ATRIAL FIBRILLATION: RELATION TO THE METABOLIC SYNDROME, SMOKING, AND DEVELOPMENT OF A CLINICAL RISK SCORE

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ABSTRACT

This document provides information on the pathophysiology and epidemiology of atrial fibrillation, along with details on three manuscripts that together form the basis of a doctoral thesis. Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice and poses a great economic burden on the healthcare system. Some well known cardiovascular risk factors, such as smoking and the metabolic syndrome, have not been widely studied in the context of AF. In addition, the majority of studies on AF have used primarily white cohorts from North America and Europe.

This dissertation reports the associations of the metabolic syndrome and smoking with incident AF, and provides a 10-year risk prediction score for AF using the Atherosclerosis Risk in Communities (ARIC) study. The ARIC study is a bi-racial cohort of almost 16,000 participants followed since the baseline examination in 1987-1989.

The first manuscript describes the association of the metabolic syndrome and the individual components of the metabolic syndrome with risk of incident AF over a mean follow-up of 15.4 years. A 67% increased risk of incident AF was reported for individuals with compared to those without the metabolic syndrome at baseline. Most of the metabolic syndrome components were associated with an increased AF risk, and of the individual components, elevated blood pressure appeared to contribute most to AF risk. In addition, a monotonically increasing risk of AF with increasing number of metabolic syndrome components was observed.

In the second manuscript, the associations of smoking status and amount with incident AF in ARIC were examined, and a systematic literature review on prospective cohort studies investigating the effects of smoking on AF incidence was conducted. Current and former smokers exhibited a 98% and 30% increased risk of developing AF compared to never smokers. The risk of incident AF increased with increasing cigarette-years of smoking, and appeared to be somewhat greater among current smokers than former smokers with similar cigarette-years of smoking. However, no consistent association was apparent in previously published studies on smoking and incident AF.

A 10-year risk score for AF was developed using risk factors commonly measured in clinical practice for the third manuscript. The risk score had good discrimination and better predicted who would develop AF than the Framingham AF risk score applied to the ARIC cohort. In addition, the Framingham and ARIC coronary heart disease risk scores did not predict the 10-year risk of AF well, highlighting the importance of a separate risk score to predict AF.

TABLE OF CONTENTS

1.0 LIST OF TABLES

2.0 LIST OF FIGURES

3.0 INTRODUCTION TO ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice and currently affects more than 2.2 million Americans.[1] AF is a major cause of morbidity and mortality, and is associated with increased risk of stroke,[2,3] congestive heart failure,[3] and death.[3,4] The prevalence of AF is 1% in the general population;[5] the prevalence of AF increases markedly with age and is approximately 10% for those 80 years of age or older.[5-7] AF imposes a substantial economic burden, with total annual costs for treatment of AF in the U.S. in 2001 estimated at $6.65 billion.[8] This estimate included $2.93 billion for hospitalizations with a principal discharge diagnosis of AF, $1.95 billion for the incremental inpatient cost of AF as a co-morbid diagnosis, $1.53 billion for outpatient treatment of AF, and $235 million for prescription drugs.[8] Key risk factors for AF include increasing age,[5,9,10] hypertension,[10,11] diabetes,[10-13] obesity,[14] myocardial infarction (MI),[11] congestive heart failure(CHF),[10,11] cardiac valvular disease,[9-11] and structural abnormalities such as left ventricular hypertrophy(LVH).[10,15] Therefore, with the aging population and improved survival after MI and CHF, AF is a major public health concern.

4.0 PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION

4.1 NATURAL HISTORY

Atrial fibrillation was first reported in 1906 in 2 different articles revealing that "auricular fibrillation" affected humans, was common in patients with heart disease, and could be identified by a new instrument, the electrocardiograph.[16] AF is a cardiac arrhythmia caused by disorganized and rapid atrial depolarizations without effective atrial contraction.[17] AF is characterized on the electrocardiogram (ECG) by the absence of distinct P-waves, the presence of rapid atrial oscillations, and variable RR intervals.[18] Originally, AF was thought to arise by multiple circuit re-entry, and this theory has held until recently; current evidence now suggests that ectopic activity, single circuit re-entry, and multiple circuit re-entry may all be involved in the pathophysiology of AF.[19] AF is often precipitated by underlying anatomically and histologically abnormal atria. The most frequent pathological changes are atrial dilation, fibrosis, abnormal muscle fibers, and healthy atrial muscle fibers coexisting in close proximity.[20] In addition to histological changes, the onset of AF usually requires a trigger, such as acute atrial stretch, changes in parasympathetic and sympathetic stimulation, atrial premature beats or supraventricular tachycardia, and accessory pathway-mediated tachycardia.[21] The following diagram depicts the multiple factors involved in the pathogenesis of AF:

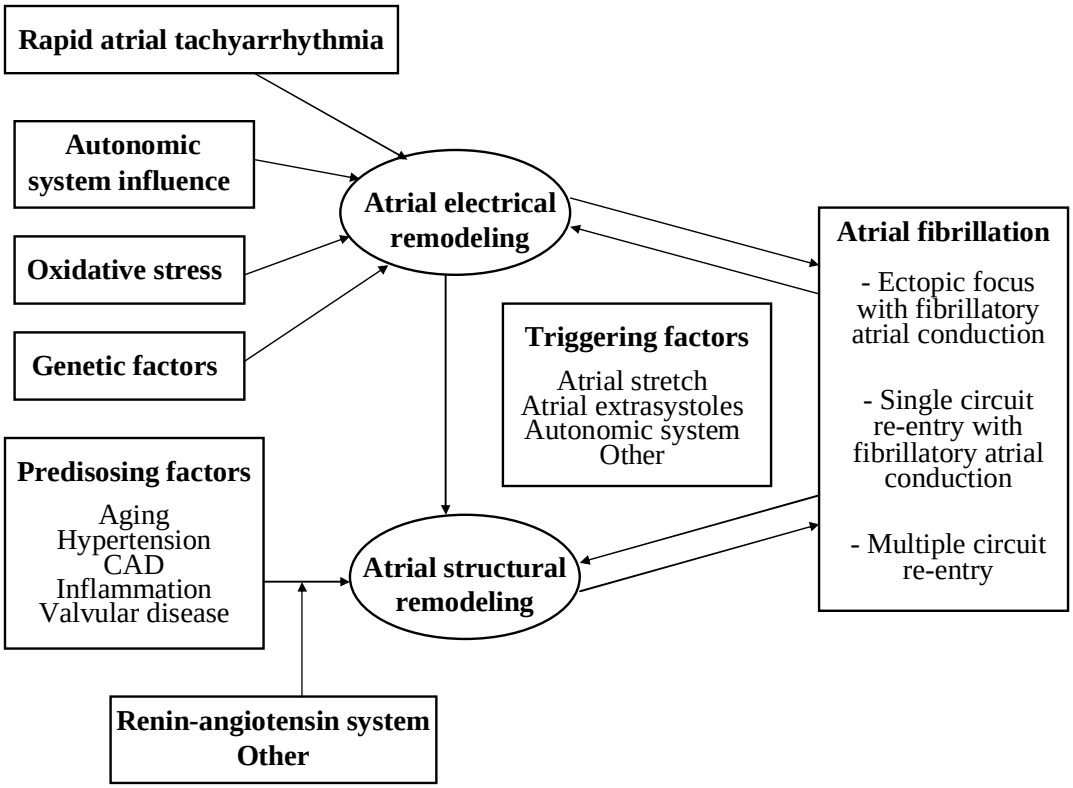


Figure 4.1: Factors involved in the pathogenesis of atrial fibrillation. Adapted from Leonardi, M & Bissett, J. *Curr Opin Cardiol*. 2005;20:417-23.

After initiation, AF may persist because of the persistence of the trigger or because of electrical remodeling that promotes AF without the persistence of the trigger.[22]

The two commonly recognized pathophysiologic processes underlying AF include 1) enhanced automaticity in 1 or more rapidly depolarizing foci, typically in the superior pulmonary veins, and 2) re-entry involving 1 or more circuits (known as the multiple wavelet hypothesis). However, it is important to note that these two processes are not mutually exclusive and may coexist.[23] In the first scenario, a single focal discharge in the pulmonary veins, or short bursts of multiple focal discharges, may initiate AF.[24] In addition, AF may begin as a rapid atrial tachycardia from the pulmonary veins, but result

in electrical remodeling that promotes multiple circuit re-entry AF.[25] Multiple circuit re-entry AF involves fractionization of wave fronts through the atria and self-perpetuation of daughter wavelets.[23] A large atrial mass with a short refractory period and delayed conduction increase the number of wavelets, suggesting that this mechanism is more likely in sustained AF.[23] The mechanisms involved in AF are summarized in the figure below:

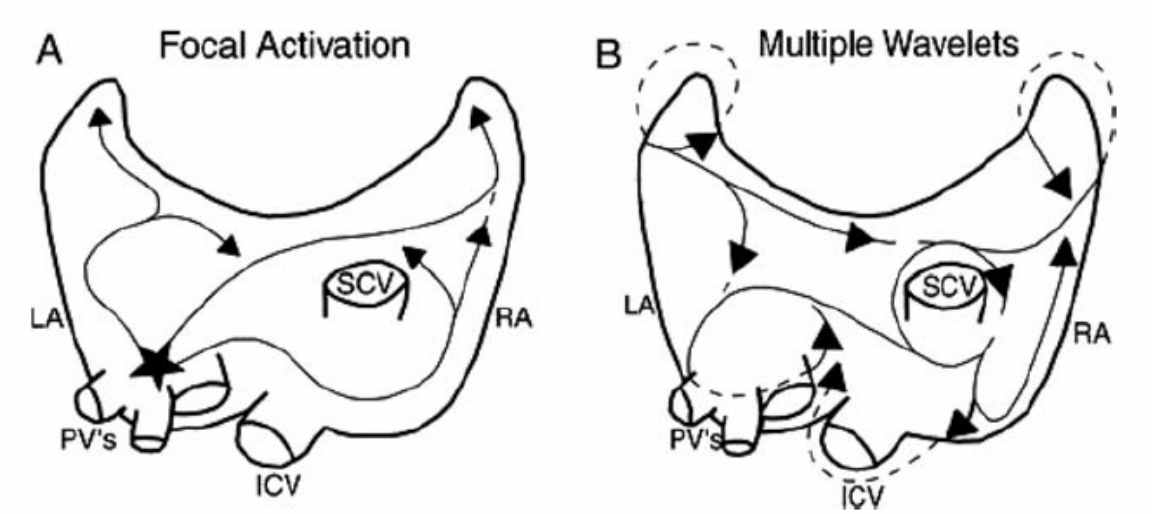


Figure 4.2: Posterior view of electrophysiological mechanisms in atrial fibrillation. A) Focal activation: the initiating focus (indicated by the star) often lies within the pulmonary veins. B) Multiple wavelet re-entry: wavelets (indicated by the arrows) randomly re-enter tissue previously activated by the same or another wavelet. From Fuster, V et al. *J Am Coll Cardiol*. 2006;48:854-906.

Regardless of the mechanism initiating the arrhythmia, atrial electrical properties are modified in a way that promotes the occurrence and maintenance of AF.[18]

4.2 CLASSIFICATION OF ATRIAL FIBRILLATION

AF can be classified as either a first-detected episode or recurrent.[26] Recurrent AF can be further categorized into subtypes based on its duration and response to treatment. AF is considered "paroxysmal" if it terminates spontaneously within 7 days. An episode that lasts longer than 7 days and is unlikely to self-terminate, therefore requiring electrical or pharmacological cardioversion for termination, is considered "persistent." "Permanent" AF is defined as longstanding AF (greater than 1 year) in which cardioversion is not attempted or when cardioversion is not successful.[26,27] Permanent AF appears to account for approximately half of all AF cases. In a study of 756 general practice AF patients in France, 22.1% had paroxysmal AF, 51.4% had permanent AF, and 26.4% had persistent AF.[28]

In addition, AF in individuals younger than 60 years of age and in the absence of underlying heart disease, hypertension, or diabetes is termed "lone" AF.[29] Finally, the term "nonvalvular" AF refers to AF in individuals without rheumatic mitral valve disease, prosthetic heart valve, or valve repair.[23]

4.3 ATRIAL FIBRILLATION AND ATRIAL FLUTTER

AF and atrial flutter (AFL) are two different types of atrial tachyarrhythmias and, thus, a distinction between the two conditions should be made. Briefly, AFL is characterized by a single re-entrant circuit in the right atrium, an atrial rate of 250-350 beats/min, a regular ventricular rhythm, and generally a 2:1 atrioventricular conduction

resulting in a ventricular rate of 150 beats/min.[18,30] On ECG, broad, saw-toothed F waves are apparent in AFL,[18,30] as seen below:

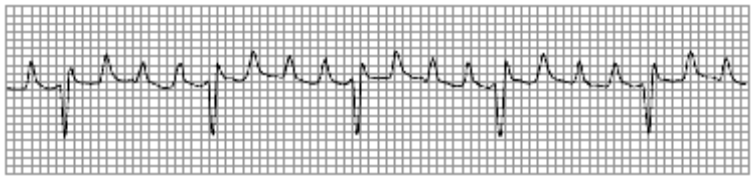


Figure 4.3: Flutter waves in atrial flutter. From Goodacre, S & Irons, R. *BMJ*. 2002;324:594-7.

AF can be distinguished from AFL because it is often caused by multiple-wavelet re-entry sweeping around the atrial myocardium chaotically, but rarely completing a re-entry circuit.[30] Additionally, an atrial rate of 350-600 beats/min, an irregular ventricular rhythm, and a ventricular rate of 100-180 beats/min are characteristic of AF.[30] On ECG, an absence of distinct P-waves before the QRS complex, rapid atrial oscillations, and variable RR intervals are seen on a rhythm strip in AF.[18,30]

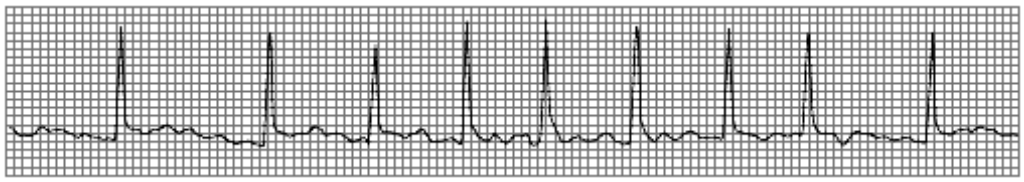


Figure 4.4: Rhythm strip in atrial fibrillation showing variable RR intervals and lack of P-waves. From Goodacre, S & Irons, R. *BMJ*. 2002;324:594-7.

5.0 CLINICAL ASPECTS OF ATRIAL FIBRILLATION

5.1 DIAGNOSIS

AF is often undetected because many individuals with AF are asymptomatic[31] or have few symptoms. Some patients with AF may have minimal to no symptoms, whereas others may have severe symptoms. Symptoms, when present, include palpitations, fatigue, lightheadedness, dyspnea with exertion, and acute pulmonary edema.[31,32] Some patients experience symptoms only during paroxysmal AF, and over time as AF becomes permanent, symptoms such as palpitations may disappear.[23]

Because many individuals with AF lack symptoms, AF is often diagnosed by routine ECG examination, in the course of a stroke or MI, on implanted pacemaker, or during ambulatory ECG monitoring.[31] On ECG, AF is detected by the replacement of consistent P-waves with rapid oscillations varying in amplitude, shape, and timing, and an irregular ventricular response.[18] The RR intervals may also be irregular when atrioventricular (AV) block or ventricular or AV junctional tachycardia is present.[18,23] In addition, an irregular, sustained, wide QRS complex suggests AF with conduction over an accessory pathway or AF with bundle-branch block.[23]

Initial evaluation of a patient with suspected AF involves determining whether the arrhythmia is paroxysmal or persistent, identifying its cause, and defining any associated factors pertinent to the etiology, tolerability, and management. Furthermore, the diagnosis of AF requires confirmation by ECG by at least a single-lead recording during

AF.[23] The following describes the minimum work-up and additional testing in the diagnosis of AF:[23]

Minimum Evaluation

1. History and physical examination, to define:
    - Presence and nature of symptoms associated with AF
    - Clinical type of AF (first episode, paroxysmal, persistent, permanent)
    - Onset of first symptomatic attack or date of discovery of AF
    - Frequency, duration, precipitating factors, and modes of termination of AF
    - Response to any pharmacological agents that have been administered
    - Presence of any underlying heart disease or other reversible conditions (e.g., hyperthyroidism or alcohol consumption)
2. Electrocardiogram, to identify:
    - Rhythm (verify AF)
    - Left ventricular hypertrophy
    - P-wave duration and morphology or fibrillatory waves
    - Pre-excitation
    - Bundle-branch block
    - Prior myocardial infarction
    - Other atrial arrhythmias
    - To measure and follow the RR, QRS, and QT intervals in conjunction with antiarrhythmic drug therapy
3. Transthoracic echocardiogram, to identify:
    - Valvular heart disease
    - Left atrial and right atrial size
    - Left ventricular size and function
    - Peak right ventricular pressure (pulmonary hypertension)
    - Left ventricular hypertrophy
    - Left atrial thrombus

- Pericardial disease

4. Blood tests of thyroid, renal, and hepatic function
    - For a first episode of AF, when the ventricular rate is difficult to control

Additional Testing

1. Six-minute walk test
    - If the adequacy of rate control is in question
2. Exercise testing
    - If the adequacy of rate control is in question
    - To reproduce exercise-induced AF
    - To exclude ischemia before treatment of selected patients with a type IC antiarrhythmic drug, such as flecainide or propafenone
3. Holter monitoring or event recording
    - If diagnosis of the type of arrhythmia is in question
    - As a means of evaluating rate control
4. Electrophysiological study
    - To identify left atrial thrombus (in the left atrial appendage)
    - To guide cardioversion
5. Chest radiograph, to evaluate:
    - Lung parenchyma, when clinical findings suggest an abnormality
    - Pulmonary vasculature, when clinical findings suggest an abnormality

5.2 TREATMENT

Treatment is improving for AF, reflected in decreasing case-fatality in recent years. Although the death rates for AF have been increasing, likely due to increasing AF incidence, a few studies in Europe describe a trend of decreasing case-fatality.[33-35] In Scotland, hospitalizations for newly-diagnosed AF doubled between 1986 and 1995, but

case-fatality over the following 2 years decreased from 25% to 22% in men and from 27% to 25% in women.[33] In Denmark, total mortality among AF patients decreased 12-13% between 1980 and 1993.[35]

Treatment for AF includes strategies to control rate, correct rhythm disturbance, and prevent thromboembolism. Current guidelines recommend a ventricular rate of 60-80 beats/min at rest and 90-115 beats/min during exercise in patients with AF.[23] Rate control therapy depends mainly on suppression of conduction across the AV node, and thus drugs that prolong the refractory period of the AV node are generally effective for rate control.[23] Calcium channel blockers and beta blockers are the first choice for rate control, although digoxin and amiodarone are also used.[36,37] These drugs may be administered intravenously or orally, and a combination of drugs may be needed to effectively control the ventricular rate.[23] Although rate control is generally achieved through drugs, AV nodal ablation with a permanent pacemaker implantation may be necessary in patients who do not achieve pharmacologic rate control or who develop bradycardia in response to treatment.[37]

Rhythm control strategies include administration of antiarrhythmic drugs, electrical cardioversion, the maze procedure, catheter ablation, atrial pacing, and implantation of an internal atrial defibrillator. The most commonly used antiarrhythmic agents are flecainide and propafenone, with efficacy in cardioversion of recent-onset AF ranging between 75-91% for flecainide and 79-86% for propafenone.[37] Pharmacologic agents are most effective in recent-onset AF, and other strategies of rhythm control may be necessary in patients with persistent AF. Electrical cardioversion is another rhythm control strategy that may be used with or without administration of an antiarrhythmic

drug. Electrical cardioversion involves delivering an electric shock through the chest wall to the heart, interrupting abnormal electrical circuits to restore a normal heart beat.[38] If cardioversion alone is unsuccessful, administration of an antiarrhythmic drug, such as ibutilide, may be used in conjunction with another electrical cardioversion to increase the likelihood of restoration to sinus rhythm.[32] Another procedure for rhythm control that is very effective is the maze procedure. This procedure involves isolating the pulmonary veins and surgically creating scars in the left atrium so that no area is wide enough to sustain multiple re-entry cirucuits.[32,37] The maze procedure controls AF in >90% of patients,[37] but has not been widely adopted due to the need for cardiopulmonary bypass to perform the maze procedure.[23] Catheter ablation is a much less invasive alternative to the maze procedure. Catheter ablation involves isolation of the pulmonary veins through radiofrequency with or without additional ablation of arrhythmogenic foci.[26,37] Atrial pacing is another possible rhythm control strategy, although the value of atrial pacing for prevention of recurrent AF has yet to be proven.[23] Atrial pacing prevents AF by influencing the pattern of atrial depolarization and suppressing premature atrial beats.[37] Finally, implantation of an internal defibrillator that can detect and treat, as well as prevent AF, is an option for patients with highly symptomatic, recurrent, and drug-resistant AF.

