 136). An inverse association between socioeconomic status and incident AF has been reported, which is partially mediated by other risk factors (137, 138).

In individuals with AF, most studies examining the risk of events such as stroke, dementia, heart failure, myocardial infarction (5, 6) and death have included smoking as a covariate, but have not specifically identified risk factors for events (139). Smoking was not a risk factor for incident heart failure in individuals with AF (140, 141). Neither the $CHADS_2$ nor the CHA_2DS_2-VASc scores include smoking as a risk factor for stroke. However, smoking is a risk factor for stroke in AF, even accounting for coexisting risk factors (142, 143), but this relationship was not evident in one study (144). Smoking has also been reported to predict an increased risk for intracranial bleeding, mortality (143, 145) and the combined outcome of stroke or death (144) in people with AF.

Although there are no randomized trials proving that smoking cessation reduces the risk of AF, the preponderance of evidence supports efforts to encourage individuals to avoid uptake or to quit smoking to reduce their risk. Mirroring population trends, smoking rates in individuals with AF have declined significantly over time (14). Current smoking was more strongly and consistently associated with AF compared to former smoking status in most (98, 113), but not all (114) studies (Table 7). In models excluding individuals with prior coronary heart disease and heart failure, former smoking was no longer significantly associated with incident AF (98). One biracial observational study noted a nonsignificant trend towards reduced rates of AF in individuals who had quit smoking (98).

The results of smoking cessation interventions in AF have not been well studied. Despite the potential benefits of smoking cessation in AF, individuals with AF were less likely to be prescribed smoking cessation aids than those without AF (146). One randomized trial of aggressive risk factor reduction, which included smoking cessation in individuals post AF catheter ablation, demonstrated that those randomized to risk factor reduction had lowered AF frequency, duration and symptoms (147).

Table 7. Smoking and risk of AF

Study	Design	Subjects	FU	Tobacco	AF, %		Multivariable Risk (95%CI)
(a) Population cohorts							
Alonso et al. [98] CHARGE-AF Study	Meta-analysis 3 cohorts, replication 2 cohorts	18,556 B & W; 1186 incident AF 7,672 W; 585 incident AF	5 yrs	Current smoking			HR 1.44 (1.20- 1.72)
Chamberlain et al. [108] ARIC	Cohort Incident AF	15,329 B&W 876 incident AF	Mean 13.1 yrs	<u>**Smoking status**</u> Never Ever Former Current <u>**Cigarette-yrs.**</u> 0 ≤300 >300 to ≤675 >675 **Continued vs. quit smoking**	Age-sex adjust. incidence <u>rate/10,000 py</u> 28 41 36 48 28 28 41 55		 Reference 1.58 (1.35-1.85) 1.32 (1.10-1.57) 2.05 (1.71-2.47) Reference 1.04 (0.83-1.30) 1.60 (1.30–1.95) 2.10 (1.74–2.53) 0.88 (0.65-1.17)
Pfister et al.[109] EPIC Norfolk	Cohort Incident AF	24,020 W 236 incident hospitalized AF	5 yrs	Current smoking Incident AF No Incident AF Yes	11.6% 14.0%		1.86 (1.28- 2.69) Observed in EPIC cohort free of CVD, HT, DM: HR 2.03 (1.26, 3.27)
Friberg et al.[110] Copenhagen City Heart Study	Cohort Incident AF	10,955 W 379 incident hospitalized AF	7 yrs	Never smokers Current smoking Current or ex	NA		Multivariable-adjusted Reference 2.0 (1.4–2.8) 1.8 (1.3–2.5)
Everett et al.[111] Women's Health Study	Cohort Incident AF	20,822 mostly W women 616 incident AF	Median 14.5yrs	Never Ever smoker	NA		Multivariable-adjusted Reference 1.29 (1.06-1.57) p=0.01
Rodriguez et al.[112] Multi-Ethnic Study of Atherosclerosis	Cohort Incident AF	6,721 Multi-ethnic 305 incident AF	Mean 6.98 yrs	All races Never Former Current Chinese Hispanics Non-Hispanic B Non-Hispanic W	<u>AF</u>† 42.9% 46.2% 10.9% NA	<u>No AF</u>† 50.7% 36.1% 13.2% NA	 Age- & sex-adjusted population <u>attributable fraction current smoking</u> -0.7 (-17.7 to 46.9) -0.9 (-21.1 to 15.8) 27.0 (5.8 to 43.5) 6.9 (-1.3 to 14.4)
Heeringa et al.[114] Rotterdam Study	Cohort Incident AF	5,668 W 371 incident AF	Median 7.2 yrs	Never smoker Current Former	78/1280 160/2159		Multivariable adjusted 1.51 (1.07-2.12) 1.48 (1.12-1.96)

Table 7. Smoking and risk of AF

Study	Design	Subjects	FU	Tobacco	AF, %		Multivariable Risk (95%CI)	
Huxley et al.[18] Atherosclerosis Risk in Communities	Cohort Incident AF	14,598 B&W 1520 incident AF	Mean 17.1 yrs		Incidence rate/1000py	Population Attributable Fraction	Relative hazard – adjusted **Note reference is current smokers**	
				Never	4.23	0	0.55 (0.48-0.62)	
				Former	5.76	2.06 (-2.05-6.05)	0.60 (0.52-0.68)	
				Current	7.45	9.78 (6.74-12.9)	Reference	
Schnabel et al.[115] Framingham Heart Study	Cohort Incident AF	4,764 W 457 incident AF	Max 10yrs	Current	NA		Age- and sex-adjusted 1.08 (0.88–1.33) p=0.47 Not included in multivariable risk prediction instrument	
Psaty et al.[116] Cardiovascular Health Study	Cohort Incident AF	4,844 B & W 304 incident AF	Mean 3.28 yrs	Current smoking	NA		Did not enter multivariable model	
Frost et al.[117] Danish Diet, Cancer, and Health Study	Cohort Incident AF	47,589 W 553 incident AF	Mean 5.7 yrs	Never - reference	NA		Men	Women
				Former			0.80 (0.62–1.04)	0.94 (0.65–1.36)
				Current			0.83 (0.64–1.07)	0.95 (0.66–1.35)
Wilhelmsen et al.[118] Multifactor Primary Prevention Study, Göteborg	Cohort Incident hospitalized AF	7,495 W Men 754 incident AF	Mean 25.2 yrs	Never + ex-smoker	10.6		Reference* age-adjusted	
				1-14 cig/day	9.1		0.83 (0.71-0.97)	
				>15 cig/day	11.8		1.16 (0.73-1.86)	
Nyrnes et al.[30] Tromsø study	Cohort Incident AF	22,815W 822 incident AF	Mean 11.1 yrs	Current smoking	Men	Women	Not included in multivariable model	
				No AF	37.1%	36.7%		
				AF	24.3%	22.7%		
Stewart et al.[119] Renfrew/Paisley study	Cohort Prevalent AF Incident AF	15,406 W 100 prevalent AF 537 incident of 8,532 in f/u	20 yrs	Current or former Prevalent AF	Men* 81.2%	Women* 54.1%	*Age-adjusted prevalence Not significantly associated in age-adjusted analyses; not selected for inclusion in multivariable analyses for prevalent or incident AF	
				No AF (n=15,306)	79.0%	65.8%		
				AF (n=100)				
Hergens et al.[126] Swedish cohort studies	7 Cohort studies Incident AF	127,907 W men never smoker 3,494 incident AF		Prevalence of Snus use 25%			Adjusted for age and BMI 1.07 (0.97-1.19)	
(b) Hospital-based								
Suzuki et al.[113] Shinken database	New patients attending Cardiovascular Institute Incident AF	15,221 Japanese 190 incident AF	Mean 2 yrs Max 8.1yrs	Nonsmokers	5.0/1000 py		Reference, adjusted analyses	
				Smokers	9.0/1000 py		1.47 (1.09–2.00)	
				Former	8.6/1000 py		1.33 (0.94–1.89)	
				Current	9.8 /1000py		1.81(1.17–2.79)	
				Brinkman index≥800	10.6/1000py		1.69 (1.05–2.70)	
(c)Internet-based survey								
Dixit et al.[122] Health eHeart Study	Self-referred internet self-report Prevalent AF	4,976 ~80% W 593 prevalent AF	Cross-sectional		AF	No AF	Unadjusted p-value,	
				Never	52.7%	66.5%		
				Past	43.6%	29.5%		
				Current	3.8%	4.0%	p<0.001	
				Median yrs smoked, past & current smokers	18	12	Unadjusted p-value p<0.001	
				Secondhand smoke	AF 68%	No AF 51%	Multivariable adjustment OR 1.37 (1.08-1.73) p=0.009	
				Smoking parent during gestation	39%	26%	OR 1.40(1.10–1.79) p=0.007	
				Residing with smoker				

*AF incidence not depicted by smoking status; †Personal communication Carlos J. Rodriguez, MD, MPH 10/26/2015
AF – atrial fibrillation, B – Black, BMI – body mass index, CI – confidence interval, cig. – cigarette, CVD – cardiovascular disease, DM – diabetes mellitus, FU – follow-up, HR – hazard ratio, HT – hypertension, NA – not available, OR- odds ratio, pts- patients, py - person years, W – White, yrs-years

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Air pollution

Experimental and epidemiological studies have indicated that air pollution is related to an increased prevalence of cardiovascular risk factors, for example diabetes mellitus and hypertension, as well as cardiovascular disease (148-153). Fine particular matter (PM2.5) produced by burning fossil fuels may contribute to this relationship. The underlying pathophysiology has been attributed to an increased inflammatory response to high particle exposure, influencing the autonomous nervous system (152).

Although fine particle pollution has been linked to stroke in several studies (154-156), it has not been found to be associated with the induction of AF. Likewise, epidemiological studies have failed to show a relationship between permanently higher fine particle exposure and AF incidence (157, 158) (Table 8). Short-term exposure may directly enhance AF susceptibility in patients with cardiac disease (159, 160).

Table 8. Relation of air pollution to risk of AF

Study	Design	Subjects	FU	Particle pollution	AF	Risk
Link et al.[159] Tufts Medical Center Cardiac Arrhythmia Center	Prospective cohort study; acute exposure 24 hrs prior	176; ICD pts	1.9 yrs	$PM_{2.5,}$ sulfate, NO_2, SO_2, O_3	328 episodes of AF >30s	Odds of AF increased by 26% for each 6.0 µg/m3 increase in $PM_{2.5}$ in the 2 hrs prior to the event (p=0.004)
Milojevic et al.[157] Myocardial Ischaemia National Audit Project (MINAP)	Case-cross-over design	2,867,473 CV events; mean age 73 yrs	6 yrs	CO, NO_2, PM_{10}, $PM_{2.5}$, SO_2, O3; Lags up to 4 days	310,568 pts with AF	NO_2 increased risk for AF 2.8% (0.3 to 5.4)
Bunch et al.[158] Utah's Wasatch Front	Case-crossover study design	10,457 AF hospitalizations	15 yrs	$PM_{2.5}$; day Exposure and cumulative lagged exposures for up to 21 days	100%	No association between $PM_{2.5}$ and hospitalization for AF

AF – atrial fibrillation, CV- cardiovascular, FU-follow-up, ICD – implantable cardioverter-defibrillator, $PM_{2.5}$ –particular fine particular matter, pts – patients, hrs-hours, yrs – years, s- seconds

Caffeine

Caffeine is a methylxanthine compound that is chemically similar to theophylline. Caffeine is present in tea, coffee, cola or energy drinks. It has several cardiovascular effects increasing neurohormonal and sympathetic nervous system stimulation (161). Therefore, caffeine has been addressed as a potential trigger for AF.

The acute effects of high caffeine loading or even intoxication show minor and overall inconsistent evidence for increased susceptibility to supraventricular arrhythmias (162-164). Habitual caffeine ingestion has been investigated in several prospective cohort studies (Table 9), but these failed to show any significant relationship to incident AF (165). Also, heavy coffee drinking (166) failed to demonstrate a significant relationship between caffeine and AF or flutter even in very high consumers (10 cups, 1000 mg/day). Overall, caffeine consumption on a habitual and regular basis does not seem to increase the incidence of AF (35, 166, 167). However, other forms of caffeine ingestion such as energy drinks containing other stimulants such as taurine in combination with alcohol, may possibly contribute to an increase of risk, at least in case reports (168).

Table 9. Caffeine use and risk of AF

Study	Design	Subjects	FU	Caffeine Assessment	AF	Caffeine consumption in mg/dl and corresponding hazard ratio
Conen et al.[167] Women´s Health Study	Cohort, USA	33,638 100% female mean age 53 yrs	14.4 yrs	Food Frequency Questionnaire	n=945	Quintiles: 22 1.0 135 0.88 285 0.78 402 0.96 656 0.89
Shen et al.[35] Framingham Heart Study	Cohort, USA	4,526 56% female mean age 62 yrs	4 yrs	Food Frequency Questionnaire	n=296	Quartiles: 23 1.0 142 0.84 347 0.87 452 0.98
Frost et al.[166] Danish Diet, Cancer, and Heart Study	Cohort, Denmark	47,949 54% female mean age 56 yrs	5.7 yrs	Food Frequency Questionnaire	n=555	Quintiles: 248 1.0 475 1.12 584 0.85 769 0.92 997 0.91

AF – atrial fibrillation, FU – follow-up, yrs - years

Alcohol consumption

Alcohol as a cause of AF has been recognized in the setting of acute consumption, commonly described as the "holiday heart" (169). Binge drinking (>5 drinks on a single occasion) is associated with an increased risk of new onset AF (170).

A variety of mechanisms has been proposed for the role of alcohol in contributing to AF as triggers or substrate for the arrhythmia including decreased vagal tone, hyper-adrenergic state, direct toxic effect on the cardiomyocytes, altered atrial conduction and shortening of refractoriness (171-173).

In evaluating the contribution of chronic alcohol consumption to the development of AF, an important limitation is that unlike the objective measures available for many of the established risk factors for AF, the quantification of alcohol consumption is based on self-reported levels. Most studies have found an association between heavy alcohol consumption and incident AF (Table 10). For example, the Copenhagen City Heart Study observed that men consuming >35 drinks/week had a high risk of AF (174). Similarly, the Framingham cohort study suggested that heavy alcohol consumption (>36 g/day) significantly increased the risk of AF (175). The Women's Health Study showed that consumption of >2 drinks/day was associated with an increased risk of AF (176). A consistent increase in risk of AF with chronic, heavy alcohol consumption was confirmed in a meta-analysis, which also demonstrated that the association between AF and alcohol consumption was linear (177).

Although these large epidemiological datasets have confirmed the association of heavy alcohol consumption with AF, recent studies have implicated a contributory role of even small quantities of alcohol with an increased risk of AF. Data from 2 large prospective Swedish cohorts comprising 79,000 individuals show that, when compared to <1 drink per week, the consumption of 15-21 and >21 drinks per week conferred significant risks of developing AF on multivariable analysis (178). This study identified that the risk for AF may be most pronounced with liquor; modest for wine and no excess risk was detected with

beer. In addition, one meta-analysis of 7 prospective studies suggested that there was a greater risk of AF with even low levels of alcohol consumption (178). In both men and women, each drink of alcohol was associated with an 8% increase in relative risk of AF.

The consistent epidemiologic relationship between alcohol and AF has led to the suggestion that lowering alcohol consumption may be an effective AF preventive strategy (179). Recent studies have also highlighted the importance of aggressive risk factor management, including reducing alcohol consumption, in maintaining sinus rhythm in patients with established AF. In obese and overweight individuals, these studies have established an ultimate goal of reducing alcohol consumption to ≤30 g/week (147). In the context of a directed management of risk factors, reducing alcohol consumption has contributed to short term improvements in AF burden (26) and AF ablation outcomes (147), as well as long-term maintenance of sinus rhythm (28). The above evidence perhaps confirms some atrial toxicity related to alcohol consumption. Thus, physicians must not neglect obtaining a detailed history on alcohol consumption and providing appropriate counselling to reduce alcohol intake, when necessary, in patients with AF.

Table 10. Risk of AF and alcohol consumption

Study	Design	Subjects	FU	Alcohol, drinks/day (week)	AF, n	Risk (95%CI)
(a) Population cohorts						
Mukamal et al. [174] Copenhagen City Heart study	Prospective cohort	16,415 Men and Women Free of AF at baseline	26 yrs	Men Multivariable risk <1 drinks/week ≥35 drinks/week: Adjusted for CHD, CHF, BP Women Multivariable risk <1 drinks/week 21-27 drinks/week	1071	 Reference (risk in HR) 1.45 (1.02-2.04) HR 1.63 (1.15-2.31) In men 5% of incident AF is attributable for heavy drinking Reference (risk in HR) 1.04 (0.64–1.70) p=0.87 for trend
Conen et al. [176] Women Health Study	Prospective cohort	34,715 Women <45 yrs Free of AF	12.4 yrs median	 0 drinks/day ≥2 drinks/day	653	 Reference (risk in HR) 1.6 (1.13-2.25)
Djousse et al. [175] Framingham Heart Study	Prospective cohort Case- control analysis	1,055 who developed AF 4672 controls Men and women	>50 yrs	 0 gr/day >36 gr/day	1055	 Reference (risk in OR) 1.34 (1.01-1.78)
Larsson et al. [178] Swedish Cohort Study	Prospective cohort	79,019 Men and women free of AF at baseline	12 yrs	Dose response* <1 drink/week 15-21 drinks/week >21 drinks/week	7245	 Reference (risk - RR) 1.14 (1.01-1.28) 1.39 (1.22-1.58)

				Binge drinking (>5 drinks/single occasion) Type of drinks Liquor 7-14 drinks/week >14 drinks/week Wine >14 drinks/week Beer		1.13 (1.05-1.32) 1.13 (1.01–1.28) 1.43 (1.14–1.74) 1.30 (1.06–1.61) NS
Kodama et al.[177]	Meta-analysis 14 observational cohort and case-control studies	14 studies 130,820 participants 7558 cases 9 studies 126051 participants 6341 cases	2.5-44 yrs	Overall Highest vs lowest alcohol intake Dose-response (4-86.4 gr/day)	7558 6341	Pooled OR/RR 1.51 (1.31-1-74) RR 1.8 (1.05-1.10) per 10gr alcohol per day
Larsson et al.[178]	Meta-analysis 7 prospective cohort studies	206,073 participants 12,554 cases Men, women	4.7 to >50 yrs	0 drinks/day* 1 drink/day 2 drinks/day 3 drinks/day 4 drinks/day 5 drinks/day Overall	12554	Reference (risk in RR) 1.08 (1.06- 1.10) 1.17 (1.13- 1.21) 1.26 (1.19- 1.33) 1.36 (1.27-1.46) 1.47 (1.34-1.61) 1.08 (1.06-1.10) 8% (6-10%) increase in AF risk per 1 drink/day increment
(b)Intervention studies						
Pathak et al.[147] ARREST-AF	Prospective cohort study	281 pts with AF undergoing catheter ablation 68 pts RFM 88 pts controls	2 yrs	RFM - Alcohol <30g/ week+ BP, lipids and glycemic control, weight reduction, smoking cessation vs control	-	RFM predictor of arrhythmia free survival HR 4.8 (2.04-11.4)
AF- atrial fibrillation, BP- blood pressure, CHD – coronary heart disease, CHF – chronic heart failure, CI-confidence interval, FU- follow-up, HR-hazard ratio, OR – odds ratio, RR- relative risk, RFM – risk factor modification, pts – patients, yrs- years *Standard drinks = 12 g alcohol. One standard drink corresponds to approximately 40 ml liquor, 80 ml strong wine, 150 ml wine, 330 ml class III beer (alcohol by volume, >3.5%), 50 ml class II beer (2.8% to 3.5%), or 660 ml class I beer (<2.25%).						

Recreational drugs

There are numerous reports on the effects on myocardial infarction, ventricular arrhythmias and sudden cardiac death caused by recreational (illicit) drugs such as amphetamine, cocaine and cannabis (180). However, data on these drugs as risk factors for AF per se are sparse. AF has not been reported to be associated with amphetamine, heroin or LSD abuse and there are limited reports on the abuse of cannabis, cocaine, ecstasy and anabolic-androgenic steroids with AF.