It appears that rate control may be associated with a slightly reduced risk of death and thromboembolic stroke compared to rhythm control for treatment of AF. A recent multi-center randomized trial found that in patients with AF and CHF, no differences were found in stroke, worsening heart failure, death from cardiovascular disease, death from any cause, or a composite of death from cardiovascular causes, stroke, or worsening

heart failure between rate and rhythm control strategies.[39] Likewise, in 5 prior randomized trials comparing rate control to rhythm control, no significant differences were found in adverse events between the 2 treatment strategies,[40-44] although hospitalizations were more frequent when rhythm control was used.[40-43] However, in a meta-analysis pooling these 5 randomized trials, rate control compared to rhythm control was associated with a significantly lower risk (odds ratio (OR)=0.84; 95% CI, 0.73-0.98) of a combined endpoint of all-cause mortality and stroke.[45] A nonsignificant trend of reduced risk of death and stroke when considered separately was also noted, but there was no difference in the risk of major bleeds or systemic embolism between the 2 treatment strategies.[45] The following figure depicts the results from the 5 trials comparing rate and rhythm control strategies for AF treatment, as well as pooled results from the meta-analysis:

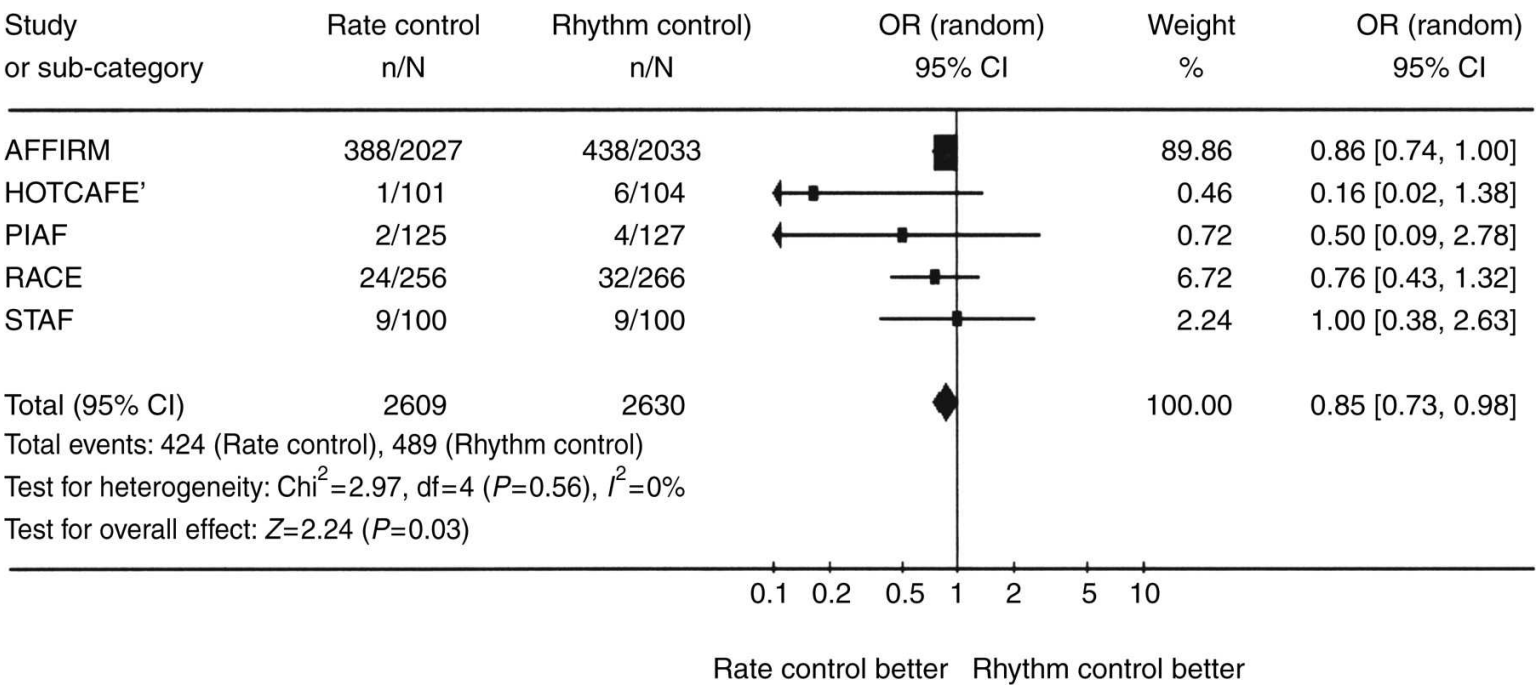


Figure 5.1: Single and pooled odds ratios comparing rate and rhythm control for atrial fibrillation for combined endpoint of all-cause mortality and thromboembolic stroke. From Testa, L et al. *Eur Heart J*. 2005;26:2000-6.

Although rate control may be associated with a better prognosis than rhythm control, rhythm control may be more suitable for young patients with highly symptomatic paroxysmal AF, whereas rate control may be more suitable for older patients with asymptomatic persistent or permanent AF.[26] In addition, rate control should be a primary approach for patients with both AF and heart failure.[46]

In addition to rate or rhythm control, anticoagulation therapy with warfarin or aspirin is warranted in most patients with AF for stroke prevention. Warfarin is indicated in patients considered at high risk for developing stroke, whereas aspirin is often recommended for those at low risk of stroke.[37] The following table describes appropriate anticoagulation therapy based on risk of developing stroke:

Risk Category	**Recommended Therapy**	
No risk factors	Aspirin (81-325 mg daily)	
One moderate-risk factor	Aspirin (81-325 mg daily) or warfarin (INR 2.0-3.0, target 2.5)	
Any high-risk factor or >1 moderate-risk factor	Warfarin (INR 2.0-3.0, target 2.5)*	
Less Validated or Weaker Risk Factors	**Moderate-Risk Factors**	**High-Risk Factors**
Female gender	Age ≥75 years	Prior stroke, TIA, embolism
Age 65 to 74 years	Hypertension	Mitral stenosis
Coronary artery disease	Heart failure	Prosthetic heart valve*
Thyrotoxicosis	LV ejection fraction ≤35%	

* If mechanical valve, target INR >2.5.
INR indicates international normalized ratio; TIA, transient ischemic attack.

Table 5.1: Stratification of stroke risk and recommended prophylaxis in patients with atrial fibrillation. Adapted from Fuster, V et al. *J Am Coll Cardiol*. 2006;48:854-906.

6.0 DESCRIPTIVE EPIDEMIOLOGY OF ATRIAL FIBRILLATION

6.1 INCIDENCE AND PREVALENCE

AF currently affects more than 2.2 million Americans,[1,5,6] and the lifetime risk for development of AF in men and women over 40 years of age is 1 in 4.[47] By the year 2050, it is expected that 10 million Americans will have AF.[48]

The incidence and prevalence of AF in the U.S. has been increasing steadily over the last couple decades. Using data from the National Hospital Discharge Survey (NHDS) from 1985 to 1999, hospitalizations for AF as the principal diagnosis increased from 14.3 to 24.8 per 10,000 in men and 15.1 to 27.8 per 10,000 in women.[49] From 1996 to 2001, a 34% increase in hospital admissions for AF was observed.[50] Based on the National Hospital Ambulatory Medical Care Survey, the rate of emergency department visits was lower, but also doubled from 0.6 to 1.2 per 1,000 U.S. population from 1993 to 2004.[51] Hospital admission rates were similar in men and women,[49-51] higher in blacks compared to whites,[50,51] and increased greatly with increasing age group.[49-51]

In addition to hospital admission data, the incidence of AF has been estimated in a few population-based cohort studies. In the Framingham Heart Study, the incidence of AF was higher in men than women and increased with age,[10,11,52] roughly doubling with each decade of age beyond 50 years.[11,52] Incidence rates increased from 6.2 and 3.8 per 1,000 person-exams in 55-64 year old men and women, respectively, to 75.9 and 62.8 per 1,000 person-exams in men and women aged 85-94 over 38 years of follow-up.[11] An incidence rate of 19.2 per 1,000 person-years was found among individuals 65 years of

age and older enrolled in the Cardiovascular Health Study.[9] Again, the incidence rates were higher in men and older individuals; in men 65 to 74 and 75 to 84 years old, the incidence rates were 17.6 and 42.7, respectively, and in women were 10.1 and 21.6 per 1,000 person-years.[9] In Olmsted County, Minnesota, the incidence rates for AF were much lower than in the Framingham Heart Study and the Cardiovascular Health Study, ranging from 3.04 per 1,000 person-years in 1980 to 3.68 per 1,000 person-years in 2000.[48] Incidence rates for AF in the Atherosclerosis Risk in Communities study were similar to those from Olmsted County; the crude incidence rates were 6.7, 4.0, 3.9, and 3.0 per 1,000 person-years in white men, white women, black men, and black women, respectively.[53]

The estimated prevalence of AF ranges from 0.1% in those 40-44 years of age to 10% among individuals 80 years of age and older.[6] A cross-sectional study of adults aged 20 and older, members of a health maintenance organization in Northern California, supported these estimates, reporting prevalences that ranged between 0.1% in those younger than 55 to 9% in persons aged 80 years or older.[5] Similar to the pattern of incidence rates, the prevalence of AF is also increasing in recent decades. For example, the AF prevalence among Medicare patients ($\geq$65 years of age) increased from 3.2% in 1992 to 6.0% in 2002,[54] and in the Framingham Heart Study, the age-adjusted prevalence increased from 3.2% to 9.1% in men and from 2.8% to 4.7% in women from the year 10 exam (1968-1970) to the year 20 exam (1987-1989).[55]

The overall incidence and prevalence of AF in Canadians, Europeans, and Australians is comparable to that in the U.S.; likewise, the incidence and prevalence is higher in older age groups, and has been increasing in recent years.[56-67] However, the

prevalence of AF is lower among Asians compared to North Americans and Europeans.[68-70] In Koreans, the prevalence of AF was 0.7% in those older than 40 and 2.1% in those older than 65.[68] In Chinese, the overall prevalence of AF was 1.5% and among those older than 80 was 5.8%.[69] Finally, the prevalence of AF among acute hospital admissions was 2.8% in Kuala Lumpur, Malaysia.[70] These prevalences in Asians are much lower than those reported in Americans. For comparison, the overall prevalence of AF pooling 3 large population-based studies in the U.S. and 1 in Australia was 2.3%; the prevalences of AF were 5.9% and 10% in individuals over 65 and over 80 years of age, respectively.[6]

Although numerous studies have reported the incidence and prevalence of AF, the majority of studies were in Caucasian populations. Additionally, reports of the incidence and prevalence of AF are likely underestimates because of the exclusion of asymptomatic AF and the inability to recognize many cases of paroxysmal AF. In particular, studies that rely on only a single ECG to diagnose AF likely miss many cases of AF. Therefore, a full understanding of the incidence and prevalence of AF is lacking, especially among non-Caucasian racial groups.

6.2 RECURRENCE AND PROGRESSION

It has been estimated from general practice AF patients in France, that one-third of patients with paroxysmal AF had recurrences during 1 year of follow-up.[28,71] Among Danish paroxysmal AF patients with at least 2 documented AF episodes in 1 year, 7% had weekly AF episodes, 40% had less than weekly episodes but more than 10 total

episodes, and 53% had less than 10 episodes over 1 year.[72] Over half of patients with persistent and permanent atrial fibrillation who presented to a hospital in Athens, Greece for internal cardioversion had AF recurrences within 1 year, with a median time to AF relapse of 21 days.[73] Therefore, it appears that the recurrence of AF is very common in all types of AF. However, many episodes of AF may go undiagnosed, so the recurrence of AF may be underestimated.

The progression from paroxysmal to permanent AF has been estimated at 8% over 1-year[28,74] and 18% after 4 years of follow-up.[74] However, patients with first AF who have comorbidities, such as diabetes and heart failure, are at higher risk for progression to permanent AF than those with lone AF.[75] Only 1 of 54 (1.8%) patients with lone AF, compared to 15 of 52 (28.8%) patients without lone AF, progressed to permanent AF within 5 years of emergency-department admission for first episode of paroxysmal AF.[75] The progression from persistent to permanent AF appears to be much higher than the progression from paroxysmal to permanent AF. During 1 year of follow-up, 40% of persistent AF patients progressed to permanent AF in one study,[76] whereas the progression was 58% in another study.[77]

6.3 MORTALITY

Death rates due to AF have been increasing in recent decades. In the U.S., age-standardized death rates (per 100,000) for AF as either the underlying cause of death or listed as one of the up to 20 conditions on the death certificate ranged between 27.6 in

1980 to 69.8 in 1998.[78] Death rates increased with age, and were highest among white men, followed by white women, black men, and black women.[78]

Mortality risk is particularly high within the first few months after diagnosis of AF. In a community-based Olmsted County, MN cohort, the risk of death was 9.6-times greater within the first 4 months of newly diagnosed AF compared to an age- and gender-matched Minnesota population.[79] Among AF or atrial flutter patients in the Marshfield, WI area compared to age- and sex-matched community controls, mortality was 7.8-fold higher after 6 months of follow-up.[80] In both studies, the risk of death in those with compared to those without AF was much lower after longer follow-up, with hazard ratios ranging from 1.7 over 21 years of follow-up to 2.5 over 7 years of follow-up.[79,80]

7.0 RISK FACTORS FOR ATRIAL FIBRILLATION

7.1 DEMOGRAPHIC RISK FACTORS

As previously discussed, age is a major risk factor for AF. The odds ratio of developing AF doubles with each decade of age,[11] resulting in a rapid increase in prevalence from 0.1% in those under 55 to 9-10% among those over 80 years of age.[5,6] The median age of patients with AF is 75, and approximately 70% of individuals with AF are between 65-85 years of age.[6]

The Atherosclerosis Risk in Communities study reported an exponential increase in AF incidence with age, with crude incidence rates ranging from less than 1 per 1,000 person-years in those 45-49 years to almost 50 per 1,000 person-years in those aged 80 years and older.[53] The following figure depicts the increasing AF incidence with age in men and women from the Atherosclerosis Risk in Communities study, along with AF incidence rates from Olmsted County, MN, the Cardiovascular Health Study, and the Framingham Heart Study:

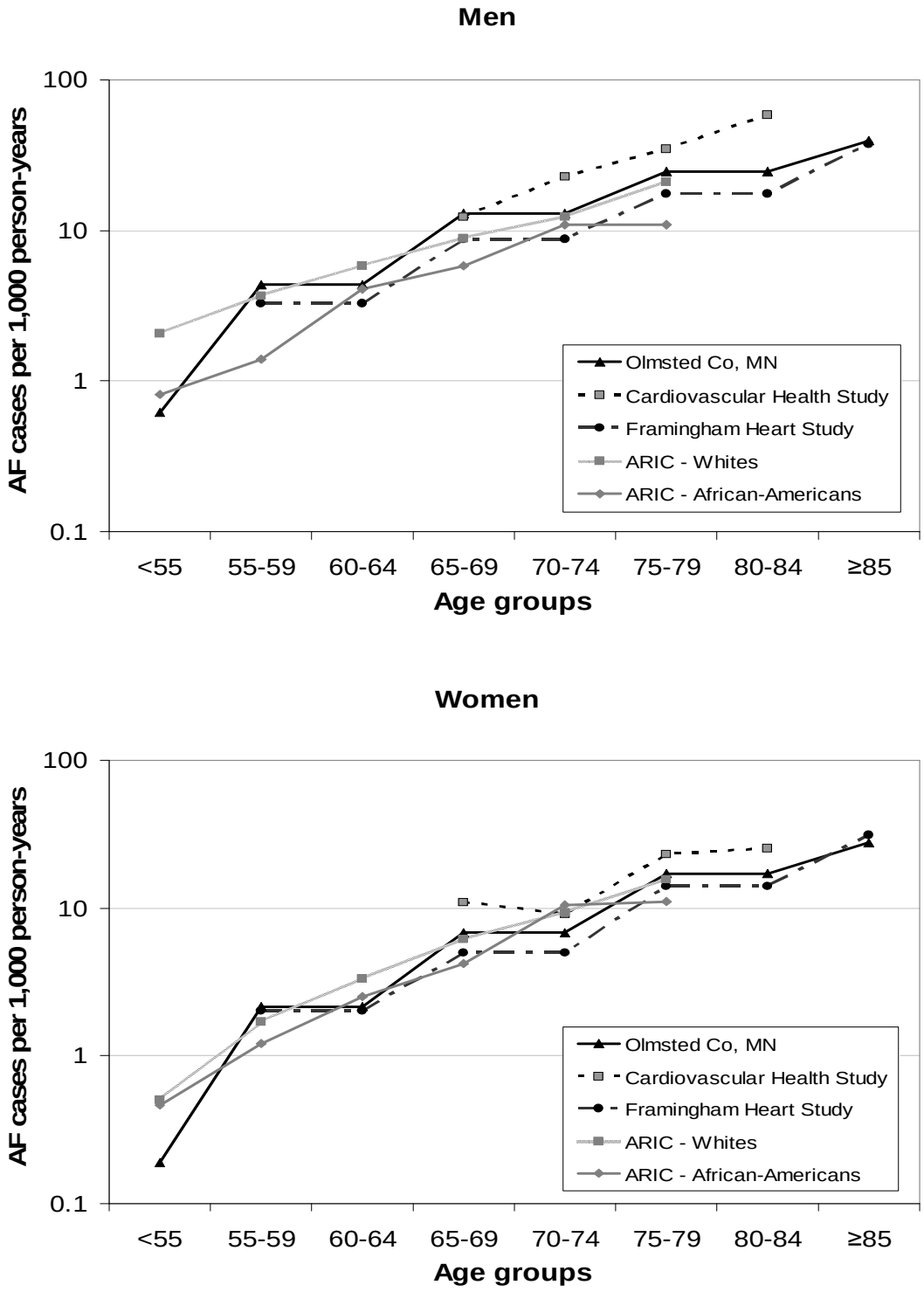


Figure 7.1: Incidence of atrial fibrillation in men and women from the Atherosclerosis Risk in Communities study, Olmsted County, MN, the Cardiovascular Health Study, and the Framingham Heart Study. From Alonso, A et al. *Am Heart J*. 2009;158:111-7.