Cannabis is the most commonly used recreational drug, which is increasing in Europe. A systematic review and a case series with literature review reported that all cases of cannabis-related AF were among young people without co-morbidities (181, 182). The underlying mechanism is probably adrenergic stimulation and disturbance in microvascular flow facilitating AF development by increased pulmonary vein ectopy. Cannabis abuse leading to AF is not benign in young and healthy subjects as it may contribute to

atrial remodeling long-term (183). AF caused by cannabis abuse may be more malignant in older patients having other risk factors for thromboembolism. The burden of this problem is probably underestimated, given that most illicit cannabis users avoid seeking medical care unless serious disease is present.

Physicians should carefully examine for recreational drug abuse in young new onset AF patients without known predisposing factors. One case report describes AF in a healthy adolescent who had used ecstasy (184). Anabolic androgenic steroids are often used by young athletes to increase their capacity. Thus AF in a young healthy athlete should raise the suspicion that illicit drugs may be a possible cause and lead to careful search for drug abuse in order to prevent AF and more serious cardiac consequences (185, 186).

Medications

A number of cardiovascular and non-cardiovascular drugs have been associated with increased risk of AF (Table 11). Drug-induced AF has received relatively little attention, and the exact incidence is not known.

Many cardiovascular (adenosine, dobutamine, ivabradine) and non-cardiovascular [nonsteroidal anti-inflammatory drugs (NSAIDS), high-dose corticosteroids, and respiratory medications as aminophylline] drugs can induce AF (187-189). Adenosine is reported to induce AF when used for terminating supraventricular tachycardia with atrioventricular nodal involvement. Many patients undergoing cardiac surgery and treated with the inotrope dobutamine may develop postoperative AF. However, AF is usually transient and of short duration. Evidence of chemotherapy-induced AF has been summarized (187, 190). Anthracyclines, melphalan, interleukin-2 and cisplatin appear to be associated with AF, in addition to cancer itself that creates an inflammatory arrhythmogenic milieu (191). Several case reports of antipsychotic drugs associated with AF have been published (192), include with olanzapine (used for treatment of schizophrenia and bipolar disorder) . The antiemetic drug ondansetron is probably related to AF (187).

Whether bisphosphonate drugs against osteoporosis are associated with AF remains somewhat controversial. A systematic review and meta-analysis from 2014 concluded that AF risk is increased by 40% with intravenous use and 22% by oral use (193). A more recent meta-analysis stated that bisphosphonates

may modestly increase the risk of AF, but given the large reduction in fractures with these drugs, the authors did not recommend changes in treatment (194).

Drug-induced AF can occur through pharmacological stimulation promoting ectopic impulses or by modulating the underlying substrate. Further research is perhaps needed to determine the incidence and risk factors of drug-induced AF, and particularly whether specific medications increase the risk of thromboembolism or mortality. In patients with a new-onset AF, it is reasonable to review the pharmacological history to identify whether any of the prescribed drugs may be responsible for the arrhythmia and make a balanced judgment on the risks and benefits of the drug use. Drug-induced AF may appear in healthy patients, but occurs more frequently in the elderly, after cardiac surgery, and if comorbidities and risk factors associated with AF are present. These risk factors include polypharmacy, hypertension, major heart disease, chronic obstructive pulmonary disease and sleep apnea.

Table 11. Medications associated with risk of incident AF

	Medications
Common (> 20 %)	Dobutamine[187], Cisplatin[187, 190]
Infrequent (5-20 %)	Anthracyclines[187, 190], Melphalan[187, 190], Interleukin-2[187, 190], NSAIDS[189], Bisphosphonates[193, 194]
Rare (<5 %)	Adenosine[187], Corticosteroids[187], Aminophylline[187], Antipsychotics[192], Ivabradine[188] Ondansetron[187]

Psychological distress

Psychological distress is prevalent among AF patients (195, 196, 197, 198, 199); approximately 25-50% have symptoms of anxiety and/or depression and fear and worry are common (195-202). There is some evidence from ICD patients that acute emotional distress (particularly anger and anxiety) (197, 203, 204) and depression (205) may be antecedents to ventricular arrhythmias but there are no data in ICD patients regarding atrial arrhythmias. Only three studies have specifically examined the impact of psychological distress on incident AF (206-208).

The Framingham Offspring Study examined the association between Type A behaviour, anger, and hostility and incident AF. In age-adjusted analyses, anger-out predicted incident AF in women, while trait anger, symptoms of anger, and hostility predicted onset of AF in men (206) (Table 12). On multivariable analyses, symptoms of anger, hostility, and trait-anger predicted the 10-year incidence of AF in men but not in women (206). Another analysis of this cohort investigated the effect of tension and anxiety on the development of AF (207). In age-adjusted analyses, tension and anxiety predicted development of AF in men only. After adjustment for confounders, only tension was an independent predictor of incident AF but only among men (207).

The absence of an association between psychological distress and development of AF in women was confirmed in the Women's Health Study (208). In this cohort of 30,746 female health professionals aged ≥45 years who were free from cardiovascular disease at baseline, 771 (2.51%) developed AF over a median 10-year follow-up period. Psychological distress was not associated with incident AF in age-adjusted or multivariable analyses (208). These findings require replication in other more diverse populations since these cohorts were predominantly white, middle-class, and middle-aged (204-208) and the effect sizes in the Framingham Offspring study were modest (207, 208).

Psychological distress, particularly depression, is more commonly associated with adverse lifestyle choices (smoking, excessive alcohol intake, poor diet, physical inactivity), poorer adherence to medication etc., all of which may increase the likelihood of development of other risk factors for AF, and hence predispose people to incident AF. It is also plausible that the autonomic nervous system may be the conduit by which AF is linked with psychological distress and vice versa. The current evidence is therefore limited and equivocal, and future research is needed.

Table 12. Psychological distress and risk of AF

Study	Design	Subjects N (% women)	FU, yrs	Psychological distress measures	AF, n (%)	Age-adjusted risk RR (95% CI)	Multivariable-adjusted risk RR (95% CI)
Eaker et al[206] Framingham Offspring	Prospective, observational cohort	3,682 (52%)	10	Type A behaviour Anger	**Women:** 62/1908 (3.2%)	**Women:** Anger-out 1.3(1.0-1.6); p<0.05	**Women[a]:** NS

Study		Mean age 48.5 (10.1) yrs		Hostility	**Men:** 132/1750 (7.5%)†	**Men:** Trait anger 1.2 (1.0-1.4); p<0.05 Symptoms of anger 1.2 (1.1-1.4); p<0.05 Hostility 1.3 (1.1-1.6); p<0.05	**Men[a]:** Trait anger 1.1 (1.0-1.4); p=0.04 Symptoms of anger 1.2 (1.1-1.4); p=0.008 Hostility 1.3(1.1-1.5); p=0.03
Eaker et al[207] Framingham Offspring Study	Prospective, observational cohort	3,682 (52%) Mean age 48.5 (10.1) yrs	10	Tension Anxiety	**Women:** 62/1908 (3.2%) **Men:** 132/1750 (7.5%) †	**Women:** ‡ **Men:** Tension 1.28 (1.08-1.52) Anxiety 1.16 (1.01-1.33)	**Women[a]:** Tension 0.83 (0.63–1.11) Anxiety 1.03 (0.81–1.31) **Men[a]:** Tension 1.24 (1.04-1.48) Anxiety 1.10 (0.95–1.27)
Whang et al[208] Women's Health Study	RCT, plus observational follow-up	30,746 women without CVD at baseline Age: ≥45 years	10.5	MHI-5* MHI-5 score: 86-100 76-85 53-75 <53	 359 235 129 48	 Reference 0.86 (0.73-1.02) 0.91 (0.74-1.11) 1.08 (0.80-1.47) p-value for trend 0.61	 Reference 0.87 (0.73-1.03) 0.89 (0.72-1.09) 0.99 (0.72-1.35) p-value for trend 0.34

[a] Adjusted for age, diabetes, hypertension, history of myocardial infarction or history of congestive heart failure, and valvular heart disease (defined as any diastolic murmur or ≥3 out of 6 systolic murmur).
† not reported by each psychological measure; ‡ not reported for women; * score <53 indicates significant global distress
AF- atrial fibrillation, CI- confidence interval, CVD- cardiovascular disease, FU- follow-up, MHI-5 - Mental Health Inventory 5-items, NS- not significant in multivariable analyses, RCT- randomised controlled trial, RR- relative risk, SD- standard deviation, yrs-years

Physical activity and inactivity

Physical activity has profound benefits on lowering cardiovascular morbidity and mortality and physical inactivity is a major risk factor for cardiovascular disease. The effects of physical activity on the development of AF are less well documented and intervention studies on physical activity and the development of AF are lacking (Table 13).

The risk of AF depends on the interaction between individual susceptibility, environment and the degree of physical activity (209). Vigorous exercise may increase risk of sudden cardiac death, and even AF in some instances; however, habitual moderate physical activity may have several benefits that can reduce the incidence of AF. Lowering heart rate, blood pressure, better glucose and lipid control, weight loss, improved endothelial function, and lower systemic inflammation are some of the benefits of exercise that may decrease the development of AF (97). On the other hand, vigorous activity can cause acute cathecholamine fluxes, autonomic tone changes, and atrial stretch, all contributing to AF risk (210-215). Autonomic influences should also be taken into consideration to decrease aggravation of AF (210, 216).

The Euro Heart Survey on AF showed that an autonomic trigger pattern, either adrenergic, vagal or mixed was present in 33% of patients; however, physicians did not choose rhythm or rate control medications according to those triggers (216), and inappropriate therapy in vagal AF patients enhanced progression of AF.

As stated earlier, obesity begets AF, and increased cardiorespiratory fitness is protective against incident AF. Indeed, the CARDIO-FIT study showed that arrhythmia free time was greatest in obese patients with high cardiorespiratory fitness. In this study, AF burden and symptom severity significantly decreased in the group with cardiorespiratory fitness gain over 2 metabolic equivalent tasks (METs) (27)

Different studies have suggested a possible relationship between endurance training and the development of AF, although this has not been confirmed in all studies or a Cochrane meta-analysis (217-224). Most studies have looked at the effects of endurance training and vigorous exertion in young and middle aged adults. In a study of 44,410 men, intense endurance training at age 30 increased risk of AF later in life whereas moderate intensity decreased AF risk (225). Similar findings were reported in older athletes (226). A meta-analysis of several small studies showed that risk of AF development in athletes was more than in nonathletes, but referents were not age matched and there was variance in the level of endurance across studies (227). Age, years of training and type of sport will all affect the outcome, therefore it is not possible to deduct a net conclusion from these studies except that vigorous endurance exercise may have a possible and small facilitating effect on AF.

In older adults, prospective epidemiological studies have shown a U-shaped relationship between level of physical activity and risk of AF. For example, the Cardiovascular Health Study demonstrated that leisure time activity was associated with lower AF incidence in a graded manner with lower risk as the intensity increased (226). AF incidence was lower in those with moderate exercise compared to no exercise (HR 0.72, 95% CI 0.58 to 0.89). However high-intensity exercise was not associated with a significantly reduced risk of AF (HR 0.87, 95% CI 0.64 to 1.19). There is also a graded inverse relationship between cardiorespiratory fitness and incident AF especially in obese patients (228). In a large population based Swedish cohort, the risk of AF decreased with increased leisure time exercise in middle aged and elderly women (229). Inactivity and obesity may lead to diastolic dysfunction and left atrial enlargement, and

therefore increased AF risk whereas exercise training improves diastolic function and reduces left atrial volume (230).

Current evidence would suggest that moderate physical activity is associated with better cardiovascular health, decreased mortality and decreased risk of AF. The on-going Routine versus Aggressive upstream rhythm Control for prevention of Early atrial fibrillation in moderate heart failure (RACE 3) trial is investigating whether the combination of renin–angiotensin–aldosterone system (RAAS) modulators, statins, and cardiac rehabilitation interventions to promote a better lifestyle including physical activity, weight reduction and a healthy diet, may reduce progression of AF (231).

Table 13. Physical activity and risk of AF

Study	Design	Subjects	Age, years	FU, years	Physical activity	AF,%	Risk
Population cohorts							
Qureshi et al. [228] (FIT project) patients referred for treadmill	Retrospective	69,885	54.5	5.4	Graded by treadmill	7	1 Met higher decreases AF risk by 7 %
Drca et al.[229] Swedish Mammography Cohort Healthy	Prospective	36,513 women	60	10	Level of leisure activity	7.9	AF risk decreases with increased level of activity
Mozaffarian et al. [226] Cardiovascular Health Study	Prospective	5,446 Men and women	Over 65	10	Exercise intensity	19	AF less with low to moderate exercise
Grimsmo et al. [220] Cross country skiers	Prospective	122 and 117	Over 54	28-30	High in all	12.8	Endurance training increases AF
Myrstad et al. [232] Male, cross country skiers	Retrospective	3,712	Over 53		High in all	12.5	Endurance training increases AF
Lee et al. [219] Leisure-time running	Longitudinal cohort study	309,540 Men and women	40-45	4	Leisure time activity	0.4	AF increases with self-reported activity in men
Thelle et al. [233] Walkers and runners	Proportional hazards analysis of	14,734	All ages	6.2	Walking or running	1.9-2.7 (arrhythmia)	AF similar in walkers and runners Arrhythmia decreases per MET
Aizer et al.[234] Physicians Health Study Healthy men	Prospective	16,921	40-84	12	Degree of physical activity	9.8	Vigorous activity increases AF

AF – atrial fibrillation, FU – follow-up, MET – metabolic equivalent task, pts- patients

Genetic predisposition and risk of AF

About 5% of patients with AF and 15% with lone AF referred for evaluation of arrhythmias have family history of arrhythmias (235). Population-based studies demonstrated association between family history and risk of AF development (236-241) (Table 14), which become stronger with increased numbers of affected 1st degree relatives and younger age. Several genes and loci linked to AF and its substrate were identified in

families, individuals, and different populations (242-244), still there are genes in development state with unknown effects and risk associated with AF (245, 246). AF with genetic predisposition is defined as monogenic when related to inherited cardiomyopathies and as polygenic in presence of common gene variants associated with early AF onset in population (247, 248).

The evidence of genetic predisposition to AF is evolving, and more studies are needed to clarify the role of various genes in AF development and as the genetic predisposition is a non-modifiable risk factor more studies are needed to establish whether intervention on modifiable risk factors can decrease risk of AF in populations with genetic predisposition.

Table 14. Genetic predisposition and risk of AF – population-based studies

Study	Design	Subjects	FU	Familial AF history	AF,%	Risk* (95%CI)
Fox et al[236] Framngham Heart Study	Prospective cohort Population-based epidemiological study	2243 O 1165 women 1078 men At least 30 yrs	16 yrs	681 – at least 1 parent had documented AF	N=70	Parental AF vs No FH OR 1.85 (1.12-3.06; p =0.02) Parental AF vs No FH <75 yrs (O and P) OR 3.23 (1.87-5.58; p<0.001) Parental AF vs No FH <75 yrs (O w/o overt clinical heart disease) OR 3.17 (1.71-5.86; p<0.001)
Arnar et al.[237] Iceland cohort	Population-based cohort	5269 pts with AF	-	AF risk in 1st- 5th degree relatives	-	1st degree relative RR 1.77 (1.67=1.88 p=0.001) 1st degree relative <60 yrs old RR 4.67 (3.57-6.08, p=0.001)
Gundlund et al.[238] Denmark cohort	Population-based study	**New-onset AF** 67,310 mothers- 64yrs 103,822 fathers -70yrs 11,800 siblings-46yrs		**AF screening:** 133,516 maternal O 221,774 paternal O 21, 448 sibling O	 2536(1.9%) 2906(1.3%) 292 (1.4%)	RR compared to general Denmark population 3.37 (3.21–3.53) 2.81 (2.69–2.93) 5.20 (4.61–5.85)
Zoller et al.[239] Sweden cohort	Population-based case-controlled study	300,586 individuals with AF/AFl multiplex families		 1 parent ≤49yrs 2 parents ≤49yrs ≥1 sibling ≤49 yrs ≥2 siblings ≤49 yrs	Case vs Control 22.6% vs 13.6% 22.8% vs11.9% 2.0% vs 0.2% 2.1% vs 0.5% 14.7% vs 5.6% 8.1% vs 2.3% 2.9% vs 0.6% 1.4% vs 0.2%	 OR 1.95(1.89-2.00) OR 2.33 (2.23-2.44) OR 3.6 (3.3-3.92) OR 5.04 (4.36-5.28) OR 3.08 (3.0-3.16) OR 4.06 (3.79-4.41) OR 5.72(5.28-6.19) OR 8.51(6.49-11.15)
Lubitz et al.[240] Framingham Heart Study	Prospective cohort	4421 participants	-	 Familial AF - 1185 Premature familial AF (<65 yrs) -351	Overall 440 Familial AF vs no FH 5.8% vs 3.1%	Presence of any 1st degree familial AF vs no HR 1.4 (1.13-1.74, p=0.002) Presence of premature familial AF (<65yrs) HR 2.01 (1.49-2.71, p<0.001) Number of 1st degree relative with AF- risk per each additional affected member HR 1.24 (1.05-1.46, p=0.01)
Oyen et al.[241]	Prospecti	3,985,446	31yr	1st degree relative	n =269	IRR 3.48 (3.08–3.93)

Denmark cohort	ve cohort	individuals Lone AF - 9,507 subjects <60 yrs	s	2nd degree relative Number of affected 1st degree relatives 1 affected ≥2 affected Age at onset of lone AF for cohort member and 1st degree relative <30 yrs for both <40yrs for both	n=19 n=264 n=5 N/A n=31	IRR 1.64 (1.04–2.59) IRR 3.45 (3.05-3.9) IRR 6.24 (2.59-15.0) IRR 8.53 (3.82-19.0) IRR 5.42 (3.8-7.72)
AF – atrial fibrillation, CI – confidence interval, FH – family history, FU – follow-up, HR – hazard ratio, IRR – incidence rate ratio, O – offspring, OR- odds ratio, P- parent, pts- patients, RR –relative risk, yrs-years						

Hyperthyroidism and other endocrine disorders

Among endocrine disorders, hyperthyroidism and diabetes mellitus (see above) are commonly associated with risk of developing AF (31, 104, 249, 250), while hypothyroidism poses no or reduces risk for arrhythmia (249, 251, 252).

Observational cohort and registry studies (Table 15) reported AF incidence rates of 4.6-13.8% in overt hyperthyroidism, 8.5-12.7% - in subclinical hyperthyroidism and 7.3% in high-normal euthyroidism [based on thyroid stimulating hormone (TSH) level] (249-251, 253-257).

The risk of new-onset AF in hyperthyroidism depends on the level of thyroid dysfunction. AF is increased by 42% in overt hyperthyroidism, by 31% in subclinical hyperthyroidism, and by 12% in high-normal euthyroidism (249). Patients with subclinical forms are 1.68 fold more likely to develop AF during long-term follow-up, and those with suppressed TSH values have been shown to possess 2.54 fold higher risk of incident AF compared to euthyroid populations (249, 251, 253, 254, 256). Though the evidence on risk of AF in individuals with high-normal euthyroidism is limited, the Rotterdam study demonstrated an increased risk of AF in individuals with high-normal thyroid function (based on TSH level) (257) and in subjects <65 years old with higher free thyroxine levels within normal range (258). Nonetheless the evidence on demographic and cardiovascular disease risk factors associated with AF in thyroid dysfunction is scarce. In overt hyperthyroidism, age >65years, male sex, comorbidities like coronary artery disease, chronic heart failure and valvular heart disease were reported as predictors of arrhythmia (260). In the subclinical form, age and sex were shown to affect the incident risk of AF, being significant in all age categories in women, and young male individuals, except in the older (>65 years) male population (249). In

a recent meta-analysis (256), the risk of AF in subclinical hyperthyroidism was associated with male sex, but was not altered by the presence of cardiovascular disease or its risk factors. In another study, subclinical hyperthyroidism was shown to be a predictor of AF in elderly individuals, along with advanced age category (>75 years), male sex, diabetes mellitus, hypertension and heart failure (257).

AF risk diminishes during antithyroid treatment (249), with spontaneous restoration of sinus rhythm in about 76% of patients (259) and reduction of arrhythmia on long-term monitoring (260). Sinus rhythm restoration rates are also higher in elderly patients with overt and subclinical hyperthyroidism without cardiovascular disease and its risk factors, as compared to those with comorbidities (254). After restoration of an euthyroid state and electrical cardioversion or catheter ablation for persistent AF, long-term sinus rhythm maintenance rates have been shown to be either higher in patients with hyperthyroidism (261) or did not differ from those without history of thyroid dysfunction (262, 263).