In addition, Figure 7.2 depicts an increasing prevalence of AF with age in 3 studies conducted in the U.S.:

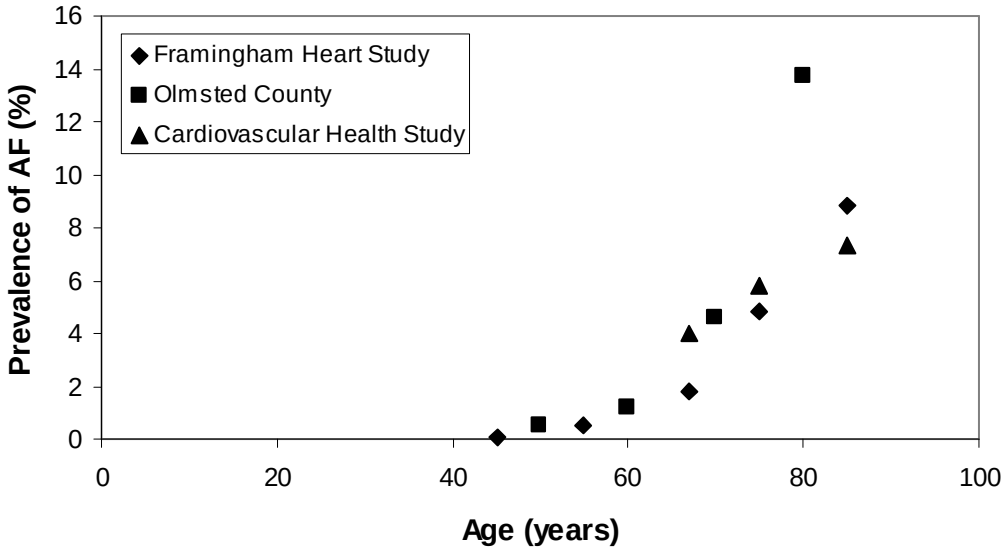


Figure 7.2: Prevalence of atrial fibrillation from the Framingham Heart Study, the Cardiovascular Health Study, and Olmsted County, MN plotted at the midpoint of the age range. Adapted from Feinberg, WM, et al. *Arch Int Med*. 1995;155:469-73.

The effect of aging on AF may reflect longer exposure to cardiovascular co-morbidities and other predisposing conditions for AF. Furthermore, aging is associated with cardiac abnormalities, such as left atrial enlargement and reduced left atrial appendage flow velocity, which may predispose to the development of AF.[23]

Male gender has also been established as a risk factor for AF. In both the Framingham Heart Study and the Atherosclerosis Risk in Communities study, men had a 1.5-fold greater risk of developing AF than women.[11,53] The overall and age-specific prevalence of AF is generally higher in men compared to women.[5,55,81,82] However, this gender difference was not found in older individuals from the Cardiovascular Health Study; the prevalence of AF in men and women was 5.9% and 2.8%, respectively, in the

65-69 year age group and was 5.8% and 5.9% for those 70-79 years of age.[83] Therefore, although male gender is a risk factor for AF, it should be recognized as a disease with equal importance in elderly women as in men.

Although data is limited on racial/ethnic differences in the risk of developing AF, the prevalence of AF is lower among Asians compared to whites from North America and Europe.[68-70] In addition, it appears that AF is twice as common in Caucasians compared to African Americans. The hazard ratio for incident AF in African Americans compared to Caucasians was 0.59 (95% confidence interval (CI), 0.38-0.92) in the Atherosclerosis Risk in Communities study.[53] The prevalence of AF among those aged 50 years or older in the ATRIA Study was 2.2% in whites and 1.5% in blacks.[5] Among veteran males, the prevalence of AF was 5.7% in whites and 3.4% in blacks.[84] U.S. emergency department visit rates from 1993-2004 were also more common in whites, with rates of 0.9 and 0.5 per 1,000 in whites and blacks, respectively.[51] The prevalence of AF among stroke patients is also two-fold greater in whites compared to blacks,[85,86] and among patients with heart failure, African Americans had a 49% lower odds of AF compared to Caucasians.[87] Whether this racial difference in AF prevalence does exist or is an artifact of study design is unknown. Since African Americans generally have a higher prevalence of cardiovascular risk factors than Caucasians,[88] additional studies are warranted to determine if racial differences in susceptibility to AF exist, and if so what risk factors account for the difference in AF prevalence between African Americans and Caucasians.

7.2 STRUCTURAL CARDIAC ABNORMALITIES

Although cardiac structural abnormalities are often present in patients with AF, the echocardiographic precursors for AF were not reported before the Framingham Heart Study investigation;[15,89] the increased risk associated with a 4mm increment in the sum of septal and left ventricular wall thickness was 28% in the Framingham Heart Study.[15] Additionally, left atrial enlargement (per 5mm increment) and left ventricular fractional shortening (per 5% decrement) were associated with a 39% and 34% significantly increased risk of incident AF, respectively.[90] Finally, mitral annular calcification may be associated with increased risk of AF, but this association is potentially mediated through left atrial enlargement.[91]

7.3 TRADITIONAL CARDIOVASCULAR RISK FACTORS

One of the most prevalent, independent, and modifiable risk factors for AF is hypertension. In the Framingham Heart Study, the odds of developing AF were nearly 2-fold higher among men and women with hypertension compared to those who were normotensive.[10] With longer follow-up (38 years) and adjustment for age and other risk factors for AF, the odds ratio for hypertension was 1.5 in men and 1.4 in women.[11] Because of its high prevalence, the population-attributable risk for AF resulting from hypertension was 14%, the highest of all risk factors investigated in that study.[11] Hypertension is associated with structural cardiac abnormalities, such as left ventricular hypertrophy, impaired ventricular filling, left atrial enlargement, and slowing of atrial conduction velocity, which favor the development of AF.[92] Therefore, hypertension may

be an upstream factor causing structural changes in the heart which, in turn, may result in the development of AF. Additionally, evidence that increased pulse pressure is a risk factor for AF suggests that increases in cardiac load and aortic stiffness may contribute to AF risk.[93]

Diabetes is another major risk factor for AF, with multivariate-adjusted odds ratios ranging from 1.4 and 1.6 in men and women in the Framingham Heart Study[11] to 2.1 among veterans based on Veterans Health Administration Hospitals discharge diagnoses.[12] Additionally, patients with new-onset diabetes mellitus had a hazard ratio of 1.49 for incident AF compared to patients without diabetes, and diabetics also had more persistent AF (hazard ratio (HR)=1.87) than non-diabetics.[13] It is unclear why diabetes is an independent risk factor for AF, although it has been speculated that diabetes may cause metabolic stress on the atrium or that diabetes could cause irritability of the atrium through its association with systemic illnesses, such as infection or renal failure.[94]

Obesity, and more recently the metabolic syndrome have become recognized as AF risk factors. For example, per unit increment in body mass index (BMI), the odds of AF, intermittent AF, and sustained AF were 3%, 7%, and 4% higher, respectively, compared to the odds of AF among those with a 1-unit lower BMI.[95] A meta-analysis pooling 5 population-based cohort studies reported a 49% increased risk of developing AF among obese participants compared to nonobese individuals.[96] In fact, a significant increased risk of AF among obese individuals was found in all of these cohort studies.[97-101] However, this association of obesity with AF was inconsistent and did not hold when pooling 11 post-cardiac surgery studies.[96] Two Japanese studies have also reported the impact of the metabolic syndrome on risk of AF. In both studies, an increased risk of

developing AF was found among individuals with the metabolic syndrome.[102,103] Obesity appeared to be an important component associated with greater incidence of AF,[102,103] although elevated blood pressure, low high-density lipoprotein cholesterol (HDL-c), and impaired glucose tolerance were also indicated in 1 study as increasing the risk of developing AF.[102] The mechanisms relating the metabolic syndrome to increased risk of developing AF are not fully understood. It has been reported that both the metabolic syndrome and obesity affect atrial anatomy by increasing atrial size,[104,105] and obesity has also been associated with left ventricular hypertrophy.[103,106] Additionally, inflammation, oxidative stress, and increased circulating free-fatty acids,[97,105] along with obstructive sleep apnea,[107] may also contribute to the development of AF in obese individuals.

Limited evidence also points to inflammation and atherosclerosis as predisposing factors to developing AF, however the data are conflicting. In cross-sectional analyses within the Cardiovascular Health Study, the odds of having AF at baseline were 80% higher for individuals in the fourth quartile of C-reactive protein (CRP) compared to those in the first quartile of CRP.[108] Those in the fourth compared to the first quartile of CRP at baseline were also at a 1.31-times higher risk (95% CI, 1.08-1.58) of developing AF during an average 6.9 years of follow-up.[108] A review of the literature concluded that inflammation may play a role in the initiation, maintenance, and perpetuation of AF, although it was unclear whether inflammation is a cause, or merely a consequence of AF.[109] The Rotterdam Study reported an increased risk of incident AF with the highest vs. the lowest quartile of carotid intima-media thickness (HR=1.90) and severe vs. the absence of carotid plaques (HR=1.49) over a median follow-up of 7.5 years and after adjustment for other AF risk factors.[110] However, these results conflict with previous

findings from the Cardiovascular Health Study that found no association of subclinical measures of atherosclerosis with incident AF.[9,83] Therefore, the potential role of inflammation and atherosclerosis with AF have not been established; further studies are needed to determine whether or not these factors increase the risk of developing AF.

7.4 CARDIOVASCULAR CO-MORBIDITIES

Individuals who develop AF are also more likely to have MI, valvular heart disease, CHF, or to have undergone recent cardiac surgery than those of similar age who do not have AF. The multivariate-adjusted hazard of developing AF was more than 3-fold higher among individuals with a history of MI (HR=3.62), CHF (HR=3.37), or valvular heart disease (HR=3.15) than those without a history of these cardiovascular co-morbidities in the Manitoba Follow-Up Study.[57] In both the Framingham Heart Study and the Cardiovascular Health Study, CHF and valvular heart disease were also associated with an increased risk of incident AF,[11,83] although MI was only a risk factor for men in the Framingham Heart Study.[11] CHF appears to confer the highest risk of AF compared to the other aforementioned cardiac diseases, with odds ratios for AF of 4.5 and 5.9 for men and women, respectively, after adjustment for AF risk factors.[11] Additionally, AF is a common complication of cardiovascular surgery, affecting approximately 32-33% of patients following coronary artery bypass graft (CABG) surgery.[111,112] The incidence of AF is also greater in surgical intensive care unit patients than the general population,[113] although cardiovascular surgery patients have much higher incidences of AF following surgery.

7.5 ADDITIONAL CO-MORBIDITIES

Some additional conditions that increase the risk of developing AF include reduced lung function, sleep apnea, and thyroid disease. Risk of incident AF was 1.8-fold higher for individuals with low lung function (forced expiratory volume in 1 second (FEV_1) between 60-80% of predicted) compared to normal lung function (FEV_1>80% predicted).[114] Data from the Cardiovascular Health Study support these findings;[9] however, results from the Framingham Heart Study contradict the association between lung function and AF.[11] Patients with pulmonary disease may be more susceptible to AF because of changes in blood gases, abnormalities in pulmonary functions, and hemodynamic changes due to pulmonary hypertension. In addition to pulmonary hypertension, hypoxia, inflammation, and acidemia, and associated right heart strain and dilation may promote the development of AF.[115]

Obstructive sleep apnea (OSA) also appears to predispose to AF. Almost half of patients undergoing treatment for AF had OSA compared to a third of patients without AF referred to a general cardiology practice.[116] In a retrospective cohort study, OSA was found to be an independent risk factor only among individuals less than 65 years of age, and this association was independent of the effect of obesity on AF.[107] It is unknown why OSA would be a risk factor for AF only among individuals <65 years of age but not those 65 years of age or older. In addition, the mechanisms by which OSA increases the risk of AF are not fully understood, but may include diastolic dysfunction and/or increased left atrial size as a consequence of OSA that predisposes an individual to developing AF.[107]

Hyperthyroidism has long been implicated as a risk factor for AF. Among participants 60 years or older in the Framingham Heart Study's 15th biennial exam, a low serum thyrotropin concentration (≤0.1 mU per liter, which is indicative of hyperthyroidism) was associated with a 3-fold higher risk of incident AF over 10 years of follow-up compared to those with normal thyrotropin concentration (>0.4 to 5.0 mU per liter).[117] This association was independent of other known risk factors for AF, and the age-adjusted incidence rates of AF were 28 and 10 per 1,000 person-years for those with low and normal thyrotropin concentrations, respectively.[117] The Cardiovascular Health Study also found an increased risk of AF with hyperthyroidism, with an adjusted hazard ratio for AF of 1.98 comparing individuals with subclinical hyperthyroidism to those with normal thyroid function.[118] Recently, an increased risk of AF was also reported among individuals with high-normal thyroid function in the Rotterdam Study. Within the normal range of thyroid-stimulating hormone (TSH), 0.4-4.0 mU/L, individuals in the lowest quartile of TSH had almost twice the risk of developing AF compared to those in the highest quartile (HR=1.94; 95% CI, 1.13-3.34).[119] Furthermore, individuals with subclinical hyperthyroidism had a higher prevalence of AF, after adjustment for sex, compared to those with normal thyroid function (9.5% vs. 4.7%, respectively).[120] The adjusted odds ratio for AF comparing those with subclinical hyperthyroidism to those with normal thyroid function was 2.27,[120] similar to results from the Cardiovascular Health Study.

7.6 GENETIC PREDISPOSITION

AF also appears to have a genetic component. In the Framingham Heart Study, offspring with at least 1 parent with AF had a 1.85-fold higher odds of AF compared to those without parental AF.[121] Figure 7.3 depicts the increased future risk of AF in offspring of a parent with AF.

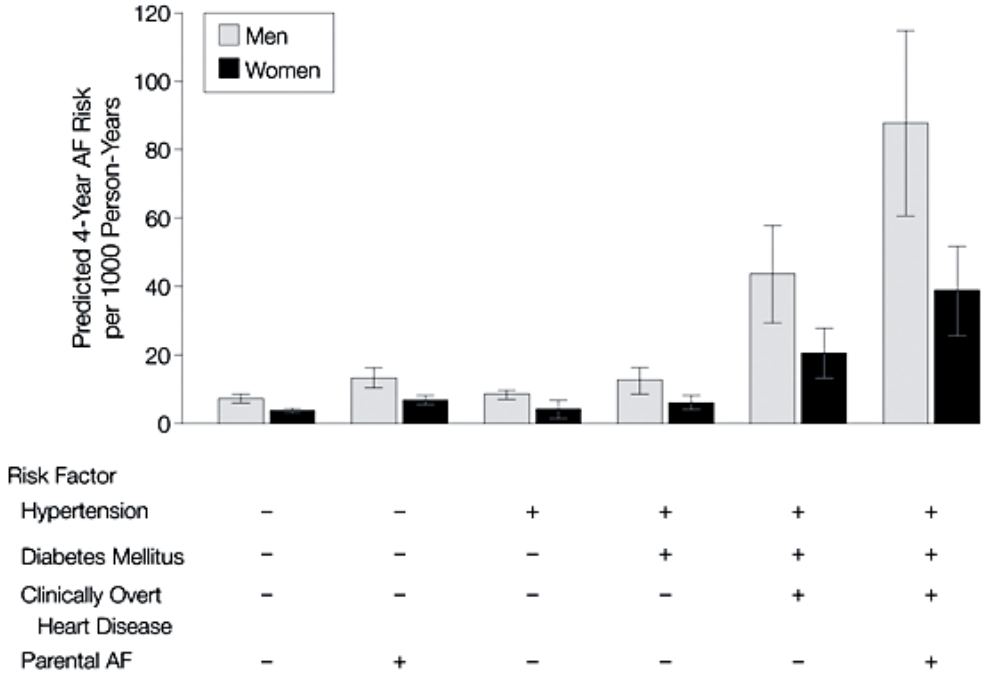


Figure 7.3: Risk of atrial fibrillation by parental atrial fibrillation status in the Framingham Offspring Cohort. From Fox, CS, et al. *JAMA*. 2004;291:2851-5.