Hyperthyroidism had been long considered to be associated with higher thromboembolic risk (65), but recent studies demonstrated that thyroid disease is not an independent predictor of AF related complications such as thromboembolism and stroke (264-266).

Thus, prevention of AF in overt and subclinical hyperthyroidism should include measures, such as controlling thyroid function, treatment of associated cardiovascular diseases and modification of risk factors. More research is needed regarding risk factors and prevention of AF in populations with high-normal euthyroidism based on TSH level and normal thyroid function with higher free thyroxine levels within normal range.

Table 15. Risk of AF in thyroid dysfunction

Study	Design	Subjects	FU	Thyroid function	AF, %	Risk (95%CI)
Selmer et al.[249]	Cohort	586,460	5.5 yrs	Euthyroid	2.9	Reference
				Overt Hyperthyroid	4.6	IRR 1.42 (1.22-1.63)
				Subclinical Hyperthyroid	-	IRR 1.31 (1.19-1.44)
				Overt Hypothyroid	2.5	IRR 0.67 (0.5-0.9)
				Subclinical Hypothyroid	-	IRR 0.87 (0.7-0.97)
				TSH levels		
				Reduced TSH	-	IRR 1.16 (0.99-1.36)
				Suppressed TSH	-	IRR 1.41 (1.35-1.89)
				High-normal Euthyroid (TSH levels)	-	IRR 1.12 (1.03-1.21)
Cappola et al.[251] Cardiovascular Health study	Cohort	3,233 >65 yrs	13 yrs	Euthyroid	5.2	Reference
				Subclinical Hyperthyroid	8.5	HR 1.98 (1.29-3.03) [α]
				Overt Hypothyroid	4.8	HR 0.96 (0.52-1.79) [α]

				Subclinical Hypothyroid	3.9	HR 1.13 (0.94-1.36) [α]
Frost et al.[250]	Cohort	40,628	30 d	Overt Hyperthyoid	8.3	-
Auer et al.[254]	Retrospective	23,638 elderly	-	Euthyroid Overt Hyperthyroid Subclinical Hyperthyroid	2.3 13.8 12.7	- - RR 5.2 (2.1-8.7)
Gammage et al.[255]	Cohort	5,860 >65 yrs	-	Euthyroid Subclinical Hyperthyroid Subclinical Hypothyroid Serum free T4	4.7 9.5 4.2 -	Reference OR 1.87(1.01-3.57) [β] - OR 1.09 (1.03-1.15)
Sawin et al. [253] Framingham Heart Study	Cohort	2,007	10 yrs	Euthyroid Reduced TSH 0.1-0.4 μU/L Suppressed TSH <0.1 μU/L	8.4 12.2 21.3	 RR 1.6 (1.0-2.5) RR 3.8 (1.7-8.3)
Colett et al.[256] Thyroid studies collaborators	Meta-analysis	52,674	8.8 yrs	Subclinical Hyperthyroid Reduced TSH Suppressed TSH	- - -	HR 1.68 (1.16-2.43) HR 1.63 (1.1-2.4) HR 2.54 (1.08-5.99)
Heeringa et al.[257]	Registry	1,426	8yrs	High-normal Euthyroid (TSH levels) TSH - 0.4-1.04 mU/L	7.3	HR 1.94 (1.13-3.34)[γ]
Kim et al.[252] Framingham Heart study	Cohort	5,055	10yrs	TSH 0.45-4.5 μU/L TSH 4.5-10.0 μU/L TSH 10.0-19.9 μU/L	5.4 7.0 4.0	Reference HR 1.23 (0.77-1.97) HR 0.57 (0.21-1.54)

[α] Adjusted for age, sex, CVD, thyroid medication use, atrial size, SBP, fasting glucose. VHD, b-blockers and diuretics use
[β]Adjusted for male, age>70, DM, HF, HT
[γ] Adjusted for age, sex, smoking, BMI, SBP, HT, HF, MI, LVF, DM
AF – atrial fibrillation, BMI – body mass index, CI – confidence interval, CVD – cardiovascular disease, d – days, DM – diabetes mellitus, HF- heart failure, HR – hazard ratio, HT- hypertension, IRR – incidence rate ratio, LVF – left ventricular function, MI – myocardial infarction, OR – odds ratio, pts – patients, RR – relative risk, SBP- systolic blood pressure, TSH – thyroid stimulating hormone, VHD- valvular heart disease, yrs- years
Definitions of thyroid dysfunction[249]
Euthyroidism - TSH 0.2-5.0 mIU/L, Free thyroxine 9-22 pmol/L, Total thyroxine 60-140 mmol/L
Overt hypothyroidism -TSH >5.0 mIU/L, Free thyroxine <9 pmol/L, Total thyroxine <60 mmol/L
Subclinical hypothyroidism - TSH >5.0 mIU/L, Free thyroxine 9-22 pmol/L, Total thyroxine 60-140 mmol/L
Overt hyperthyroidism – TSH<0.2 mIU/L, Free thyroxine >22 pmol/L, Total thyroxine >140 mmol/L
Subclinical hyperthyroidism - TSH <0.2 mIU/L, Free thyroxine 9-22 pmol/L, Total thyroxine 60-140 mmol/L
TSH level dependent thyroid dysfunction[249]
Euthyroidism - TSH 0.4-5.0 MiU/L, Free thyroxine 9-22 pmol/L, Total thyroxine 60-140 mmol/L
High normal euthyroidism - TSH 0.2-0.4 mIU/L, Free thyroxine 9-22 pmol/L, Total thyroxine 60-140 mmol/L
Subclinical hyperthyroidism (reduced TSH) - TSH 0.1-0.2 mIU/L, Free thyroxine 9-22 pmol/L, Total thyroxine 60-140 mmol/L
Subclinical hyperthyroidism (suppressed TSH) - TSH <0.1 mIU/L, Free thyroxine 9-22 pmol/L, Total thyroxine 60-140 mmol/L

Electrophysiological considerations

Atrial premature beats triggering AF

Atrial fibrillation can be maintained by rapid focal firing or by reentrant activity. The actual mechanism by which triggers (ectopic beats) initiate AF is unclear, but an important topic of research. Prior reports have mapped spontaneous ectopic triggers for AF and demonstrated their spatial diversity in both atria and prematurity in rate (267). Several mechanisms produce abnormal impulse formation that can cause focal ectopic activity: abnormal automaticity and triggered activity. Abnormal automaticity relies on an increased phase 4 depolarization in cells that normally have a flat phase 4. The (upregulation of the) pacemaker current I_f (funny current) may play an important role in this mechanism.

Triggered activity consists of depolarizations occurring after the action potential: delayed after depolarizations (DADs) or within the action potential: late phase 3 early after depolarizations. These triggers

often originate from predilected sites in the atria, such as the ostia of the pulmonary vein sleeves (267). DADs are thought the most common cause of focal atrial ectopic firing and are caused by diastolic Ca^{++} leak from the sarcoplasmic reticulum via SR Ca^{++} -release channels (RyR2) and the Na^{+}/Ca^{++} exchange (NCX) (268).

To maintain AF, these ectopic beats must be sustained to produce rapid driver activity or form the trigger to initiate reentry in a vulnerable substrate. AF remodels the atrial electrical properties to promote both initiation and propagation. It is well known that electrical remodeling consists of shortening of the duration of the action potential and depressed intracellular Ca^{++} transients. Besides the involvement of the regular ion channels, also the I_{Na} late current plays a possible role.

Structural remodeling plays another important role in the initiation and maintenance of AF (269). Various pathways play a role including the RAAS, inflammation and fat deposition leading to enlarged atria, hypertrophy, fibrosis, and myolysis (270-276). Indeed, the first manifestation of AF usually occurs after years of atrial remodeling (273). Once AF develops, it causes marked changes in atrial electrophysiology ('electrical remodeling') in addition to further deterioration of the structural remodeling processes, constituting a vicious cycle in which 'AF begets AF' (271), making it challenging to restore and maintain sinus rhythm (273, 274).

Molecular Mechanisms

Abnormal cellular Ca^{++} handling is typically seen in AF patients. Defective Ca^{++} handling promotes spontaneous ryanodine receptor (RyR2) mediated Ca^{++} release in atrial cells of patients with AF. Phosphorylation of RyR2 and CAMKII is increased in AF. Increases in NCX expression/activity are also common noted in AF.

Supraventricular tachyarrhythmias causing AF

Supraventricular tachyarrhythmias (SVT) and pre-excitation may associate with AF (275-278). In 169 paroxysmal SVT outpatients, AF incidence was 19% over 2.5 years, assessed by remote monitoring (Fig. 1) (277). Atrial flutter and AF coexist even more often, one arrhythmia potentially reinforcing the other (279). Finally, flutter is frequently accompanied by atrioventricular nodal re-entry tachycardia (AVNRT) (280).

Causal mechanisms include tachycardia related atrial ischemia or dispersion of conduction and refractoriness, which can be facilitated by background atrial remodeling. Enhanced vagal tone is another mechanism (281). Digitalis may cause shortening of atrial refractoriness (282) and also associate SVT or atrial flutter with AF. The same may hold for adenosine, which may elicit AF when given for termination of SVT, and potentially cause hemodynamic deterioration (283). Due to conduction slowing, flutter may emerge under drug treatment for AF through activation of a sleeping circuit, seen especially with flecainide or propafenone (class-Ic flutter) (284). Late onset AVNRT may occur upon cardiovascular ageing, in turn producing triggers and substrate for both AVNRT, as well as AF and flutter (285). Similarly, atrial remodeling (e.g. in the setting of hypertension) may connect atrial tachycardia and atrial flutter to AF. Last, but not least, AF and SVT may also simply associate due to presence of both arrhythmia mechanisms including frequent pulmonary vein ectopy, as part of paroxysmal AF, but triggering the SVT substrate meanwhile.