AF also showed strong evidence of heritability in an Icelandic study. In this study, first-degree relatives of patients diagnosed with AF were nearly twice as likely to develop AF as the general population.[122] In patients diagnosed with AF before age 60, first-degree relatives were nearly 5 times more likely to have AF.[122] Some familial studies have even suggested that AF, particularly lone AF, has a Mendelian pattern of inheritance.[123,124]

Several possible genes and loci involved in AF have been identified. These include mutations in genes involved in potassium channels and current, sodium channels, and the rennin-angiotensin system. Genes involved in the potassium channel and potassium current associated with AF include KCNA5,[125] KCNQ1,[126] KCNJ2,[127] KCNE2,[128] KCNH2,[129] mink,[130] and the G-protein β3 subunit gene.[131] A Kv1.5 loss-of-function mutation in the KCNA5 gene encodes a voltage-gated potassium channel in the atria, and may be a risk factor for repolarization deficiency and AF.[125] Polymorphisms in the KCNQ1 gene are implicated in the initiation of AF,[126] although some suggest these mutations require an environmental factor to manifest AF[132] and are relatively uncommon in AF.[133] The Kir2.1 gain-of-function mutation in the KCNJ2 gene increases the activity of the inward potassium channel, possibly initiating and/or maintaining AF.[127] The KCNE2 gain-of-function mutation, through potassium channel alterations that are favorable to multiple wavelet re-entry, is also possibly involved in the initiation and/or maintenance of AF.[128] A polymorphism in the KCHN2 gene may also favor re-entrant AF.[129] Finally, both the minK gene and the G-protein β3 subunit gene play a role in cardiac electrophysiology; however, the minK gene may predispose to AF,[130] whereas a polymorphism in the G-protein β3 subunit gene appears to reduce the risk for development of AF.[131]

Polymorphisms in genes involved in the sodium channel and the rennin-angiotensin system may also play a role in AF. A missense mutation in the sodium channel gene SCN5A was found to co-segregate with AF and heart failure.[134] Inconsistent results have been reported for an insertion/deletion polymorphism in the ACE gene. The deletion allele was associated with both lone AF and secondary AF in

one study,[135-137] but was only found to be associated with AF in combination with the angiotensinogen A-20C polymorphism of the angiotensinogen gene in another study.[137] The angiotensinogen A-20C polymorphism alone also predicts an increased risk of AF.[137] Additional polymorphisms of the angiotensinogen gene, M235T, G-6A, and G-217A, are implicated in nonfamilial AF.[138]

Finally, a recent genome-wide association study (GWAS) found a strong association between two sequence variants on chromosome 4q25 and AF.[139] These variants do not correspond to a known gene, but are adjacent to the PITX2 gene, which has a critical function in the left-right asymmetry of the heart.[139] These associations of variants on chromosome 4q25 and AF were replicated in a meta-analysis of 4 independent cohorts[140] and in an additional meta-analysis of GWAS data.[141] The latter meta-analysis of GWAS data also identified a novel locus for AF on chromosome 16, ZFHX3.[141] Despite these recent discoveries, the genetics of AF are incompletely understood and additional genome-wide association studies are needed to identify other genetic determinants of AF.

7.7 DIET AND BEHAVIORAL RISK FACTORS

A few dietary components affect the development of AF, the most studied of which is alcohol consumption. High alcohol consumption appears to increase the risk of AF, although low to moderate consumption does not. For example, increasing consumption of alcohol was associated with an increased risk of AF in men, but not in women, in the Danish Diet, Cancer, and Health Study.[142] No association was found in women who consumed much less alcohol than the men; thus, there appeared to be no

association of moderate alcohol consumption with AF.[142] The Copenhagen City Heart Study also found no association of alcohol with AF in the moderate range of alcohol intake, but the consumption of 35 or more drinks per week among men increased the risk of incident AF by approximately 50%.[143] The Framingham Heart Study confirms little association with moderate alcohol consumption, but found an increased risk of AF among men consuming more than 3 drinks per day.[144] The Cardiovascular Health Study did not support these findings, but surprisingly, found an inverse association between alcohol intake and AF.[9] In subsequent analyses, they found that current moderate alcohol consumption did not increase the risk of AF.[145] The majority of participants in the Cardiovascular Health Study consumed low to moderate amounts of alcohol, and thus the association of heavy alcohol consumption and AF could not be determined.[145] The totality of evidence with respect to alcohol intake and the development of AF suggests a threshold effect, where heavy alcohol consumption of at least 3 drinks per day is a risk factor for AF, whereas low to moderate alcohol consumption does not increase the risk of AF.

A protective effect of long-chain n-3 fatty acids with development of AF has been reported. Consumption of tuna or other broiled or baked fish, but not fried fish or fish sandwiches, was associated with a lower incidence of AF over 12 years of follow-up in an elderly cohort.[146] After multivariate analyses, individuals who consumed 1-4 and $\geq$5 servings of tuna, baked and broiled fish per week had 28% and 31% lower risk of AF, respectively, than those with <1 serving per week.[146] These results have not been supported by other studies;[147,148] however, limited power and possible adverse effects of fried fish may have confounded these associations. Therefore, further investigation is

warranted on the association between n-3 fatty acids, and in particular baked and broiled fish consumption, and the risk of incident AF.

Although smoking is a major risk factor for cardiovascular disease, few studies have reported on its association with AF. Nicotine in cigarette smoke has been linked to the development of atrial fibrosis, which in turn may predispose an individual to developing AF.[149] In rats, nicotine was associated with increased atrial vulnerability to inducible AF; however, this association was only found in young rats and did not hold in older rats.[150] Despite these proposed mechanisms, data on the relationship between smoking and AF are conflicting. A study among men hospitalized for AF found no association between smoking and AF, even among those who smoked more than 15 cigarettes a day.[151] In the Framingham Heart Study, cigarette smoking was associated with a 40% increased odds of developing AF among women, but no association between smoking and AF was found in men.[11] Finally, current and former smokers in the Rotterdam Study had 51% and 49% increased risk, respectively, of developing AF after a median of 7.2 years of follow-up.[152]

Vigorous physical activity appears to increase the risk of AF, in particular, lone AF. Vigorously exercising middle-aged men had a 5.5-fold greater odds of lone AF compared to the general Finnish population.[153] Other studies of long-term sports practice in men have found somewhat weaker associations with AF. In one study, the proportion of sportsmen among lone AF patients was 63% compared to 15% among the general population of more sedentary individuals.[154] Both current sport practice and current sport practice with a lifetime practice >1500 hours were associated with an approximately 3-fold higher prevalence of lone AF in men compared to controls from the general

population.[155] The Physician's Health Study reported an almost 2-fold increased risk of developing AF among men who vigorously exercised 5-7 days per week compared to non-exercisers, but only in those younger than 50 years of age.[156] In contrast, work related physical activity was not associated with risk of hospital discharge diagnosis of AF or AFL in the Danish Diet, Cancer, and Health Study.[157] Furthermore, light to moderate physical activity appears to significantly lower the risk of AF incidence in older adults.[158] The mechanisms predisposing individuals who vigorously exercise to developing AF are unknown. However, possible mechanisms include the slight dilation of heart cavities and increases in vagal tone as a result of exercise that predispose to development of AF in the absence of other cardiovascular disease or risk factors for AF.[155]

8.0 EFFECT OF ATRIAL FIBRILLATION ON OTHER CLINICAL OUTCOMES

8.1 STROKE

One of the most common and devastating consequences of AF is the development of stroke. The main mechanism of stroke development in patients with AF is embolism of a thrombus due to blood stasis in the left atrial appendage.[23] However, up to 25% of stroke in patients with AF may be a result of other cardiac sources of embolism, atheromatous pathology in the proximal aorta, or intrinsic cerebrovascular diseases.[159,160]

It is estimated that 1 in 6 strokes occur in patients with AF, and approximately 10% of ischemic strokes are due to embolism of left atrial thrombi.[161] In Olmsted County, MN residents diagnosed with first AF between 1980 and 2000, 11% sustained a first ischemic stroke over a mean follow-up of 5.5 years.[162] After 20 years of follow-up in the Renfrew/Paisley Study, AF was an independent predictor of fatal or nonfatal strokes in both men (HR=2.5) and women (HR=3.2).[163] In the Framingham Heart Study, participants with AF were 5 times as likely to develop stroke as those free of AF over 34 years of follow-up.[2] Among individuals with CHD or CHF, AF increased the risk of stroke 2-fold in men and 3-fold in women. Almost 31% of strokes were accompanied by AF, and the attributable risk of stroke increased significantly with age, from 1.5% for those aged 50-59 to 23.5% for individuals 80-89 years of age, as shown below:[2]

	Age Group, years			
	50-59	60-69	70-79	80-89
Attributable risk (%)	1.5	2.8	9.9	23.5
Events occurring with AF (%)	6.5	8.5	18.8	30.7

Table 8.1: Attributable risk of stroke for atrial fibrillation by age. Adapted from Wolf, PA, et al. *Stroke*. 1991;22:983-8.

8.2 HEART FAILURE

AF may also precipitate the onset of CHF, although either condition may predispose to the other.[164,165] AF and CHF have many risk factors in common, such as older age, hypertension, valvular heart disease, myocardial infarction, and diabetes.[165] Furthermore, left atrial enlargement, increased left ventricular wall thickness, and reduced left ventricular fractional shortening are also common in both AF and CHF.[164] Alterations in neurohormonal activation, electrophysiologic parameters, and mechanical factors may contribute to the development and maintenance of both CHF and AF, as shown in the figure below:

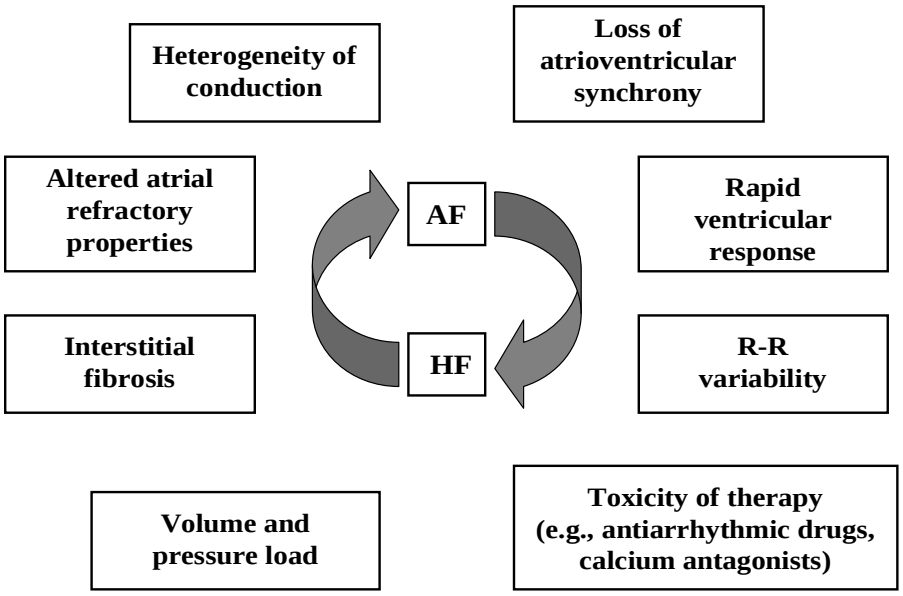


Figure 8.1: A number of mechanisms contribute to the initiation and maintenance of atrial fibrillation and congestive heart failure. Adapted from Maisel, WH & Stevenson, LW. *Am J Cardiol*. 2003;91(suppl):2D-8D.

The nature of the relationship between CHF and AF can be seen in data from the Framingham Heart Study. Of participants who developed both AF and CHF during follow-up, 38% had AF first, 41% had CHF first, and 21% had both diagnosed the same day.[166] In the Framingham Heart Study, the incidence of CHF in those with AF was 33 per 1,000 person-years,[166] whereas the incidence was somewhat higher in Olmsted County, MN patients with first AF at 44 per 1,000 person-years.[167] Additionally, the cumulative incidence of CHF in Olmsted County AF patients was 7.8% within the first year, and after 5 years of follow-up, 20% of AF patients had developed CHF.[167] Finally,

the risk of CHF among AF patients in the Renfrew/Paisley Study was 3.4 times higher than patients without AF.[163]

8.3 DEATH

As previously described in section 6.3, AF is associated with an increased risk of death. AF may be an independent risk factor for death. In the Olmsted County, MN community-based study, the hazard ratio for death in those with AF compared to those without AF was 1.88 in men and 1.84 in women; the mortality hazard ratios were nearly double that in participants who also had stroke.[162] AF was independently associated with a 50% increased odds of death in men and a 90% increased odds of death in women in the Framingham Heart Study.[4] In secondary analyses in those free of valvular heart disease, a doubling of mortality with AF was seen in both sexes.[4] AF was also an independent predictor of all-cause mortality in the Renfrew/Paisley Study, with hazard ratios of 1.5 and 2.2 in men and women, respectively.[163] A similar independent association between AF and mortality was also reported in the Marshfield Epidemiologic Study Area.[80] The following figure depicts the risk of death from AF, after multivariate adjustment, in 3 population-based studies:

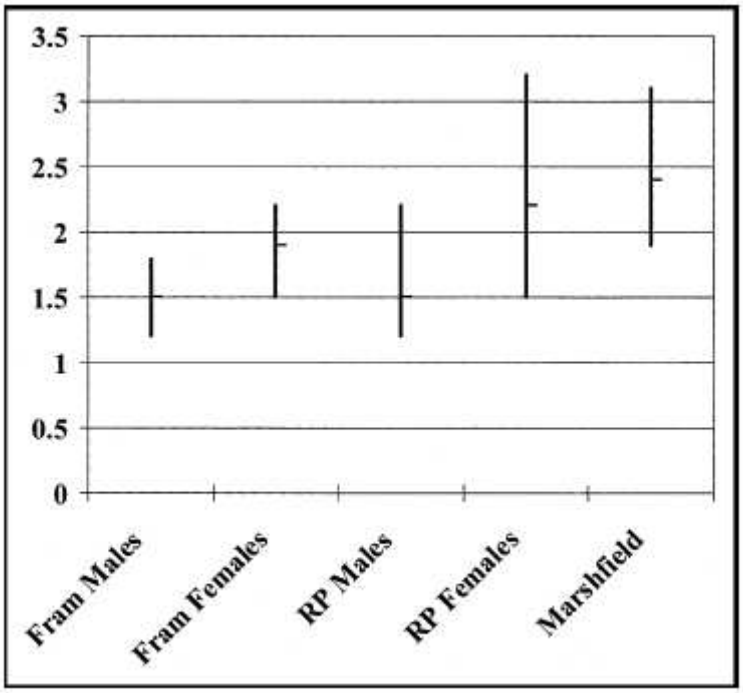


Figure 8.2: Adjusted relative risk of death from atrial fibrillation with 95% confidence limits from the Framingham Heart Study, the Renfrew/Paisley Study, and the Marshfield Epidemiologic Study Area. From Greenlee, RT & Vidaillet, H. *Curr Opin Cardiol*. 2005;20:7-14.

In addition, AF is a risk factor for death among patients with a recent CABG surgery, MI, or stroke. Postoperative AF after CABG surgery was associated with 1.7-fold greater odds of in-hospital mortality and 1.5-fold greater odds of long-term mortality compared to patients who had CABG surgery without development of postoperative AF.[168] In addition, AF complicating acute MI is associated with approximately double the risk of mortality compared to MI patients without AF.[169] Patients with AF who develop stroke are also at an increased risk of death. In a Japanese study of almost 16,000 acute ischemic stroke patients, the 28-day mortality was 11.3% among those with AF compared to 3.4% among patients who did not have prior AF.[170] Another study found that AF was an independent predictor of in-hospital mortality in women but not in

men.[171] Finally, among patients with CHF, incident AF may increase the risk of death;[172] however, past or chronic AF does not appear to increase the risk of mortality among individuals with CHF.[172,173]

9.0 THE ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY

9.1 STUDY OBJECTIVES

The Atherosclerosis Risk in Communities (ARIC) study is a multi-center population-based prospective cohort study designed to investigate the etiology and natural history of atherosclerosis, the etiology of clinical atherosclerotic diseases, and variation in cardiovascular risk factors, medical care, and disease by race, gender, location, and date.

9.2 RECRUITMENT

The ARIC study recruited for its prospective cohort probability samples of adults aged 45-64 years from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis suburbs, Minnesota; and Washington County, Maryland.[174] Blacks and whites were recruited from Forsyth County, only blacks from Jackson, Mississippi, and predominantly whites from the other two communities. Recruitment varied by community and the sampling frames for selection were based on selection of housing units, possession of a valid driver's license or state identification card, and eligibility for jury duty. Approximately 4,000 individuals were recruited from each community for a total of 15,792 participants (8710 women) enrolled from 1987 to 1989.

9.3 DATA COLLECTION

Enrollment and the baseline exam occurred between 1987 and 1989, in which participants completed a home interview and clinic visit. Follow-up exams occurred every three years for a total of 4 visits. The response rates for visits 2 (1990-1992), 3 (1993-1995), and 4 (1996-1998) were 93%, 86%, and 81%, respectively. During each visit, participants received an extensive examination, including anthropometry, electrocardiography, ultrasound, respiratory function assessment, sitting blood pressure, and blood collection used for genotyping and determination of lipids, clinical chemistry, and hemostasis variables. Additionally, interviewer-administered questionnaires on medical history, social and demographic characteristics, and behaviors, including smoking and alcohol intake, physical activity, and diet were administered. During the baseline visit only, a 2-minute rhythm strip was also collected on each participant. Annual contacts by telephone are also conducted to maintain contact with participants and to assess changes in health status, including cardiovascular events, hospitalizations, and deaths. Hospitalizations are additionally identified by surveillance of local hospital discharge lists and deaths are identified by surveillance of local death certificates and obituaries, or a National Death Index search. The ARIC study was approved by the institutional review boards at all study sites and written informed consent was obtained from all ARIC participants.

9.4 DETECTION OF ATRIAL FIBRILLATION

ECGs during the baseline visit were used to identify individuals with prevalent AF or atrial flutter. Incident AF diagnoses through December 31, 2005 were identified through ECGs performed during follow-up visits, hospital discharge codes (*International Classification of Diseases, Ninth Revision* (ICD-9) codes 427.31 or 427.32), and death certificates (ICD-9 code 427.3 or *International Classification of Diseases, Tenth Revision* (ICD-10) code I48).

All ECGs were recorded using MAC PC Personal Cardiographs (Marquette Electronics, Inc., Milwaukee, WI). A standard supine 12-lead resting ECG was recorded at least one hour after smoking tobacco or ingestion of caffeine. ECGs were then transmitted by telephone to the ARIC ECG Reading Center for coding and interpretation. Baseline ECG recordings were used to identify AF predictors, which included P wave terminal force, P wave duration, P wave area and P-R duration. ECG recordings during the follow-up visits were used to measure incident AF. ECG recordings during follow-up that were automatically coded as AF were visually re-checked by a trained cardiologist to confirm the diagnosis.

In addition to ECGs, hospital discharge records and death certificates were used to identify incident AF events. Annual follow-up telephone calls were placed to cohort participants in order to identify hospitalizations and deaths. Hospital discharge records were gathered from all hospitalizations, and AF was identified by an ICD-9 code of 427.31 or 427.32 on the discharge record. AF was also identified when any cause of death on a death certificate was coded as AF (ICD-9 code 427.3 or ICD-10 code I48).

AF occurring simultaneously with heart revascularization surgery (ICD-9 code 36.X) or other cardiac surgery involving heart valves or septa (ICD-9 code 35.X) was not considered an incident event and follow-up was continued beyond that episode for incident AF not associated with cardiac surgery.

In ARIC participants without AF or atrial flutter in the first exam, the incidence date of AF was considered the earliest of the following dates: ECG-based AF identified at a follow-up exam, a first hospital discharge diagnosis of AF, or AF in the death certificate.