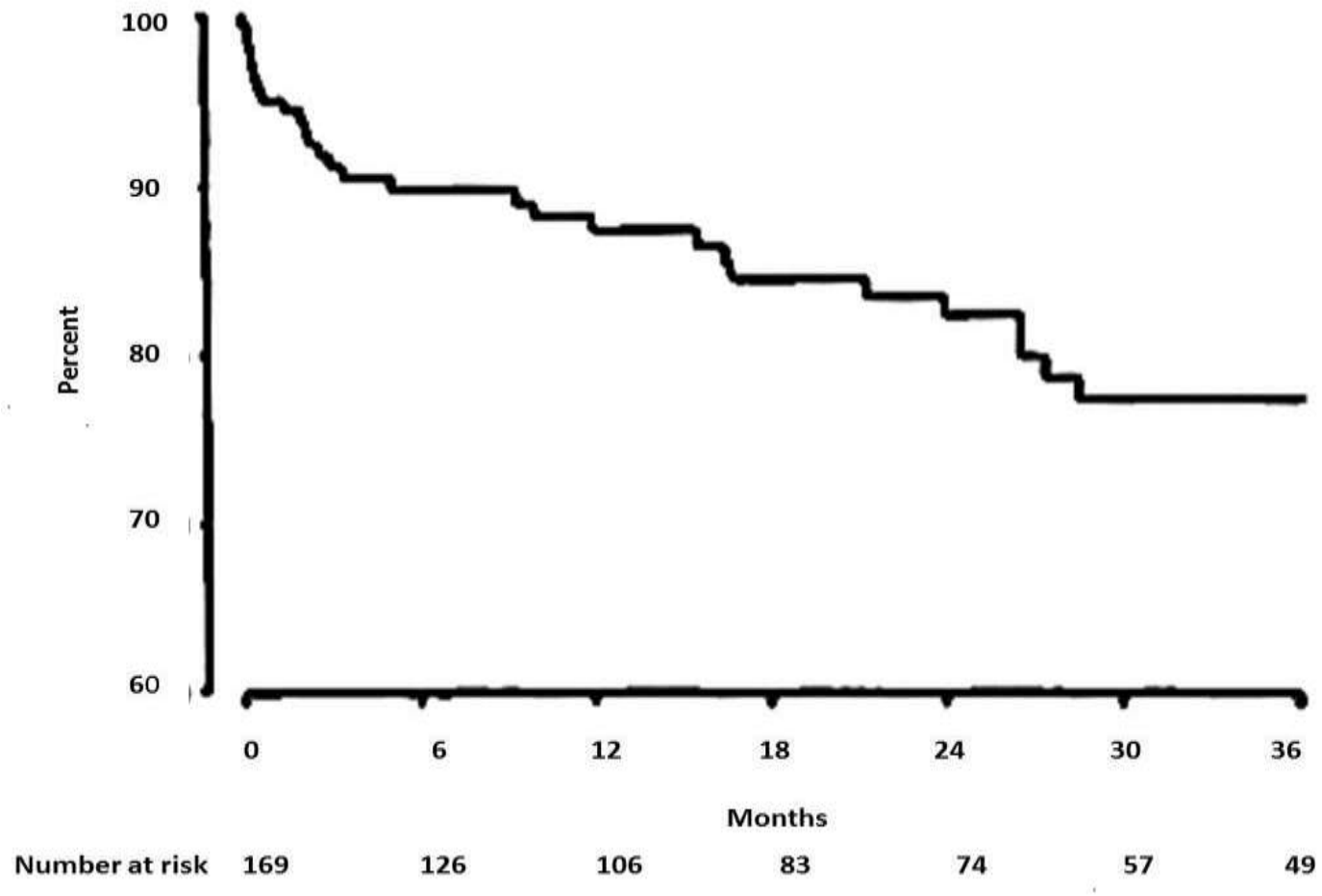

Figure 1. Graph showing time to occurrence of symptomatic atrial fibrillation in all 169 patients with paroxysmal supraventricular tachycardia. Y-axis reflects percentage of patients free from atrial fibrillation.

(Reprinted from reference 277: J Am Coll Cardiol Vol.25, Hamer ME, Wilkinson WE, Clair WK, Page RL, McCarthy EA, Pritchett EL. Incidence of symptomatic atrial fibrillation in patients with paroxysmal supraventricular tachycardia. number, p. 984-8, Copyright 1995, with permission from Elsevier)

In pre-excitation syndrome, the very presence of the accessory atrioventricular pathway (i.e. in the absence of atrial remodeling like in 'classic' AF) has been associated with local atrial arrhythmogenesis and hence AF. Conduction dispersion emerges during retrograde pathway conduction after ventricular premature beats or during orthodromic tachycardia. Asymptomatic pre-excitation usually is not associated with AF, although younger patients as well as those with inducible SVT or AF and those with a short anterograde refractory period may be at risk (286). AF and pre-excitation, together with premature conduction disease, may occur in a rare genetic form of hypertrophic cardiomyopathy due to AMP kinase gene mutation deregulating cellular energy homoeostasis (287).

When PAF and SVT associate, medical (including upstream anti-remodeling) therapy may apply for both although ablation of both mechanisms seems most appropriate. Ablation of SVT or flutter may abolish AF or make it better amenable to rhythm control, although frequently electrophysiologists will perform pulmonary vein isolation at the same time. Ablation of the accessory pathway, in patients with overt pre-excitation suffering from AF, may prevent further AF attacks (288) and is the preferred treatment also to prevent rare sudden death due to ventricular fibrillation. If these patients refuse ablation or complications are expected (e.g. atriovenricular block), then medical therapy may be indicated (286, 289). Usually flecainide or propafenone are prescribed and amiodarone may be needed in the presence of concurrent cardiac disease. After ablation of class Ic flutter it is advocated to continue drug treatment for suppression of the initial AF although after isthmus ablation AF attacks may subside spontaneously. To avoid repeat procedures, SVT mechanisms should be checked electrophysiologically during any AF ablation, especially in the younger non-remodelled AF patients (Fig. 2).

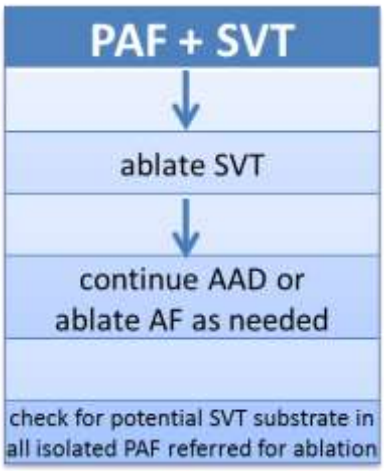

Figure 2. Management of supraventricular tachycardias causing AF

(AF – atrial fibrillation, AAD – antiarrhythmic drug, PAF – paroxysmal AF, SVT – supraventricular tachycardia)

Post-operative atrial fibrillation

AF after cardiac surgery occurs in approximately 30% of patients (290), and is also frequent after thoracic surgery. This arrhythmia is associated with higher occurrence of heart failure and stroke, both resulting in increased hospitalization and healthcare costs (291); and also correlating with a higher rate of other serious complications [increased risk of in-hospital morbidity and mortality, and increased long-term risk of stroke] (292). Post-operative AF usually is developed between day 1 and 4 after surgical intervention. The mechanisms underlying the development of AF after cardiac surgery are not completely understood, but are thought to be multifactorial (291). Numerous predisposing factors such as advanced age, hypertension, diabetes, left atrial enlargement, left ventricular hypertrophy, type of intervention and presence of cardiac valvular disease, intraoperative and post-operative factors such as atrial injury or ischemia, can favor the development of post-operative AF (293).

Different drugs have been investigated to prevent post-operative AF. Centrally-acting β-adrenergic receptor blocking agents tend to reduce sympathetic efferent activity and promote cardiac vagal outflow (294). Current guidelines strongly recommend using β-blockers to reduce post-operative AF incidence (65) and for that reason, preoperative β-blocker administration is standard in all patients without contraindications. Indeed, the European guidelines recommend that treatment should be started at least 1 week before surgery with a β1-blocker without intrinsic sympathomimetic activity (65). A large meta-analysis of 27 randomized controlled trials with 3,840 patients, reported that the incidence of post-operative

AF in control patients was 33% compared to 19% in those taking β-blockers, although an inexplicable and marked heterogeneity was found between trials (295). The importance of β-blockers is also affirmed by the two to five-fold increase in AF after cardiac surgery, when β-blockers are discontinued postoperatively (296).

The effectiveness of sotalol vs. placebo and sotalol vs. conventional β-blockers in preventing AF after surgery has been analyzed in several clinical trials. A recent meta-analysis (297) analyzed 8 trials (1,294 patients in total) evaluating the effect of sotalol to reduce post-operative AF, and demonstrated a reduction in AF incidence (37% in placebo group vs. 17% in sotalol group) with no significant heterogeneity between trials. Sotalol and other β -blockers were compared directly in 4 trials including 900 patients (295). Once again, sotalol reduced the incidence of postoperative AF from 22% in the other β -blocker group to 12% in the sotalol group with no significant heterogeneity. However, the use of sotalol places patients at risk of bradycardia and torsade de pointes, especially in those with electrolyte disturbances, reason why its use in post-operative AF is limited (65).

Several studies have analyzed the impact of amiodarone on post-operative AF, with more than 10 randomized placebo-controlled trials. In a recent meta-analysis (297), prophylactic amiodarone decreased the incidence of postoperative AF (OR 0.43; 95% CI 0.34–0.54) and significantly shortened the duration of hospital stay, reduced the incidence of stroke and of post-operative ventricular tachyarrhythmia, but not post-operative mortality (298). European guidelines recommend considering preoperative amiodarone for patients at high risk for post-operative AF (65).

It is recognized that the use of statins is associated with a 22–34% lower risk of post-operative AF (65). The largest and most robust trial of atorvastatin carried out to date, the Atorvastatin for Reduction of Myocardial Dysrhythmia After cardiac surgery study (ARMYDA-3) (299), demonstrated that atorvastatin treatment conferred a 61% reduction in risk of post-operative AF in multivariable analyses. A recent large randomised trial did not show beneficial effects of rosuvastatin on incidence of complications or AF after cardiac surgery (300).

Other drugs have been studied (297, 301), but most show conflicting results. For example, no significant effect of RAAS related medications on the occurrence of AF following cardiac surgery (291) and

safety concerns about the potential risk of associated renal dysfunction. A meta-analysis demonstrated a significant reduction in post-operative AF using corticosteroids (302), but we should take into account the potential adverse effects on glucose metabolism, wound healing, and infection. Other drugs explored included magnesium supplements, colchicine, non-steroidal anti-inflammatory drugs and antioxidant agents (i.e. polyunsaturated fatty acids or N-acetylcysteine) (301).

Current European guidelines recommend β-blockers and amiodarone as prophylactic therapies for post-operative AF. However, new pharmacologic agents, with anti-inflammatory and remodeling properties could take a place in the prevention of post-operative AF. Further research in this field is needed.

Upstream therapies to prevent AF

Upstream therapy refers to the use of non-ion-channel antiarrhythmic drugs that modify the atrial substrate upstream of AF to prevent new-onset AF (i.e. primary prevention) or recurrent AF (i.e. secondary prevention). It includes treatment with RAAS blockers [ACEIs, ARBs, and mineralocorticoid receptor antagonists (MRAs)], statins and possibly n-3 PUFAs (303, 304). RAAS blockers may prevent or reduce atrial structural remodeling by decreasing fibrosis and improving hemodynamics. Interestingly, recent data support the favorable effects of physical activity, i.e. moderate exercise on AF burden (226).

Upstream therapy has been encouraging in animal experiments, hypothesis-generating small clinical studies and primary prevention studies (303, 304). However, only few data support its beneficial effect for secondary prevention of AF. ACEIs and ARBs seem valuable, especially when added to amiodarone (274, 305). Mineralocorticoid receptor antagonists may be even more effective in preventing AF recurrences but few data are available (306, 307).

Statins, known for their lipid-lowering capacities, have pleiotropic properties such as reduction of inflammation and oxidative stress. Through these properties, statins may play a protective role against AF development. However, results regarding effectiveness of statins have been inconclusive (304).

The effects of PUFAs have been well demonstrated in animal model, but limited evidence in secondary prevention of AF is available (303, 304).

Favourable effects of lifestyle changes, including moderate exercise, have been demonstrated in selected patients (26, 27, 147, 201). In a recent randomized trial, in obese AF patients, weight management, including physical activity and counselling, was compared to general lifestyle advice (26). In addition to a significant reduction of body mass index, AF symptoms and burden were significantly reduced in the aggressive weight management group. This finding was confirmed in the Long term Effect of Goal directed weight management on AF Cohort: a 5 Year follow-up (LEGACY) trial, again in obese AF patients (28). Progressive weight loss was associated with a reduced AF burden and symptoms and, interestingly, left atrial volume.

Overall, upstream therapy may be effective in primary prevention. The disappointing results regarding secondary prevention of AF may have been caused by inclusion of patients in whom the extent of remodeling was too severe and irreversible due to a long history of AF and underlying diseases (273, 274). Inclusion of patients, in whom remodeling processes are less advanced, may improve outcome, in addition to tailoring certain upstream therapies to distinct patient groups (e.g. lifestyle changes in obese inactive patients).

Risk factors leading to AF development as risk factors for thromboembolic complications

Stroke prevention is central to the management of AF (308), and many of the risk factors leading to AF development are also risk factors for its thromboembolic complications. Whilst AF increases the risk of stroke 5-fold, this risk is not homogeneous and depends on the presence of various stroke risk factors (309). Some risk factors are independent predictors of stroke risk, and have been used to formulate various stroke risk stratification schemes, such as the CHA_2DS_2-VASc score, which is now recommended in guidelines (310). There are also various stroke risk modifiers, such as obstructive sleep apnea (311) and renal

impairment (312), that have been associated with an increased stroke risk per se, although their additive predictive (and practical) value over and above validated stroke risk scores is less certain. Whether treatment of sleep apnea with continuous positive airway pressure reduces stroke risk is unproven (311).

Some risk factors within the CHA_2DS_2-VASc score, such as age, prior stroke or thromboembolism, vascular disease and female sex, are non-modifiable. Also, prior heart failure especially if associated with a hospital admission with decompensation, confers an excess of stroke risk (313). Hence, efforts to minimize hospitalisations and decompensation of heart failure may help. Diabetes mellitus is less modifiable, but duration of diabetes may predispose to an even higher risk of stroke and thromboembolism 107).

In a systematic review of stroke risk factors, a history of hypertension or uncontrolled hypertension conferred an increase in stroke risk (309), but clearly, well-controlled hypertension has a lower risk of stroke compared to uncontrolled hypertension (314). Hypertension is also the commonest comorbidity associated with AF. Thus, patients with AF should have blood pressures approximately 130/80mmHg, reflecting the fact that AF could be considered a manifestation of hypertensive target organ damage, and given that stroke risk starts to rise beyond SBPs of 130mmHg (314).

Other potentially modifiable risk factors such as obesity, smoking and alcohol excess have been related to an increased risk of stroke and mortality (33, 315, 316), although intervention studies to show how these would successfully decrease the risk of stroke in AF are lacking. Data from cohort studies very recently indicated that weight reduction and improvement in physical fitness may reduce the recurrence of AF (27). Also, rhythm control measures, such as cardioversion and ablation, may help in symptom management and improve functional status, but randomized trials, clearly showing that such interventions reduce stroke in a broad range of unselected AF cohorts are lacking (317). Observational data, in selected cohorts, suggest that successful catheter ablation may be associated with a lowered stroke risk (318) but, given that asymptomatic recurrences and late recurrence are recognized phenomena, guidelines recommend continuation of oral anticoagulation (OAC), in patients with a CHA_2DS_2-VASc score of ≥ 2, irrespective of apparent success of rhythm control (317).

Modifiable factors to reduce the risk of stroke can include attention to quality of anticoagulation control for a patient taking a VKA (e.g., warfarin). The quality of anticoagulation control is usually quantified by the average time in therapeutic range (TTR) and a TTR of >70% is recommended (319). However, TTR can be influenced by various clinical risk factors, especially in inception cohorts where warfarin is introduced (320). Thus, in newly diagnosed and previously anticoagulated naïve AF patients, a 'trial of warfarin' prior to considering a non-VKA oral anticoagulant (NOAC) is not recommended given that TTR is likely to be subtherapeutic in the early phase of warfarin initiation, leading to an increased risk of stroke (321). The SAMe-TT_2R_2 score (322) has been proposed to help decision-making between patients who are likely to do well on a VKA with high TTR (i.e. SAMe-TT_2R_2 score 0-2) and those unlikely to do well on a VKA with poor TTR (SAMe-TT_2R_2 score >2), where a NOAC would be a better first option (323, 324). Thus, simple clinical decision making, based on clinical risk factors that influence poor TTR as a stroke risk factor (within the SAMe-TT_2R_2 score), can help inform treatment decisions that would reduce the likelihood of labile INRs, and its adverse consequences such as stroke, bleeding and death (325).

Patient values/preferences

Many of the risk factors for the development of AF are to a certain extent preventable and/or modifiable via lifestyle choices such as diet, smoking, alcohol, recreational drug use, physical activity, maintenance of a healthy weight, and adherence to medication to control concomitant conditions (hypertension, diabetes, hyperthyroidism etc.) and therefore potentially under individuals' conscious control (326). In addition, risk factors are likely to be cumulative in increasing risk of incident AF (98, 111, 115). However, an individual's ability to 'control' these factors may be limited by socioeconomic circumstances, access to healthcare and medications, and health literacy etc. Therefore, primary prevention of disease requires greater public awareness of the causes and consequences of the disease and how a person can modify his/her own risk of developing it. Thus, improving the general populations' understanding and perception of AF (what it is, how it develops, associated stroke risk), of how their lifestyle impacts their risk

of developing AF, and identifying strategies to change their health beliefs and health behaviours to reduce their risk of progressing to AF, requires both an individual approach plus global public health campaigns. Since lifestyle choices have significant impacts on all diseases, healthcare professionals should utilise contacts with patients to discuss diet, smoking, alcohol/drug use, and exercise, offer appropriate education, advice, and intervention(s), and support people to adopt and maintain health-promoting behaviours to help reduce their risk of developing AF (and other diseases).

Table 16a. Consensus statements on AF prevention I: risk factors and lifestyle modification

Risk factor/ trigger	Recommendations for clinical practice	Recommendations for research
Obesity	Inform overweight and obese patients of greater risk of developing AF and a subsequent risk of stroke and death. Assess BMI and start lifestyle programs if BMI is overweight or obese	More studies are needed on how to effectively prevent weight gain and promote weight loss in individuals who are overweight or obese More randomized controlled studies with long-term follow-up (>5 years) are needed to clarify the obesity paradox.
General dietary considerations	Recommend healthy nutrition and lifestyle to reduce risk of AF Mediterranean diet enriched with olive oil may reduce risk of AF and its complications	More studies are needed on: The effect of unhealthy nutrition on risk of AF Whether modification of diet reduces risk of arrhythmia
Blood lipids, fish consumption	Inform patients with low HDL and high triglyceride levels of risk of AF and its complications Recommend to patients with abnormal blood lipids consumption of a diet "that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils, and nuts; and limits intake of sweets, sugar-sweetened beverages, and red meats"[64] Recommend combination of diet with moderate physical activity and maintenance of a healthy lifestyle and weight	Lacking direct evidence, more studies are needed to define whether modification of blood lipids reduces the risk of AF.
Obstructive sleep apnea	Inform patients with obstructive sleep apnea that there is a greater risk of developing AF and their subsequent risk of stroke and death. Assess by anamnesis (snoring, daytime fatigue) the possibility of OSA. Refer to specialised clinic, as needed.	More studies are needed: To investigate how comorbidity in patients with obstructive sleep apnea affects the risk of AF. To show the benefit of diagnostic efforts and the effect of treatment with CPAP. On adequate assessment of presence of OSA in AF population. To show reduced risk of AF in well powered RCTs using systematic therapeutic approach together with other lifestyle changes
Hypertension	Uncontrolled blood pressure is associated with AF risk Adequately assess patients at risk Control BP to reduce AF risk	Additional well-conducted secondary AF prevention trials will be important to define target SBP optimal to prevent AF Implement in RCTs together with other lifestyle management
Diabetes mellitus	Longer duration of diabetes and worse glycemic control are associated with increased AF risk Control diabetes to reduce AF risk	More research is needed on the effect of glycemic control on AF risk in patients with diabetes