10.0 MANUSCRIPT 1 – METABOLIC SYNDROME AND INCIDENCE OF ATRIAL FIBRILLATION

10.1 OVERVIEW

Objective: To determine the association of the metabolic syndrome (MetSyn) with incident atrial fibrillation (AF) in a population-based cohort of blacks and whites. **Background:** The MetSyn has been implicated in the development of AF; however, knowledge of this association among blacks is limited. **Methods:** We determined prospectively the risk of incident AF through December 2005 in relation to baseline (1987-1989) MetSyn status in 15,094 participants of the Atherosclerosis Risk in Communities (ARIC) study. **Results:** Over a mean follow-up of 15.4 years, 1238 incident AF events were identified. The multivariable-adjusted hazard ratio (HR) for AF among individuals with, compared to those without, the MetSyn was 1.67 (95% CI, 1.49-1.87). The HRs were 1.76 (95% CI, 1.35-2.29) and 1.64 (95% CI, 1.45-1.87) among blacks and whites, respectively (p for interaction=0.73). The multivariable-adjusted HRs (95% CI) for AF for each MetSyn component were 1.95 (1.72-2.21) (elevated blood pressure), 1.40 (1.23-1.59) (elevated waist circumference), 1.20 (1.06-1.37) (low HDL cholesterol), 1.16 (1.03-1.31) (impaired fasting glucose), and 0.95 (0.84-1.09) (elevated triglycerides). A monotonically increasing risk of AF with increasing number of MetSyn components was observed, with a HR of 4.40 (95% CI, 3.25-5.94) for those with all 5 MetSyn components compared to those with 0 components. **Conclusion:** In this large cohort, the MetSyn and most of its components were associated with a higher risk of AF in both blacks and whites. Given the high prevalence of the MetSyn, strategies to prevent

its development or to control individual components may considerably reduce the burden of AF.

10.2 INTRODUCTION

The metabolic syndrome (MetSyn) is defined as a clustering of three or more of the following five atherosclerotic risk factors: abdominal obesity, elevated triglycerides (TG), low high-density lipoprotein cholesterol (HDL-c), elevated blood pressure, and impaired glucose tolerance.[175] Although the significance of the MetSyn as a well-defined clinical entity is uncertain, previous research has implicated this disorder and some of its individual components in the development of atrial fibrillation (AF). Two studies conducted in Japanese populations found an increased risk of AF among individuals with the MetSyn.[102,103] Of the MetSyn components, both of these studies found obesity to be strongly associated with incidence of AF,[102,103] although elevated blood pressure, low HDL-c, and impaired glucose tolerance were also related to AF in one study.[102] The mechanisms relating the MetSyn to increased risk of developing AF are not fully understood. The MetSyn affects atrial anatomy by increasing atrial size,[104,105] possibly increasing AF risk as a consequence. Alternatively, the MetSyn may predispose to the development of coronary heart disease (CHD) or heart failure (HF), in turn increasing the risk of AF.

Knowledge on the association of the MetSyn with AF risk among African-Americans is limited. Some studies have suggested that atrial fibrillation is less common in blacks than whites.[5,9,53] However, it is well known that blacks have a higher

prevalence of the MetSyn and most of its components than do whites.[88] Therefore, our study aimed to determine the association of the MetSyn and its individual components with the risk of incident AF in a population-based cohort of blacks and whites. We hypothesized that the incidence of AF would be higher among those with the MetSyn at baseline compared to those without the MetSyn, and that the risk of AF would increase with increasing number of MetSyn components, but that these associations may differ in blacks and whites.

10.3 METHODS

Study Population

The Atherosclerosis Risk in Communities (ARIC) study is a prospective cohort investigation aimed to identify risk factors for atherosclerosis and cardiovascular disease. ARIC recruited probability samples of adults aged 45-64 years from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis suburbs, Minnesota; and Washington County, Maryland.[174] Blacks and whites were recruited from Forsyth County, only blacks from Jackson, Mississippi, and predominantly whites from the other two communities. A total of 15,792 participants (8710 women) were enrolled from 1987 to 1989, and completed a home interview and clinic visit. Three follow-up clinic visits were conducted, each spaced three years apart (1990-92, 1993-95, 1996-98). In addition, participants are being followed-up by annual telephone interviews and active surveillance of the ARIC community hospitals. The

ARIC study was approved by institutional review boards at each participating center, and written informed consent was obtained from participants at every clinic visit.

Atrial Fibrillation Ascertainment

Electrocardiograms (ECGs) during the baseline visit were used to identify individuals with prevalent AF or atrial flutter. Incident AF diagnoses through December 31, 2005 were identified from 3 sources: ECGs performed during study follow-up visits through 1998, hospital discharge records through 2005, and death certificates through 2005.

All ARIC examination ECGs were recorded using MAC PC Personal Cardiographs (Marquette Electronics, Inc., Milwaukee, WI). A standard supine 12-lead resting ECG was recorded at least one hour after smoking tobacco or ingestion of caffeine at each clinic visit. ECGs were then transmitted by modem to the ARIC ECG Reading Center for computer coding. ECG recordings during follow-up that were computer coded as AF were visually re-checked by a cardiologist to confirm the diagnosis.[176]

Annual follow-up telephone calls were placed to cohort participants in order to identify hospitalizations and deaths. In addition, local hospitals were surveyed for potential cardiovascular events. Hospital discharge records were gathered from all hospitalizations, and AF was identified by an ICD-9 discharge code of 427.31 or 427.32 among any of the discharge diagnoses. AF was also identified when any listed cause of death on a death certificate was coded as AF (ICD-9 code 427.3 or ICD-10 code I48). AF occurring simultaneously with heart revascularization surgery (ICD-9 code 36.X) or

other cardiac surgery involving heart valves or septa (ICD-9 code 35.X) was not considered an incident event and follow-up was continued beyond that episode for incident AF not associated with cardiac surgery. Prior analysis within the ARIC cohort to determine the validity of hospital discharge diagnoses for AF reported 84% sensitivity and 98% specificity in the ascertainment of AF events.[53]

Metabolic Syndrome Definition

Study participants were asked to fast for 12 hours before the clinic visit, during which a blood sample was obtained and a physical exam was performed. Blood collection and processing techniques for the ARIC study have been previously described.[177] Enzymatic methods were used to measure TG.[178] HDL cholesterol was measured enzymatically after dextran sulfate-Mg^{2+} precipitation of other lipoproteins.[179] Serum glucose was determined by the hexokinase method. Waist circumference was measured at the level of the umbilicus. Blood pressures were measured 3 times in the sitting position after 5 minutes of rest using a random-zero sphygmomanometer, and the last 2 blood pressure measurements were averaged.

The MetSyn was defined using the American Heart Association and National Heart, Lung, and Blood Institute (AHA/NHLBI) criteria as having 3 or more of the following conditions: 1) a waist circumference of $\geq$88 cm in women or $\geq$102 cm in men, 2) fasting TG $\geq$150 mg/dL (or on lipid medication), 3) HDL-c <50 mg/dL in women or <40 mg/dL in men (or on lipid medication), 4) blood pressure $\geq$130/$\geq$85 mmHg and/or a history of treated hypertension, and 5) fasting glucose $\geq$100 mg/dL or a history of diabetes (or on diabetes medication).[180] A sensitivity analysis was conducted excluding

diabetics. Since results did not differ from models including diabetics, those with diabetes were included in the elevated fasting glucose category in all models. However, non-fasters above the cut-point for TG or fasting glucose and not taking lipid or diabetes medication were set to missing for TG and/or fasting glucose.

Additional Baseline Measurements

Race was self-reported by participants as one of the following: black, white, Asian, or American or Alaskan Indian. Total years of education, as well as smoking and drinking status and amount were determined by self-report. Responses to number of cigarettes smoked per day and duration of smoking were used to calculate pack-years of smoking. The weekly number of glasses of wine, bottles/cans of beer, and shots of liquor were used to determine average alcohol intake in grams per week. The sports index for physical activity during leisure time ranged from 1 (low) to 5 (high), and was based on the questionnaire developed by Baecke et al.[181] Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Participants were asked to bring all medications with them during clinic visits. A prescription or self-report was used to determine cholesterol and blood pressure medication use. A participant was categorized as diabetic if they had a fasting glucose $\geq$126 mg/dL (or non-fasting glucose of $\geq$200 mg/dL if a fasting sample was not available) or reported a physician diagnosis of diabetes or were currently taking medication for diabetes. Prevalent CHD at baseline included individuals with a history of myocardial infarction (MI), MI adjudicated from the baseline ECG, or history of coronary bypass or angioplasty of the coronary arteries.

Prevalent HF was identified using the Gothenburg criteria[182] or self-report of HF medication use in the past 2 weeks.

Statistical Analysis

All analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC). Of the 15,792 ARIC participants, we excluded those who were not of black or white race (N=48), blacks from Minneapolis and Washington County (N=55), those with prevalent AF or atrial flutter identified by the baseline ECG (N=37), those with unknown AF status at baseline (N=224), those with unreadable ECG at baseline (N=85), and those with unknown MetSyn status at baseline (N=249).

Person-years of follow-up were computed from the baseline exam date until a first AF diagnosis, death, lost to follow-up, or December 31, 2005, whichever came first. Race-specific baseline participant characteristics by the MetSyn status were compared using chi-squares for categorical measures and t-tests for continuous variables. Overall and race-specific age- and sex-adjusted incidence rates for AF by the MetSyn status at baseline were calculated using Poisson regression. Multivariate-adjusted hazard ratios for AF were estimated in the full cohort and separately in blacks and whites using Cox proportional hazards regression after adjusting for the following baseline characteristics: age, sex, race (full cohort analysis), center (Forsyth County, NC; Jackson, MS; Minneapolis suburbs, MN; Washington County, MD), education (less than high school, high school graduate to vocational school, any college), smoking status (current, former, never), and smoking amount (pack-years). Further adjustment for alcohol and sports index was not conducted because they no longer confounded the association between the

MetSyn and AF after adjustment for the previously mentioned variables. We estimated hazard ratios for AF by the MetSyn status at baseline, individual components of the MetSyn at baseline after additional adjustment for the other MetSyn components, and by number of MetSyn components present at baseline in individuals with known values for all MetSyn components. The Cox model was also modified allowing for the MetSyn, measured during clinic visits 1-4, as a time-dependent variable. Multiplicative interactions with sex and race were tested and found to be nonsignificant; however, hazard ratios for the full cohort and separately for blacks and whites are reported based on the hypotheses. Finally, a macro by Zhang and colleagues[183] was used to estimate a direct adjusted cumulative incidence curve of AF by number of MetSyn components at baseline, based on a stratified Cox model. Interaction tests between the MetSyn and log of follow-up time and the log-log survival curves were plotted to show that the proportional hazards assumption was met for the Cox regression models.

10.4 RESULTS

After exclusions, 15,094 individuals remained in our dataset for analysis. The baseline characteristics of the study sample are described in Table 10.1. Those with the MetSyn at baseline were less well educated, had higher mean BMI's, were less physically active, and had more comorbidities than did participants without the MetSyn at baseline. At baseline, 45.7% of blacks and 39.6% of whites had the MetSyn (Table 10.2). A higher percentage of blacks had elevated waist circumference, elevated blood pressure, and impaired fasting glucose compared to whites; however, whites more frequently had

elevated TG and low HDL-c. Of those who had values for all MetSyn components at baseline (N=14,816), 4.9% of blacks and 6.8% of whites had all 5 components of the MetSyn.

Over a mean follow-up of 15.4 years, 1238 incident cases of AF were identified. The age- and sex-adjusted incidence rates for AF were 60 and 36 per 10,000 person-years in participants with and without the MetSyn at baseline, respectively (Table 10.3). In blacks, the age- and sex-adjusted incidence rates for those with and those without the MetSyn were 52 and 30 per 10,000 person-years, respectively; the corresponding incidence rates in whites were 62 and 38 per 10,000 person-years. The hazard ratios for AF among individuals with, compared to those without, the MetSyn was 1.67 (95% CI, 1.49-1.87) in the entire cohort. The hazard ratios were 1.76 (95% CI, 1.35-2.29) and 1.64 (95% CI, 1.45-1.87) among blacks and whites, respectively; however, these were not statistically significantly different (p for interaction=0.73). In addition, hazard ratios for models with the MetSyn status as a time-dependent variable were not appreciably different from models using only baseline MetSyn status (data not shown). Considering only AF events identified in ECGs done at study visits (121 AF events), the hazard ratio of AF in those with MetSyn compared to those without was 1.96 (95% CI, 1.36-2.83).

We also stratified our analysis by prevalent CHD and HF at baseline in order to investigate potential mediation of the MetSyn and AF association through CHD and HF (Table 10.3). The prevalence of the MetSyn was much higher in those with CHD or HF at baseline compared to those without (70.3% and 38.3%, respectively). For those who did not have prevalent CHD or HF at baseline, the association between the MetSyn and incident AF was similar to that of the entire cohort (HR, 1.53; 95% CI, 1.35-1.74);

however, the association did not hold among blacks with CHD or HF at baseline. The incidence rate of AF among those with prevalent CHD or HF at baseline was higher, but the hazard ratio for the association of MetSyn with AF was attenuated in comparison to that of the entire cohort or the subgroup of participants without prevalent CHD or HF. In a model excluding those with prevalent CHD or HF at baseline and then censoring incident CHD or HF during follow-up, the hazard ratio for AF was attenuated (HR, 1.30; 95% CI, 1.10-1.54) in comparison to the model in the entire cohort ignoring incident CHD or HF (HR, 1.67; 95% CI, 1.49-1.87).

Of the individual components of the MetSyn, elevated blood pressure appeared to contribute most to AF risk, with almost a two-fold increased risk of AF for those with elevated blood pressures (Table 10.4). Elevated waist circumference conferred a 40% (95% CI, 23%-59%) increased risk, low HDL-c a 20% (95% CI, 6%-37%) increased risk, and impaired fasting glucose a 16% (95% CI, 3%-31%) increased risk of incident AF, whereas elevated TG was not associated with incidence of AF (HR, 0.95; 95% CI, 0.84-1.09). Time-dependent analyses with all individual MetSyn components as time-dependent variables provided similar results (data not shown). In addition, a monotonically increasing risk of AF with increasing number of MetSyn components was observed, with a hazard ratio of 4.40 for those with 5 MetSyn components compared to those with 0 components. Figure 10.1 depicts the cumulative probability of incident AF by number of MetSyn components in the full cohort. A greater number of MetSyn components corresponded to higher cumulative probabilities of AF over up to 19 years of follow-up. The cumulative risk of AF was 5.1% among those with 0 MetSyn components and 20.4% among those with 5 MetSyn components at baseline.

10.5 DISCUSSION

In this population-based prospective study with up to 19 years of follow-up, individuals with the MetSyn at baseline had a 67% increased risk of incident AF, with similar results in both blacks and whites. In addition, the risk of AF increased successively with each MetSyn component present, with more than a 4-fold increased risk for those with all 5 MetSyn components compared to those with 0 components during the baseline exam. Of the individual components, elevated blood pressure was the most strongly associated with AF risk, but all other MetSyn components, with the exception of high TG, were also associated with an increased risk of incident AF.

Our results are consistent with a prospective study based on annual health check-ups in a Japanese population, which reported a 61% increased risk of AF among individuals with the MetSyn according to AHA/NHLBI guidelines.[102] In addition, all components of the MetSyn except for TG were found to increase the risk of incident AF.[102] However, their results were only adjusted for age and sex, and were not additionally adjusted for the other components of the MetSyn. We found an increased risk for AF for all components of the MetSyn, except TG, even after adjustment for additional confounders and the other components of the MetSyn. Watanabe and colleagues also found an increased risk of AF with the MetSyn when using the National Cholesterol Education Program Third Adult Treatment Panel (NCEP-ATP III) definition of the MetSyn.[102]

Another prospective study of patients admitted to a cardiovascular care center in Japan reported a 2.8-fold increased odds of AF among those with the MetSyn. Obesity/overweight was associated with a 3-fold greater odds of AF.[103] This study,

however, did not find evidence of an association between any other components of the MetSyn and AF, though its limited sample size (32 AF cases, 560 controls) and the study design could explain the inconsistency with our results.

Several studies have reported the associations of high blood pressure, diabetes, and obesity alone with the risk of AF. The Cardiovascular Health Study reported an 11% increased risk of AF for each 10 mmHg increase in systolic blood pressure.[9] Among women participating in the Women's Health Study, a linear trend of increasing AF risk with increasing systolic and diastolic blood pressure was found, and an increased risk of AF was even found in systolic blood pressure categories in the nonhypertensive range.[184] In the Framingham Heart Study, the odds of developing AF among those with hypertension was 1.5 in men and 1.4 in women, and the population-attributable risk for AF resulting from hypertension was 14%, the highest of all risk factors investigated in that study.[11] In the same study, diabetes was associated with a 1.4 and 1.6-fold increased odds of AF in men and women, respectively.[11] In addition, the odds ratio for AF comparing diabetics to non-diabetics was 2.1 among veterans based on Veterans Health Administration Hospitals discharge diagnoses,[12] and patients with new-onset diabetes mellitus had a hazard ratio of 1.49 for incident AF compared to patients without diabetes.[13] Finally, obesity has been implicated in the development of AF. Per unit increment in BMI, the odds of AF, intermittent AF, and sustained AF were 3%, 7%, and 4% higher, respectively, compared to the odds of AF among those with a 1-unit lower BMI.[95] A meta-analysis pooling 5 population-based cohort studies reported a 49% increased risk of developing AF among obese participants (BMI$\geq$30) compared to nonobese (BMI<30) individuals.[96] A significant increased risk of AF among obese

individuals was found in all 5 of these cohort studies.[97-101] Although the cutpoints for hypertension and diabetes used in these studies are slightly different than those used to define the MetSyn, and the MetSyn uses waist circumference instead of BMI, these studies provide additional evidence that these individual MetSyn components are risk factors for AF.

The mechanisms underlying the association between the MetSyn and AF are unclear. The metabolic syndrome and obesity may affect atrial anatomy by increasing atrial size,[104,105] and obesity has also been associated with left ventricular hypertrophy.[103,106] Hypertension is associated with left ventricular hypertrophy, impaired ventricular filling, left atrial enlargement, and slowing of atrial conduction velocity.[92] Finally, diabetes may cause metabolic stress on the atrium or irritability of the atrium through its association with systemic illnesses, such as infection or renal failure.[12] Therefore, hypertension, obesity, and diabetes may be causing cardiac structural changes or metabolic stress or irritability of the atrium among individuals with the MetSyn, which in turn, may result in the development of AF. In addition, the MetSyn and its individual components may increase the risk of AF through the development of CHD and HF. In our analysis, we found that among individuals with prevalent CHD or HF at the baseline exam, the association between the MetSyn and AF was attenuated overall and appeared to be absent among blacks. In another analysis among individuals free of CHD or HF at baseline and censoring those who developed CHD or HF after the baseline exam, the hazard ratio for incident AF was 1.30 (95% CI, 1.10-1.54), suggesting that CHD and HF may be mediators of the association between the MetSyn and AF.