Risk factor/ trigger	Recommendations for clinical practice	Recommendations for research
Tobacco smoking	Intensively encourage children, young and older adults not to begin smoking. In individuals who smoke support smoking cessation to prevent AF incidence, recurrence, symptoms, and complications. **Primordial prevention**. Support efforts to prevent the uptake of tobacco smoking. **Primary prevention**. Encourage individuals to quit smoking. **Secondary prevention**. In individuals with AF promote efforts to quit smoking to improve AF frequency, duration, and symptoms	Investigate whether electronic cigarettes and second hand smoke are associated with an increased risk of new-onset AF, and in individuals with prevalent AF, whether electronic cigarettes and second hand smoke are associated with AF recurrence and AF symptoms. In individuals with AF, examine the efficacy and effectiveness of smoking cessation interventions to decrease the risk of stroke, myocardial infarction, chronic kidney disease, dementia, and all-cause mortality.
Air pollution	No association with chronic exposure; patients prone to AF should refrain from severe pollution exposure.	Overall data are scarce and should be increased specifically aimed at incidence of AF in patients with known cardiac disease.
Caffeine	No increase in risk, rather a reduced association, even for heavy consumption.	Data should be extended to randomized intervention studies addressing caffeine consumption in patients with paroxysmal AF
Alcohol	Moderate-heavy and binge drinking increases AF risk To reduce AF risk: Recommend to avoid binge drinking (>4 drinks in women and >5 drinks in men on a single occasion) Recommend to refrain consumption to no more than 2 drinks per day for men and 1 drink per day for women Obtain a detailed history on alcohol consumption Provide appropriate counseling to reduce alcohol consumption in patients with AF	More intervention studies are needed on the effect of alcohol consumption reduction on AF risk
Medications	Many drugs increase AF risk. In patients with new-onset AF, review the pharmacological history to identify whether any of the prescribed drugs may cause the arrhythmia.	More research on the effects on AF incidence for drug induced new-onset AF is needed, as many studies show conflicting results. Also more research is needed on which medications cause increased risk of AF.
Recreational drugs	Recreational drugs (cannabis, ecstasy and anabolic androgenic steroids) may increase risk of AF. Examine for recreational drug abuse in new-onset AF Encourage avoidance of recreational drugs.	More research is needed on the effect of illicit drugs, particularly cannabis, on new-onset AF, as most of the evidence is from case reports
Psychological distress	Identify significant psychological distress, particularly depression and anxiety, and treat appropriately to reduce the likelihood of adverse lifestyle choices (smoking, excessive alcohol intake, poor diet, physical inactivity) and poorer adherence to medication and lifestyle modification, all of which may increase the likelihood of development of other risk factors for AF, and hence predispose people to incident AF and other chronic diseases.	Further investigation of the impact of psychological distress on the development of AF in more diverse populations is warranted since the current limited evidence is based predominantly on white, middle-class, and middle-aged cohorts, and is only evident in men.
Physical activity	Recommend daily moderate exercise to reduce risk of AF	Role of physical activity clearly warrants further research, plus genetics involved in AF in excessive sports
AF – atrial fibrillation, BMI – body mass index, BP – blood pressure, CPAP – continuous positive airway pressure, HDL – high-densiy lipoprotein cholesterol, OSA – obstructive sleep apnea, RCT – randomised controlled trial, SBP – systolic blood pressure		

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847 **Table 16b. Consensus statements on AF prevention II: management of associated conditions**

Risk factor/ trigger	Recommendations for clinical practice	Recommendations for research
Hyperthyroidism	Overt and subclinical hyperthyroidism increase AF risk Control thyroid function in patients at risk of AF Treat associated cardiovascular diseases and consider modification of risk factors	More research is needed regarding risk factors and prevention of AF in populations with high-normal thyroid function (based on TSH level) and individuals with higher level of free thyroxin within normal range.
Supraventricular tachyarrhythmias and paroxysmal AF	In patients with SVT and paroxysmal AF: Ablate SVT, continue antiarrhythmic drugs or ablate AF as needed. Checking for potential SVT substrate should be considered in patients with isolated PAF referred for ablation	Additional studies on prevention of AF in patients with SVT are needed

Risk factor/ trigger	Recommendations for clinical practice	Recommendations for research
Postoperative AF	Beta-blockers and amiodarone are indicated for prophylaxis of postoperative AF	More research is needed on use of pharmacological agents with anti-inflammatory and anti-remodeling properties for prevention of postoperative AF
Upstream therapies	-	Long term effects of long-term secondary prevention with upstream therapies starting early after onset of AF
AF –atrial fibrillation, PAF – paroxysmal atrial fibrillation, SVT – supraventricular tachycardia, TSH – thyroid stimulating hormone		

Conclusions

In the present document, the determinants and triggers of atrial fibrillation (AF) are extensively discussed and it appears clear that prevention of this disorder requires a tailored approach to the individual patient. Moreover, certain modifiable risk factors, such smoking, alcohol abuse and lack of physical activity are deemed important components of a preventive strategy (33, 315, 316).

In order to reduce the risk of AF, both an individual approach and global public health campaigns are required.

Many of the risk factors for AF are preventable and/or modifiable via lifestyle choices. As explained, modifying an inappropriate diet, quitting smoking, abstaining from alcohol and recreational drugs, and participating in regular physical activity programs are efficient strategies under the patient's control.

A lifetime approach to cardiovascular risk modification is required (Fig. 3). General physicians have a relevant role in this strategy, by monitoring their patients closely and adopting a lower threshold for educational intervention. A particular relevance to the scope is assigned to the implementation of nutritional interventions and to promote regular exercise programs and sport participation. However, the greatest effort should be paid by policy makers in order to improve the population's capability to achieve and maintain a

healthy cardiovascular lifestyle. The most adverse risk profile is actually prevalent among individuals with low socioeconomic status, poorer educational attainment, and limited access to health care.

The prevention of AF, more than other cardiovascular disorders, requires an approach that targets the global population, and a new political vision in the management of the health care system. In a society with available limited financial resources, it appears wise to modify the risk factors and quality of life of the largest majority of general population, more than developing sophisticated devices to shortly prolong the life of a few terminal patients.

Finally, special attention should be paid to the adolescent and young generations, who paradoxically are not at low cardiac risk, because of the epidemic incidence of obesity, inappropriate nutritional behavior, smoking and alcohol abuse, and a widespread sedentary lifestyle.

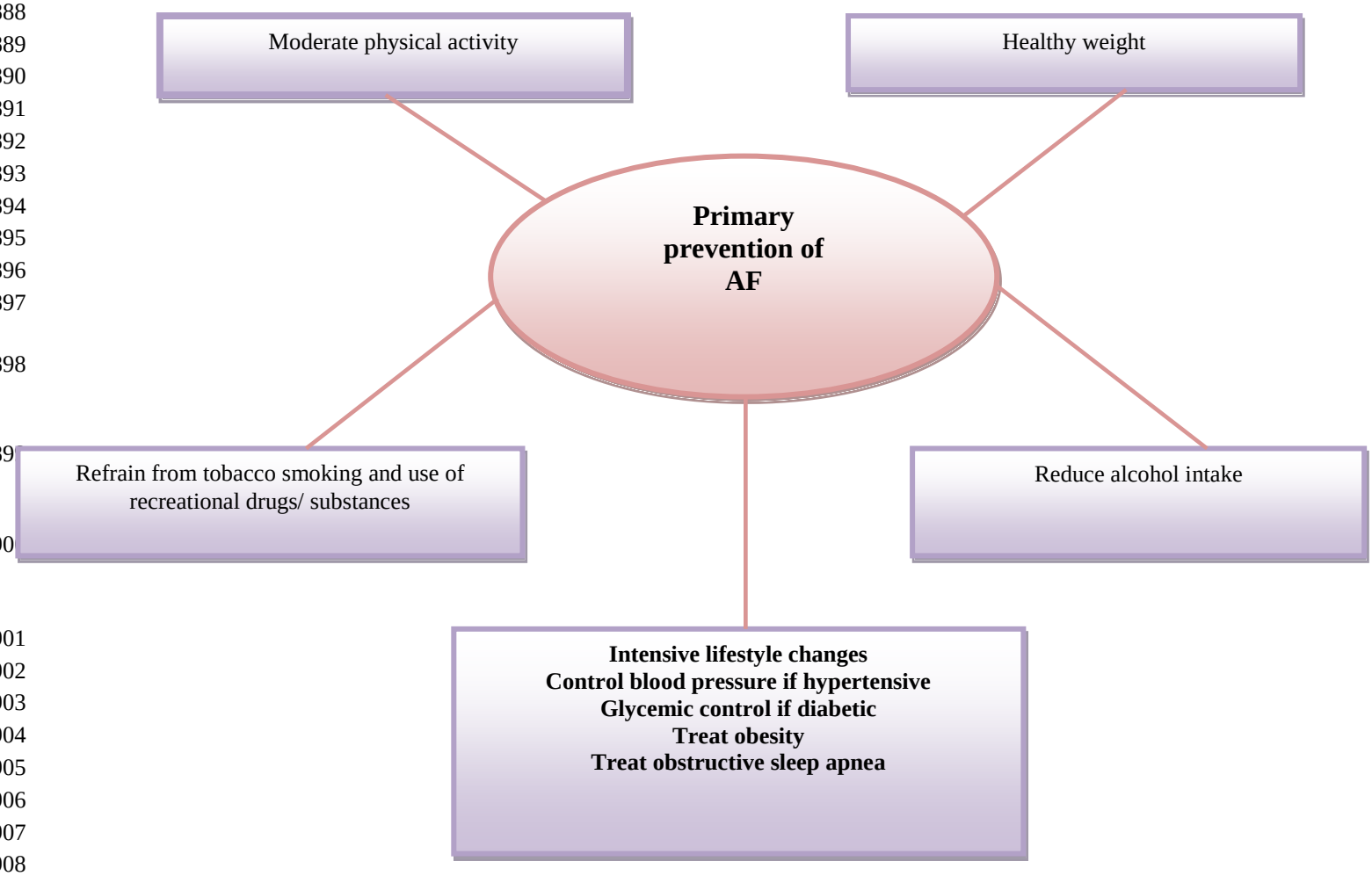

Figure 3. Lifetime approach to primary prevention of AF

(AF – atrial fibrillation)

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