The present study has certain limitations that need to be taken into account when reading the results. First, it is possible that some incident AF events were missed among individuals without symptoms or who were not hospitalized. Most AF events were ascertained by hospital discharge records; therefore, underascertainment of events could have led to misclassification of the events. Although we may have had some misclassification of events by relying mostly on hospital discharge records to identify incident AF events, our estimates of AF incidence are similar to those reported by other cohorts.[9,11,48,62,64] Further, in a sensitivity analysis including only AF events identified during exam ECGs, the hazard ratio for AF comparing those with to those without the MetSyn was 1.96, which is similar to the association found when considering all AF cases (HR=1.67). Finally, associations of genetic risk factors and AF in ARIC were similar to that of other cohort studies whose identification of incident AF events relied more on study exam ECGs rather than hospital discharge records.[141] These observations suggest that the possible misclassification of the events due to the method of AF ascertainment was minimal. Second, although we attempted to control for any misclassification in exposure status by conducting time-dependent analyses using MetSyn as a time-dependent variable, the last exposure measurement occurred during study visit 4 (1996-98), almost a decade prior to the end of follow-up for AF. Finally, we did not have any information to classify AF as paroxysmal, persistent, or permanent, eliminating the possibility of conducting sub-group analyses on type of AF.

Our study also has several strengths, including the large sample size and long follow-up of the ARIC cohort. Response rates of the annual follow-up telephone calls to participants have been larger than 90% among survivors, limiting selection bias in the

ascertainment of AF events. In addition, the availability of information on most possible confounders limits bias in our estimates due to unmeasured confounding. Finally, ARIC is a multi-center study that enrolled both black and white participants, so our results are fairly generalizable to the U.S. population of blacks and whites.

In conclusion, a 67% increased risk of incident AF was seen among individuals with, compared to those without, the MetSyn during the baseline exam, and the risk of AF increased with greater number of MetSyn components. Elevated blood pressure appeared to contribute most to AF risk, although all MetSyn components except TG were independently associated with an increased risk of AF. The MetSyn is a common disorder, and 45.7% of blacks and 39.6% of whites of our study population had the MetSyn during the baseline exam. Given the increased risk of AF among individuals with the MetSyn, strategies to reduce the development of the MetSyn or to control individual components of the MetSyn may reduce the burden of AF.

10.6 TABLES AND FIGURES

Table 10.1: Baseline Participant Characteristics by Race Group and Metabolic Syndrome Status, ARIC 1987-89.

	Blacks (N=3,882)			Whites (N=11,212)		
	No Metabolic Syndrome	**Metabolic Syndrome**	**P-value**	**No Metabolic Syndrome**	**Metabolic Syndrome**	**P-value**
Age, years	53.0 ± 5.9	54.3 ± 5.7	<0.01	53.7 ± 5.7	55.4 ± 5.6	<0.01
Male	953 (45.2)	526 (29.7)	<0.01	3057 (45.1)	2237 (50.4)	<0.01
Education						
< High school	788 (37.5)	816 (46.1)	<0.01	948 (14.0)	975 (22.0)	<0.01
HS to vocational school	594 (28.2)	509 (28.8)		3029 (44.8)	2055 (46.4)	
Any college	721 (34.3)	444 (25.1)		2791 (41.2)	1401 (31.6)	
Smoking Status						
Current	675 (32.1)	483 (27.2)	<0.01	1710 (25.3)	1054 (23.8)	<0.01
Former	516 (24.5)	416 (23.5)		2295 (33.9)	1671 (37.7)	
Never	913 (43.4)	873 (49.3)		2765 (40.8)	1710 (38.5)	
Smoking, pack-yrs	12.8 ± 20.1	11.7 ± 20.0	0.12	16.0 ± 20.9	19.5 ± 23.9	<0.01
Drinking Status						
Current	774 (37.0)	447 (25.5)	<0.01	4607 (68.1)	2630 (59.4)	<0.01
Former	449 (21.4)	450 (25.6)		1056 (15.6)	888 (20.1)	
Never	870 (41.6)	858 (48.9)		1101 (16.3)	908 (20.5)	
Alcohol, g/week	39.6 ± 113.2	22.9 ± 73.3	<0.01	46.9 ± 90.8	44.1 ± 98.9	0.12
Body mass index, kg/m^2	27.4 ± 5.5	32.3 ± 5.9	<0.01	25.2 ± 3.8	29.8 ± 4.9	<0.01

Sports score						
1.0 to 3.0	1869 (88.9)	1599 (90.5)	0.09	4967 (73.5)	3575 (80.9)	<0.01
>3.0 to 5.0	234 (11.1)	167 (9.5)		1788 (26.5)	844 (19.1)	
CHD history	53 (2.5)	101 (5.7)	<0.01	196 (2.9)	371 (8.5)	<0.01
HF history	65 (3.1)	204 (11.6)	<0.01	87 (1.3)	334 (7.7)	<0.01
Waist circumference, cm	92.9 ± 13.5	106.8 ± 13.8	<0.01	90.8 ± 11.3	104.5 ± 12.2	<0.01
Triglycerides, mg/dL	87.2 ± 35.3	146.6 ± 101.5	<0.01	102.0 ± 46.2	194.6 ± 117.3	<0.01
HDL-c, mg/Dl	61.1 ± 17.5	47.8 ± 14.7	<0.01	56.4 ± 16.6	41.3 ± 12.3	<0.01
Anti-lipid meds	3 (0.1)	52 (3.0)	<0.01	48 (0.7)	336 (7.6)	<0.01
Systolic BP, mmHg	125.2 ± 20.9	133.4 ± 21.3	<0.01	114.0 ± 15.2	125.3 ± 17.4	<0.01
Diastolic BP, mmHg	78.8 ± 12.5	80.8 ± 11.8	<0.01	69.6 ± 9.4	74.5 ± 10.4	<0.01
Antihypertensive meds	581 (27.6)	1114 (62.9)	<0.01	813 (12.0)	2066 (46.6)	<0.01
Glucose, mg/Dl	100.3 ± 30.7	139.5 ± 71.1	<0.01	97.6 ± 18.0	117.7 ± 43.1	<0.01
Diabetes	125 (6.0)	640 (36.2)	<0.01	172 (2.5)	847 (19.1)	<0.01

Values are N(%) for categorical variables and Mean ± SD for continuous variables.

Table 10.2: Prevalence of Metabolic Syndrome, Individual Metabolic Syndrome Components, and Number of Metabolic Syndrome Components Present at Baseline by Race, ARIC 1987-89.

	Blacks	Whites
Metabolic Syndrome	1774 (45.7)	4437 (39.6)
Individual Components		
Elevated waist circumference	2373 (61.1)	5630 (50.2)
Elevated blood pressure	2609 (67.2)	4600 (41.0)
Elevated triglycerides	653 (17.4)	3641 (32.7)
Low HDL cholesterol	1298 (33.9)	4801 (42.9)
Impaired fasting glucose	2086 (54.1)	5223 (46.8)
Number of Components*		
0	333 (9.0)	1628 (14.7)
1	745 (20.0)	2640 (23.8)
2	997 (26.8)	2441 (22.0)
3	932 (25.0)	2129 (19.2)
4	533 (14.3)	1500 (13.5)
5	182 (4.9)	756 (6.8)

Values are N(%).

* Individuals with missing values for any component of the metabolic syndrome were excluded from this analysis, N=14,816.

Table 10.3: Overall and Race-Specific Incidence Rates and Hazard Ratios for Atrial Fibrillation by the Metabolic Syndrome, ARIC 1987-2005.

	Overall		Blacks		Whites	
	No Metabolic Syndrome	**Metabolic Syndrome**	**No Metabolic Syndrome**	**Metabolic Syndrome**	**No Metabolic Syndrome**	**Metabolic Syndrome**
Entire Cohort						
N Events	558	680	100	144	458	536
Person-years	140,655	92,109	32,306	25,982	108,349	66,126
Incidence Rate*	36	60	30	52	38	62
Hazard Ratio†	1.00	1.67	1.00	1.76	1.00	1.64
95% CI	(ref.)	(1.49-1.87)	(ref.)	(1.35-2.29)	(ref.)	(1.45-1.87)
Without CHD/HF‡						
N Events	482	493	81	111	401	382
Person-years	133,046	78,789	30,496	22,170	102,550	56,619
Incidence Rate*	33	51	26	48	35	53
Hazard Ratio†	1.00	1.53	1.00	1.91	1.00	1.46
95% CI	(ref.)	(1.35-1.74)	(ref.)	(1.42-2.57)	(ref.)	(1.26-1.68)
With CHD/HF§						
N Events	66	163	16	29	50	134
Person-years	5,037	11,462	1,345	3,588	3,691	7,875
Incidence Rate*	99	117	112	78	98	133
Hazard Ratio†	1.00	1.28	1.00	0.62	1.00	1.52
95% CI	(ref.)	(0.95-1.71)	(ref.)	(0.34-1.16)	(ref.)	(1.08-2.12)

* Age- and sex-adjusted incidence rate per 10,000 person-years.

† Multivariate model adjusted for the following covariates at baseline: age, sex, center, educational attainment, smoking status and cigarette-years of smoking. Overall model additionally adjusted for race.

‡ Analysis among those without prevalent coronary heart disease or heart failure at baseline, N=13,289.

§ Analysis among those with prevalent coronary heart disease or heart failure at baseline, N=1,252.

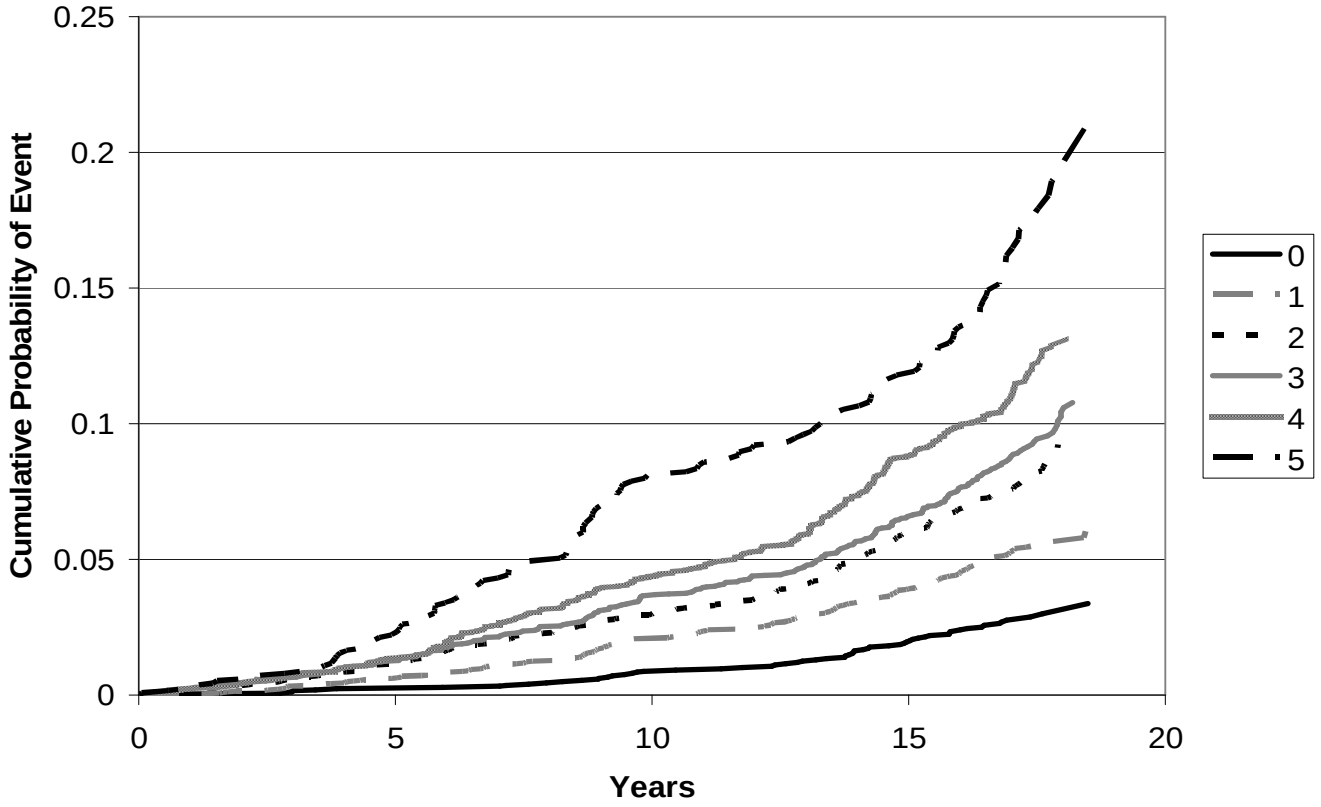
Table 10.4: Overall and Race-Specific Hazard Ratios and 95% Confidence Intervals for Atrial Fibrillation by the Individual Components of the Metabolic Syndrome and by Number of Components Fulfilled, ARIC 1987-2005.

	Overall	Blacks	Whites
Metabolic Syndrome Components*			
Elevated waist circumference	1.40 (1.23-1.59)	1.50 (1.08-2.09)	1.37 (1.19-1.58)
Elevated blood pressure	1.95 (1.72-2.21)	1.60 (1.15-2.23)	2.02 (1.76-2.32)
Elevated triglycerides	0.95 (0.84-1.09)	1.17 (0.84-1.62)	0.93 (0.80-1.07)
Low HDL cholesterol	1.20 (1.06-1.37)	1.53 (1.14-2.05)	1.14 (0.99-1.32)
Impaired fasting glucose	1.16 (1.03-1.31)	1.04 (0.78-1.38)	1.18 (1.03-1.35)
Number of Components†			
0	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
1	1.69 (1.27-2.25)	1.63 (0.70-3.75)	1.71 (1.26-2.33)
2	2.45 (1.86-3.23)	2.97 (1.35-6.51)	2.37 (1.77-3.19)
3	2.66 (2.02-3.51)	3.12 (1.42-6.89)	2.60 (1.93-3.50)
4	3.13 (2.36-4.16)	4.61 (2.07-10.28)	2.90 (2.14-3.94)
5	4.40 (3.25-5.94)	4.83 (2.00-11.66)	4.30 (3.12-5.94)

***** Multivariate model adjusted for the following covariates at baseline: age, sex, center, educational attainment, smoking status, cigarette-years of smoking, and the other metabolic syndrome components. Overall model additionally adjusted for race.

† Multivariate model among individuals without any missing values for metabolic syndrome components. Multivariate model adjusted for the following covariates at baseline: age, sex, center, educational attainment, smoking status and cigarette-years of smoking. Overall model additionally adjusted for race.

Figure 10.1: Cumulative Probability of Atrial Fibrillation by Number of Metabolic Syndrome Components at Baseline, ARIC 1987-2005.



11.0 MANUSCRIPT 2 – SMOKING AND INCIDENCE OF ATRIAL FIBRILLATION

11.1 OVERVIEW

Objective: To determine the association of smoking with incident atrial fibrillation (AF) in a population-based prospective cohort study, and to summarize associations from other prospective studies by conducting a systematic review of the literature on smoking and AF. **Background:** Cigarette smoking increases the risk of coronary heart disease, but whether smoking increases AF is uncertain. **Methods:** We determined the risk of incident AF through December 2002 in relation to baseline (1987-1989) smoking status and cigarette-years of smoking in over 15,000 participants of the prospective Atherosclerosis Risk in Communities (ARIC) study. In addition, we conducted a systematic review of prospective population-based studies reporting associations of smoking with incidence of AF. **Results:** Over a mean follow-up of 13.1 years in the ARIC study, 876 incident AF events were identified. Compared to never smokers, the multivariable-adjusted hazard ratios (HR) for AF were 1.30 (95% CI, 1.09-1.55) in former smokers, 1.54 (95% CI, 1.31-1.81) in ever smokers, and 1.98 (95% CI, 1.64-2.38) in current smokers. In the highest tertile of accumulated smoking amount (>675 cigarette-years), the incidence of AF was 1.93-times greater (95% CI, 1.59-2.34) than those who never smoked. In our systematic review, we identified 5 studies that reported associations of smoking with AF. The results of these studies varied, some indicating positive associations and others no association between smoking status and incidence of AF. **Conclusion:** Although no consistent association between smoking and AF was

apparent through our systematic review, a positive association of smoking status with incident AF was found in the ARIC study.

11.2 INTRODUCTION

Cigarette smoking promotes vasomotor dysfunction, atherosclerosis, and thrombosis, thus increasing the risk of cardiovascular disease.[185] However, evidence for an association between smoking and atrial fibrillation (AF) is limited. Cigarette smoking increases oxidative stress,[186] inflammation,[186] and atrial fibrosis,[149] all mechanisms potentially involved in the etiology of AF.[185]

A few prospective studies have reported on the association between smoking and AF. In the Framingham Heart Study, cigarette smoking was associated with a 40% increased odds of developing AF among women, but there was no association among men.[11] Compared with never smokers, the Rotterdam study reported a 51% and 49% increased risk of incident AF among current and former smokers, respectively, which did not differ by gender.[152] A 37% increased risk of AF among ever vs. never smokers was reported in the Manitoba Follow-Up Study.[57] Yet, no association was found between smoking and AF in the Danish Diet, Cancer, and Health Study[187] or the Multifactor Primary Prevention Study.[151]

These limited and inconsistent data suggest further investigation of the association between smoking and AF is warranted. Approximately 20% of U.S. adults are current smokers.[188] If an association exists between cigarette smoking and AF, smoking cessation might reduce AF occurrence. Thus, we determined the risk of incident AF in

relation to smoking status and amount in the Atherosclerosis Risk in Communities (ARIC) study. We hypothesized that the incidence of AF would be higher among those who were current and former smokers at baseline compared to those who never smoked, and the incidence of AF would increase with increasing pack-years of smoking. In addition, we conducted a systematic literature review among prospective, population-based studies of cigarette smoking and AF.

11.3 METHODS

Study Population

The ARIC study is a prospective cohort investigation aimed to identify risk factors for atherosclerosis and cardiovascular disease. ARIC recruited probability samples of adults aged 45-64 years from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis suburbs, Minnesota; and Washington County, Maryland.[174] Blacks and whites were recruited from Forsyth County, only blacks from Jackson, Mississippi, and predominantly whites from the other two communities. A total of 15,792 participants (8710 women) were enrolled from 1987 to 1989, and completed a home interview and clinic visit. Three follow-up clinic visits were conducted, each spaced three years apart (1990-92, 1993-95, 1996-98). In addition, participants are being followed-up by annual telephone interviews and active surveillance of the ARIC community hospitals. The ARIC study was approved by institutional review boards at each participating center, and informed consent was obtained from participants at every clinic visit.

Atrial Fibrillation Ascertainment

Electrocardiograms (ECGs) during the baseline visit were used to identify individuals with prevalent AF or atrial flutter for exclusion. Incident AF diagnoses through December 31, 2005 were identified from 3 sources: ECGs performed during study follow-up visits through 1998, hospital discharge records through 2005, and death certificates through 2005.

All ARIC examination ECGs were recorded using MAC PC Personal Cardiographs (Marquette Electronics, Inc., Milwaukee, WI). A standard supine 12-lead resting ECG was recorded at least one hour after smoking tobacco or ingestion of caffeine at each clinic visit. ECGs were then transmitted by modem to the ARIC ECG Reading Center for computer coding. ECG recordings during follow-up that were computer coded as AF were visually re-checked by a cardiologist to confirm the diagnosis.[176]

Annual follow-up telephone calls were placed to cohort participants in order to identify hospitalizations and deaths. In addition, local hospitals were surveyed for potential cardiovascular events. Hospital discharge records were gathered from all hospitalizations, and AF was identified by an ICD-9 discharge code of 427.31 or 427.32 among any of the discharge diagnoses. AF was also identified when any listed cause of death on a death certificate was coded as AF (ICD-9 code 427.3 or ICD-10 code I48). AF occurring simultaneously with heart revascularization surgery (ICD-9 code 36.X) or other cardiac surgery involving heart valves or septa (ICD-9 code 35.X) was not considered an incident event and follow-up was continued beyond that episode for incident AF not associated with cardiac surgery. Prior analysis within the ARIC cohort

to determine the validity of hospital discharge diagnoses for AF reported 84% sensitivity and 98% specificity in the ascertainment of AF events.[53]

Smoking Assessment

Cigarette smoking status and amount were determined by self-report. Participants were asked whether they ever smoked cigarettes, and if so, the age of smoking initiation, number of years of smoking, number of cigarettes smoked per day, and whether they currently smoked, and if not, the age they quit smoking. From responses to these questions, participants were categorized as current, former, or never smokers, and cigarette-years of smoking was calculated for current and former smokers. Information on pipe and cigar/cigarillo smoking was not included in this analysis as only 3% of ARIC cohort participants were current pipe and/or cigar smokers at baseline.

For analysis, smoking status was categorized using three different classifications: 1) current, former, never (reference), 2) ever, never (reference), and 3) current, non-current (reference). Cigarette-years of smoking was categorized into tertiles for ever smokers, and never smokers served as the reference group. In addition to smoking status and cigarette-years of smoking, we created a variable consisting of 5 categories that combined smoking status and amount. Current and former smokers were each dichotomized at 800 cigarette-years of smoking (equivalent to 40 pack-years), with never smokers serving as the reference group.

Additional Baseline Measurements

Race, education level, and drinking status were determined by self-report. The sports index for physical activity during leisure time ranged from 1 (low) to 5 (high), and was based on the questionnaire developed by Baecke et al.[181] For this analysis, we dichotomized the sports index at the 90th percentile. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. A participant was categorized as diabetic if he/she had a fasting glucose $\geq$126 mg/dL (or non-fasting glucose of $\geq$200 mg/dL if a fasting sample was not available), reported a physician diagnosis of diabetes, or was currently taking medication for diabetes. Blood pressure was measured 3 times, with the last 2 measurements averaged to determine if a participant was hypertensive, which was defined as an average blood pressure of $\geq$140 mmHg systolic and/or $\geq$90 mmHg diastolic, or blood pressure medication use in the past 2 weeks. Prevalent coronary heart disease (CHD) at baseline included individuals with a history of myocardial infarction (MI), MI indicated on the baseline ECG, or history of coronary bypass or angioplasty. Prevalent heart failure (HF) was identified by the Gothenburg criteria[182] or self-report of HF medication use in the past 2 weeks.

Statistical Analysis

The following analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC). Of the 15,792 ARIC participants, we excluded those who were not of black or white race (N=48), blacks from Minneapolis and Washington County (N=55), prevalent AF (N=37) or missing AF status (N=244) at baseline, and those with unreadable baseline ECGs (N=85). We additionally excluded missing and unknown

smoking status (N=14) and/or missing cigarette-years of smoking (N=265) at baseline in models where appropriate.

Person-years of follow-up were computed from the baseline exam date until a first AF diagnosis, death, lost to follow-up, or December 31, 2005, whichever came first. Baseline participant characteristics by smoking status were compared using chi-squares for categorical measures and analysis of variance (ANOVA) for continuous variables.

Analyses were conducted for each of the 5 categorizations of baseline cigarette smoking. Overall and race-specific age- and sex-adjusted incidence rates for AF at baseline were calculated using Poisson regression. Multivariate-adjusted hazard ratios of smoking for AF were estimated in the full cohort and separately in blacks and whites using Cox proportional hazards regression after adjusting for the following baseline characteristics: age, sex, race (full cohort analysis), ARIC field center, education (less than high school, high school graduate to vocational school, any college), BMI, drinking status (current, former, never), sports index ($\geq$3.5, <3.5), diabetes, hypertension, CHD, and HF. Even though CHD and HF may be intermediate factors in the pathogenesis of AF, these were included as covariates in our models because we felt that CHD and HF may also confound the relationship between smoking and AF. Multiplicative interactions with sex and race were tested in the Cox proportional hazards models and found to be nonsignificant; however, race-specific results are reported for interests sake.

In order to utilize data collected during follow-up exams, we created an additional three cohorts using exams 2, 3, and 4 as baseline. For each cohort, we excluded individuals with prevalent AF before that exam, included the same potential confounders as measured during that exam, and began follow-up at the date of the exam. For a

particular cohort, we categorized individuals as quitting smoking if they were current smokers at the previous exam and a former smoker at the current exam; those who were current smokers at both exams were considered continued smokers, and served as the referent group for this analysis. These three cohorts were then pooled into one Cox model using a robust variance estimator to take into account within-individual correlations since study participants could be included more than once.[189]

To test the proportional hazards assumption for the Cox regression models, interaction terms between smoking status/amount and log of follow-up time were tested and the log-log survival curves were plotted. The proportional hazards assumption was met for the first 16 years of follow-up, but not thereafter. Therefore, we subsequently ended follow-up at December 31, 2002 for all analyses presented here.

Systematic Review

We also conducted a systematic literature review on prospective, population-based studies reporting associations of cigarette smoking with AF. We searched the MEDLINE (1950 – June 24, 2009), Biosis Previews (1996 – June 24, 2009), ISI Web of Science (1975 – June 24, 2009), and EMBASE (1950 – July 11, 2009) databases for the following subject headings and terms: (*smoking* or *smok** or *tobacco* or *nicotine*) and (*atrial fibrillation* or *cardiac arrhythmias* or *arrhythmia* or *tachyarrhythmia*) and (*cohort* or *prospective*). We also searched the reference lists of relevant articles that were identified in our database searches. We included only studies that were prospective in nature and that provided an estimate of the association between smoking status or amount with incident AF. Two reviewers (AM Chamberlain and A Alonso) independently

identified and reviewed relevant articles from the database searches and reference lists; any discrepancies between reviewers were resolved through discussion.

We identified 5 relevant articles from our database searches, with an additional 3 articles identified by reference list searches. Three articles from the Framingham Heart Study were identified from our database searches;[10,11,52] one article summarizing previous findings from many Framingham manuscripts was excluded.[52] Of the remaining 2 articles, we included only the article with the longest follow-up.[11] An article from the Cardiovascular Health Study was also excluded; smoking was eliminated from a backwards stepwise model of risk factors for AF, but a relative risk for smoking was not reported.[9] Therefore, 5 articles in total were selected and summarized in our systematic review on smoking and AF. Estimates of the association between smoking and AF risk were obtained from each study. Between-study heterogeneity was calculated using the I^2 statistic.[190]

11.4 RESULTS

After exclusions, 15,329 participants were available for the smoking status analysis, and 15,078 were available for the cigarette-years analysis and the combined smoking status and amount analysis. Table 11.1 summarizes the baseline characteristics of the ARIC population by smoking status. Current and former smokers at baseline were less well educated, more likely to be current drinkers, were less physically active, and had more prevalent CHD and HF than never smokers.

Smoking and AF in ARIC

Over a mean follow-up of 13.1 years, 876 incident AF events were identified. Age- and sex-adjusted incidence rates, along with multivariate-adjusted hazard ratios for AF by smoking status and are reported in Table 11.2. The age- and sex-adjusted incidence rates for AF were 28, 36, and 48 per 10,000 person-years in never smokers, former smokers, and current smokers, respectively. Compared to never smokers, the risk of AF was 1.30-times (95% CI, 1.09-1.55) greater among former smokers and was 2-fold higher in current smokers (HR, 1.98; 95% CI, 1.64-2.38) than never smokers. In addition, the incidence of AF was 1.54-times (95% CI, 1.31-1.81) higher in ever smokers. In a sensitivity analysis including only AF events identified by ECG, the increased risk of AF associated with smoking remained. The hazard ratios for ECG-diagnosed AF during ARIC exams were 1.79 (95% CI, 1.11-2.90) in former smokers, 2.29 (95% CI, 1.35-3.91) in current smokers, and 1.95 (95% CI, 1.24-3.06) in ever smokers compared to never smokers. Hazard ratios were similar in blacks and whites, although the age- and sex-adjusted incidence rates for AF were lower in blacks (32 per 10,000 person-years) than whites (44 per 10,000 person-years).

We also created tertiles of cigarette-years of smoking in current and former smokers, and those in the lowest category of smoking amount had similar risk of developing AF as never smokers with zero cigarette-years of smoking (Table 11.3). Those in the second category of cigarette-years of smoking had an incidence rate of 41 per 10,000 person-years and a 58% increased risk of developing AF (95% CI, 29%-93%). The heaviest smokers (>675 cigarette-years) exhibited an AF incidence rate of 55 per 10,000 person-years and a hazard ratio of incident AF of 1.93 (95% CI, 1.59-2.34)

compared to zero cigarette-years of smoking. Associations again did not statistically significantly differ by race, with a 2.17-fold greater risk of AF among blacks in the highest tertile of smoking and a corresponding increased risk of 1.89 among whites.

In addition to examining the effect of smoking status and amount with incident AF, we dichotomized current and former smokers into light/moderate versus heavy smokers (<800 vs. ≥800 cigarette-years of smoking) (Table 11.4). Former smokers had lower incidence rates of and hazard ratios for AF compared to current smokers with the same amount of smoking. For example, former smokers with <800 cigarette-years of smoking had an incidence rate of AF of 33 per 10,000 person-years, compared to 42 among current smokers with <800 cigarette-years of smoking. Among light/moderate smokers, the hazard ratio for AF was 1.16 (95% CI, 0.96-1.41) in former smokers and 1.86 (95% CI, 1.49-2.31) in current smokers. In heavy smokers of ≥800 cigarette-years of smoking, which is equivalent to at least 40 pack-years of smoking, former smokers had a 72% increased risk of AF compared with never smokers, whereas current smokers had a 110% increased risk of developing AF over up to 16 years of follow-up. Blacks and whites showed a similar pattern, although it appeared that black heavy smokers had similar risk of incident AF regardless of smoking status.

In an attempt to further explore the association of quitting smoking with AF risk, we created 3 cohorts, using exams 2, 3, and 4 as baseline, and pooled them in a Cox model. This analysis included 5,513 individuals and 318 AF cases. Individuals who quit smoking had a slightly lower, although nonsignificant, risk of developing AF (HR, 0.85; 95% CI, 0.63-1.13) compared to those who continued to smoke.

Systematic Review of Smoking and AF

Tables 11.5 and 11.6 summarize the 5 studies we identified during our systematic review of prospective, population-based studies on smoking and the risk of incident AF. These cohort studies recruited individuals from the U.S.,[11] Canada,[57] Sweden,[151] Denmark,[187] and the Netherlands.[152] The smoking status classification differed by study, and included current vs. non-current; ever vs. never; current, former vs. never; and <15, ≥15 cigarettes per day vs. ever smoking. The Rotterdam Study reported associations of AF with smoking status along with tertiles of duration, tertiles of smoking amount, and dichotomized age within smoking status category; however, we report only current, former vs. never associations in our summary table to be more consistent with other studies. The ascertainment of AF was generally similar between studies, and included hospitalization discharge diagnoses, physician records, national registry records, and ECGs conducted during follow-up examinations. In Table 11.6, we report only the most adjusted estimate of AF for each study. The Multifactor Primary Prevention Study reported an odds ratio for AF, the Framingham Heart Study reported an odds ratio calculated from pooling biennial person-examination data, and the remaining studies report hazard ratios for incident AF. The associations of smoking with AF were inconsistent among studies. The Framingham Heart Study found a slight increased risk of AF among women current vs. non-current smokers only (OR, 1.4; 95% CI 1.0-2.0); a similar increased risk was reported in ever vs. never smokers in the Manitoba Follow-Up Study (HR, 1.37; 95%CI 1.00-1.87). The Rotterdam Study also reported an increased risk of AF that was similar in both current (HR, 1.51; 95% CI 1.07-2.12) and former (HR,

1.48; 95% CI 1.12-1.96) smokers compared with never smokers. The two remaining studies, both from Scandinavia, found no association of smoking with AF.

In order to further summarize the associations of smoking with incidence of AF, we pooled men and women, and calculated hazard ratios and odds ratios for ever vs. never smoking and current vs. non-current smoking for the studies included in our systematic review (Figure 11.1). Among studies that reported current, former vs. never smoking, a covariance of 0 between current and former smokers was assumed in order to calculate a current vs. non-current association. We additionally added results from our analysis within the ARIC study to the figure. There was no consistent association of incident AF with smoking status, whether ever vs. never or current vs. non-current. The high amount of heterogeneity between the studies (I^2=91% for ever vs. never, I^2=92% for current vs. non-current) rendered a meta-analysis and pooled estimate of the association between smoking and AF to be of limited value.

11.5 DISCUSSION

In this population-based prospective study with up to 16 years of follow-up, former and current smokers exhibited a 30% and 98% increased risk of developing AF compared to never smokers. The risk of incident AF increased with increasing cigarette-years of smoking, and appeared to be somewhat greater among current smokers than former smokers with similar cigarette-years of smoking. Associations were similar among whites and blacks.

In previously published studies on smoking and incidence of AF, there appeared to be no consistent association of incident AF with smoking status, whether ever vs. never or current vs. non-current. In addition, we did not calculate a pooled estimate of smoking risk on incidence of AF due to the high amount of heterogeneity between the studies identified. Several factors may have contributed to the heterogeneity, including differences in source population, follow-up, exposure measurement, ascertainment of AF events, and confounder adjustment. Since all studies identified by our systematic review were conducted in different countries, it is also possible that differences exist in the amount or duration of smoking among current/ever smokers by country. In the 2 Scandinavian studies reporting null results, the following study characteristics may have led to masking of associations between smoking and AF. The Multifactor Primary Prevention Study was an intervention against smoking, and only baseline data were used in analyses. Those who smoked at baseline may have been more likely to quit smoking or decrease their amount of smoking over follow-up, making them more similar to the non-smokers at baseline. Thus, an association between smoking and AF might possibly have been masked. The Danish Diet, Cancer, and Health Study had the shortest follow-up of all studies (mean of 5.7 years) and also the most stringent exclusion criteria. Participants who were hospitalized prior to baseline for endocrine diseases or cardiovascular diseases were excluded from analyses. These exclusions created a healthier cohort, and possibly eliminated those who may have been more susceptible to the effects of smoking. Although additional studies may be needed to clarify the association of smoking and AF, our study, along with the majority of studies we identified in the systematic review, reported positive associations of smoking with

incidence of AF. Therefore, cigarette smoking may contribute positively to AF risk, and thus it is worth discussing the possible biological mechanisms linking smoking to increased risk of developing AF.

Potential mechanisms linking cigarette smoking to increased incidence of AF are not fully established. Smoking could lead to a higher risk of AF indirectly through an increased incidence of other cardiovascular events, such as heart failure[191-193] or coronary artery disease.[185,194] Potential mechanisms by which cigarette smoke contributes to acute vascular events include induction of a hypercoagulable state, increased myocardial work, carbon monoxide-mediated reduced oxygen-carrying capacity of the blood, coronary vasoconstriction, and catecholamine release.[195] Furthermore, cigarette smoking likely promotes atherosclerosis through adverse effects on lipids, endothelial damage or dysfunction, hemodynamic stress, oxidant injury, neutrophil activation, enhanced thrombosis, and increased fibrinogen and blood viscosity.[195] The acute hemodynamic effects of nicotine include increases in heart rate and blood pressure,[196] which in turn may result in AF among long-term smokers. In some cases, the development of myocardial infarction due to a hypercoagulable state, enhanced thrombosis, or hemodynamic stress as a result of smoking may increase the risk of subsequently developing AF. In addition, reduced lung function and chronic obstructive pulmonary disease (COPD) have been reported to increase the risk of AF;[9,114] therefore, the association of smoking and AF may also be in part mediated by reduced lung function or COPD.

Nicotine in cigarette smoke has been shown to increase both atrial and ventricular vulnerability to fibrillation.[150,197] This increased vulnerability to fibrillation may be due to alteration of atrial myocyte ion channel conduction, either by release of

neurotransmitters or by direct interaction with ion channels. The nicotine-induced changes in heart rate and arterial pressure are associated with increases in plasma catecholamine concentrations due to stimulation of sympathetic neurotransmission.[198] Nicotine directly stimulates postganglionic sympathetic nerve endings, resulting in increased plasma concentrations of norepinephrine and epinephrine and decreased postganglionic muscle sympathetic nerve activity.[199] In addition, nicotine has been shown to block the transient outward K^+ current (I_{to}), which governs the initial phase of cardiac repolarization and influences other currents and membrane transport processes.[200] The blockage of I_{to} may be proarrhythmic due to a delay of ventricular repolarization or prolongation of the effective refractory period. Nicotine may also contribute to the development of atrial fibrosis, which has been shown to favor the occurrence of atrial arrhythmias.[149] Interstitial fibrosis causes a substantial slowing of electrical impulse propagation in cardiac tissue and affects chamber geometry.[201] A recent canine model of atrial fibrillation showed that nicotine causes downregulation of atrial microRNA's miR-133 and miR-590 in atrial fibroblasts, with an associated upregulation of transforming growth factors TGF-β1 and TGF-βRII and increased collagen production, inducing a proarrhythmic atrial fibrosis.[202] Thus cigarette smoking may increase vulnerability to AF and other arrhythmias through different nicotine-induced mechanisms, such as alterations of atrial myocyte ion channel conduction and the development of atrial fibrosis.

Our study has several strengths, including the large sample size and long follow-up of the ARIC cohort. We had information on both smoking status and cigarette-years of smoking, along with repeated measures of smoking status at all follow-up visits, which allowed us to investigate the association of both smoking status and amount with

incidence of AF. However, we also acknowledge a few limitations. First, it is possible that some incident AF events were missed among individuals without symptoms or who were not hospitalized. Most AF events were ascertained by hospital discharge records even though ECGs were also obtained during the 3 ARIC follow-up exams. Therefore, we acknowledge the possibility of underascertainment of the AF events, although we believe this possible misclassification had little impact on study results. We conducted a sensitivity analysis including only AF events identified during exam ECGs, and found that the hazard ratios for AF by smoking status categories were slightly stronger than the associations found when considering all AF cases. In addition, our estimates of AF incidence are similar to those reported by other cohorts.[9,11,48,62,64] Finally, associations of genetic risk factors and AF in ARIC were similar to that of other cohort studies that relied more on study exam ECGs rather than hospital discharge records to identify AF events.[141] Second, we did not have available information to classify AF events as paroxysmal, persistent, or permanent, which eliminated the possibility of conducting sub-group analyses on type of AF. Finally, although we attempted to investigate the effect of quitting smoking on AF risk, we did not have information on quitting smoking past ARIC visit 4. In addition, we did not have the ability to differentiate reasons for quitting smoking, such as a person being ill. Therefore, we were unable to fully capture the effect of quitting smoking among otherwise healthy individuals on their subsequent risk of developing AF. Residual confounding might explain the weak association between smoking cessation and the subsequent risk of AF.

In conclusion, previously published studies on smoking and incidence of AF have provided inconsistent results. However, we found in ARIC that current smokers had

almost twice the risk of developing AF over up to 16 years of follow-up compared to never smokers. In addition, it appeared that smokers who quit were less likely to develop AF compared to continued smokers with similar cigarette-years of smoking. Finally, associations of smoking with AF were similar among whites and blacks.

11.6 TABLES AND FIGURES

Table 11.1: Baseline Participant Characteristics by Smoking Status, ARIC 1987-89.

	Current (N=4005)	Former (N=4950)	Never (N=6374)
Age, years	53.6 (5.7)	54.8 (5.8)	54.0 (5.8)
Gender			
Male	1900 (47.4)	3054 (61.7)	1915 (30.0)
Female	2105 (52.6)	1896 (38.3)	4459 (70.0)
Race			
Black	1214 (30.3)	962 (19.4)	1880 (29.5)
White	2791 (69.7)	3988 (80.6)	4494 (70.5)
Education			
< High school	1243 (31.1)	1075 (21.7)	1302 (20.4)
HS to vocational school	1649 (41.2)	1948 (39.4)	2661 (41.8)
Any college	1107 (27.7)	1924 (38.9)	2403 (37.8)
Drinking status			
Current	2535 (63.6)	3141 (63.7)	2883 (45.4)
Former	879 (22.0)	1170 (23.7)	835 (13.2)
Never	574 (14.4)	623 (12.6)	2629 (41.4)
BMI, kg/m^2	26.4 (5.0)	28.0 (5.1)	28.3 (5.7)
Sports index			
<3.5	3581 (89.7)	4067 (82.4)	5582 (87.9)
≥3.5	410 (10.3)	870 (17.6)	768 (12.1)
Diabetes	421 (10.6)	588 (11.9)	803 (12.7)
Hypertension	1291 (32.2)	1713 (34.8)	2316 (36.5)
Coronary heart disease	208 (5.3)	367 (7.5)	160 (2.6)
Heart failure	217 (5.5)	235 (4.8)	257 (4.1)
Cigarette-years of smoking	670.8 (430.9)	463.6 (434.1)	0 (0)

Values are mean (SD) for continuous variables and N (%) for categorical variables.

All characteristics differed among smoking groups at $p<0.01$.

Table 11.2: Incidence Rates and Hazard Ratios for Atrial Fibrillation by Smoking Status Categories, ARIC 1987-2002.

	Number of Events	Person-years	Incidence Rate*	Hazard Ratio†	95% CI
Overall					
Never (ref.)	270	86,307	28	1.00	ref.
Ever	606	115,048	41	1.54	(1.31-1.81)
Former	333	64,887	36	1.30	(1.09-1.55)
Current	273	50,161	48	1.98	(1.64-2.38)
Non-Current (ref.)	603	151,194	31	1.00	ref.
Current	273	50,161	48	1.71	(1.47-1.99)
Blacks					
Never (ref.)	60	24,882	22	1.00	ref.
Ever	98	27,139	32	1.57	(1.09-2.26)
Former	44	12,357	29	1.28	(0.83-1.98)
Current	54	14,782	35	1.95	(1.28-2.96)
Non-Current (ref.)	104	37,239	24	1.00	ref.
Current	54	14,782	35	1.74	(1.21-2.52)

Whites					
Never (ref.)	210	61,425	29	1.00	ref.
Ever	508	87,909	44	1.53	(1.28-1.84)
Former	289	52,530	38	1.30	(1.07-1.58)
Current	219	35,379	53	1.99	(1.62-2.45)
Non-Current (ref.)	499	113,955	33	1.00	ref.
Current	219	35,379	53	1.71	(1.44-2.03)

*Age- and sex-adjusted incidence rates per 10,000 person-years.

† Multivariate model adjusted for the following covariates at baseline: age, sex, center, educational attainment, drinking status, BMI, sports index, diabetes, hypertension, CHD and HF. Overall model additionally adjusted for race.

Table 11.3: Incidence Rates and Hazard Ratios for Atrial Fibrillation by Cigarette-Years of Smoking Categories, ARIC 1987-2002.

	Number of Events	Person-years	Incidence Rate*	Hazard Ratio†	95% CI
Overall					
Zero (ref.)	275	87,288	28	1.00	ref.
≤308	116	38,777	27	1.05	(0.84-1.32)
>308 to ≤675	179	37,324	41	1.58	(1.29-1.93)
>675	285	34,759	55	1.93	(1.59-2.34)
Blacks					
Zero (ref.)	61	25,057	22	1.00	ref.
≤308	29	11,922	24	1.12	(0.70-1.81)
>308 to ≤675	28	8,024	34	1.61	(0.98-2.63)
>675	33	5,463	46	2.17	(1.32-3.56)
Whites					
Zero (ref.)	214	62,231	29	1.00	ref.
≤308	87	26,854	28	1.03	(0.80-1.34)
>308 to ≤675	151	29,300	43	1.58	(1.26-1.97)
>675	252	29,296	57	1.89	(1.53-2.33)

*Age- and sex-adjusted incidence rates per 10,000 person-years.

† Multivariate model adjusted for the following covariates at baseline: age, sex, center, educational attainment, drinking status, BMI, sports index, diabetes, hypertension, CHD and HF. Overall model additionally adjusted for race.

Table 11.4: Incidence Rates and Hazard Ratios for Atrial Fibrillation by Smoking Status and Cigarette-Years of Smoking Categories, ARIC 1987-2002.

	Mean Cigarette-Years	Number of Events	Person-years	Incidence Rate*	Hazard Ratio†	95% CI
Overall						
Never (ref.)	0	270	86,307	28	1.00	ref.
Former, <800	302	221	52,458	33	1.16	(0.96-1.41)
Former, ≥800	1197	99	10,526	55	1.72	(1.34-2.20)
Current, <800	452	139	34,530	42	1.86	(1.49-2.31)
Current, ≥800	1149	126	14,328	58	2.10	(1.66-2.67)
Blacks						
Never (ref.)	0	60	24,882	22	1.00	ref.
Former, <800	258	30	10,309	25	1.09	(0.67-1.75)
Former, ≥800	1281	9	1,212	50	1.90	(0.86-4.19)
Current, <800	377	39	11,687	35	1.98	(1.26-3.10)
Current, ≥800	1233	13	2,377	38	1.85	(0.93-3.68)
Whites						
Never (ref.)	0	210	61,425	29	1.00	ref.
Former, <800	313	191	42,150	34	1.17	(0.95-1.45)
Former, ≥800	1184	90	9,314	54	1.70	(1.30-2.23)
Current, <800	493	100	22,843	46	1.84	(1.43-2.37)
Current, ≥800	1131	113	11,950	62	2.14	(1.65-2.76)

*Age- and sex-adjusted incidence rates per 10,000 person-years.

† Multivariate model adjusted for the following covariates at baseline: age, sex, center, educational attainment, drinking status, BMI, sports index, diabetes, hypertension, CHD and HF. Overall model additionally adjusted for race.

Table 11.5: Summary of Prospective, Population-Based Studies on Smoking and Atrial Fibrillation.

Source	Study	Source Population	Smoking Measure	AF Ascertainment	Follow-Up
Benjamin, 1994[11]	Framingham Heart Study	5,209 men and women aged 30-62 from Framingham, MA, USA enrolled in 1948 with follow-up visits every 2 years	Current vs. Non-current smoking	ECGs at study clinic exams, hospital records, outside physician records	38 years (max.)
Krahn, 1995[57]	Manitoba Follow-Up Study	3,983 male air crew recruits for pilot training in the Royal Canadian Air Force aged 18-62 years enrolled in 1948 with annual contact by mail and examinations every 3 to 5 years	Ever vs. Never Smoking	ECGs at clinic exams, physician report of AF	33 years (mean)
Wilhelmsen, 2001[151]	Multifactor Primary Prevention Study	7,495 men aged 47-55 years from Göteborg, Sweden enrolled in 1970-73 with 1 follow-up visit in 1974-77 and followed through 1996 for AF hospitalizations	<15, ≥15 cigarettes/day vs. Non-current smokers	Hospitalizations for AF, ECGs at follow-up clinic examination	25.2 years (mean)
Frost, 2005[187]	Danish Diet, Cancer, & Health Study	27,177 men and 29,876 women aged 50-64 years from Copenhagen or Aarhus county, Denmark enrolled in 1993-97 with follow-up in the National Registry of Patients and the Civil Registration System through 2001	Current, Former vs. Never Smoking	Hospital discharge diagnoses from the National Registry of Patients	5.7 years (mean)
Heeringa, 2008[152]	Rotterdam Study	7,983 men and women aged ≥55 years from Ommoord (a suburb of Rotterdam), Netherlands enrolled in 1990-93 with 2 follow-up visits (1993-94, 1997-99)	Current, Former vs. Never Smoking	ECGs at follow-up exams, general practitioner and outpatient clinic files, hospital discharge diagnoses identified through national registry	7.2 years (median)

Table 11.6: Results Summary of Prospective, Population-Based Studies on Smoking and Atrial Fibrillation.

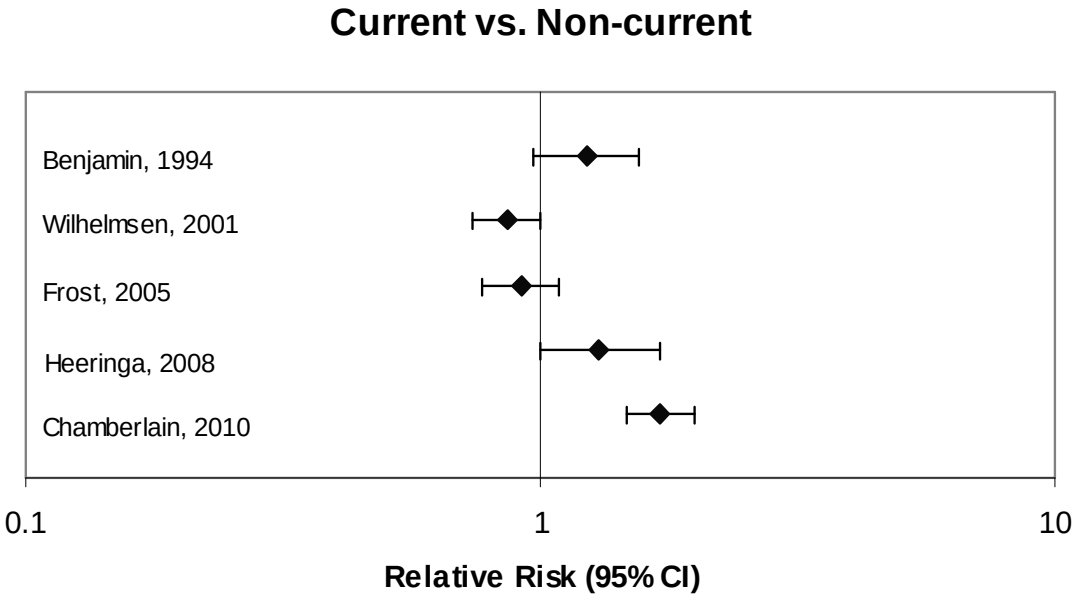
Source	Total N	AF Events	Outcome Measure	Relative Risk (95% CI)	Adjustment Variables
Benjamin, 1994[11]	4731*	226 men 244 women	Odds Ratio† (current vs. non-current)	1.1 (0.8-1.5) 1.4 (1.0-2.0)	age, diabetes, hypertension, chronic heart failure, valvular heart disease
Krahn, 1995[57]	3982	300	Hazard Ratio (ever vs. never)	1.37 (1.00-1.87)	Age
Wilhelmsen, 2001[151]	7440	754	Odds Ratio (<15, ≥15 cigarettes/day vs. non-current)	0.83 (0.71-0.97) <15 cigarettes/day 1.16 (0.73-1.86) ≥15 cigarettes/day	Age
Frost, 2005[187]	47,258	372 men§ 181 women§	Hazard Ratio (current, former vs. never)	0.83 (0.64-1.07) current 0.80 (0.62-1.04) former 0.95 (0.66-1.35) current 0.94 (0.65-1.36) former	age, height, BMI, education, alcohol, total cholesterol, hypertension treatment, systolic blood pressure
Heeringa, 2008[152]	5668	371	Hazard Ratio (current, former vs. never)	1.51 (1.07-2.12) current 1.48 (1.12-1.96) former	age, sex, BMI, hypertension, systolic blood pressure, total cholesterol, diabetes, left ventricular hypertrophy, myocardial infarction, chronic heart failure, pulmonary medication

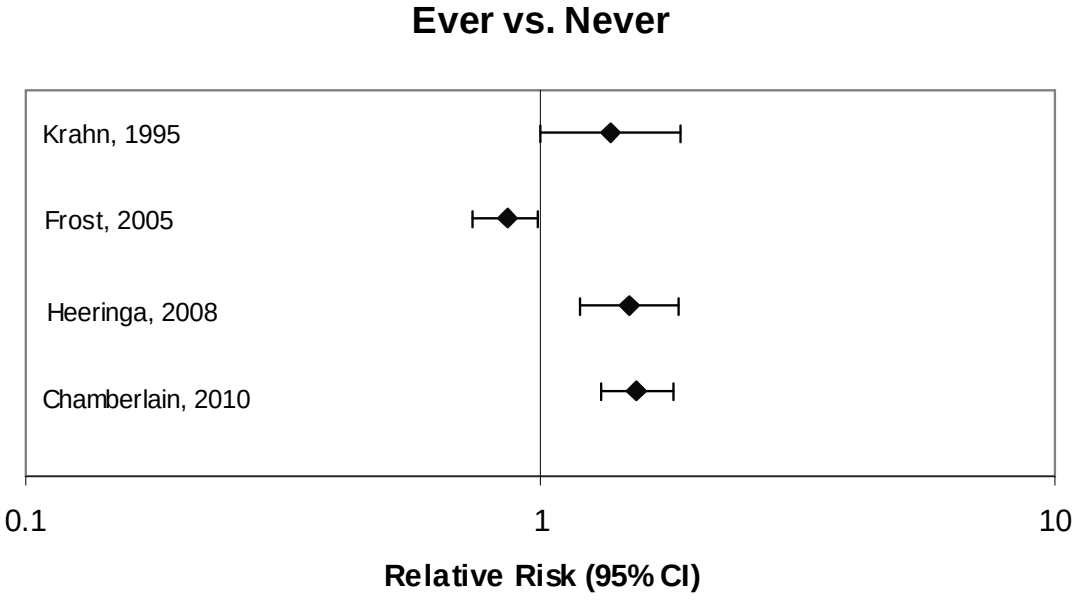
***** Total number of participants in study. N for multivariate models was lower, but was not specifically reported in the article.

† Odds ratio calculated from 2-year pooled logistic regression, where each examination with its 2-year follow-up was considered a separate person-examination.

§ Total number of AF events in the study; the multivariate proportional hazards models may have included fewer events.

Figure 11.1: Relative Risks (95%CI) of Atrial Fibrillation in Relation to Smoking Status.





12.0 MANUSCRIPT 3 – A CLINICAL RISK SCORE FOR ATRIAL FIBRILLATION

12.1 OVERVIEW

Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice, and is associated with increased stroke and cardiovascular morbidity and mortality. Individuals at high risk of developing AF might benefit from preventive treatments. A risk score for AF has been recently developed by the Framingham Heart Study; however the applicability of this risk score, derived from whites, to predict new-onset AF in non-whites is uncertain. **Methods:** We developed a 10-year risk score for incidence of new-onset AF using risk factors commonly measured in clinical practice using 14,544 individuals from the Atherosclerosis Risk in Communities (ARIC) study, a prospective community-based cohort of blacks and whites in the United States. **Results:** During 10 years of follow-up, 514 incident AF events occurred. The following variables were included in the AF risk score: age, race, body mass index, height, smoking status, systolic blood pressure, hypertension medication usage, heart murmur, left ventricular hypertrophy by electrocardiogram, diabetes, coronary heart disease, and heart failure. The area under the receiver-operating characteristics curve (AUC) of a Cox regression model including the previous variables was 0.78, suggesting moderately good discrimination. The point-based score developed from coefficients in the Cox model had an AUC of 0.76. This clinical risk score for AF in the ARIC cohort compared favorably with the Framingham Heart Study's AF (AUC=0.68), CHD (AUC=0.63), and hard CHD

(AUC=0.59) risk scores and the ARIC CHD risk score (AUC=0.58). **Conclusion:** We have developed a risk score for AF and have shown that the different physiopathologies of AF and CHD limit the usefulness of a CHD risk score at identifying individuals at higher risk of AF. A risk score developed specifically to predict AF may aid in risk stratification of patients and may be used for identification of high risk patients for enrollment in primary preventive trials of AF.

12.2 INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice.[4] AF currently affects more than 2.2 million Americans, and the lifetime risk for development of AF in men and women over 40 years of age is 1 in 4.[47] AF is an important risk factor for incident stroke[2,162,163] and heart failure,[163,167] and also carries poor prognosis in heart failure patients.[172]

Risk factors for AF include increasing age,[5,9] male gender,[5,65] obesity,[14] hypertension,[10,11] diabetes,[12,13] and cardiac structural abnormalities, such as increased left ventricular wall thickness.[15] Although some of the previously mentioned risk factors have been well studied in relation to incident AF on a population level, formulae for predicting a person's individual risk of AF are scarce. This information may aid in risk stratification and in the selection of appropriate candidates for preventive therapies.[141] A risk score for AF has been recently developed by the Framingham Heart Study.[203] The discrimination of the Framingham risk score was good (C statistic=0.78); however, since the Framingham AF risk score was developed using a white cohort, the utility of this risk

score to predict 10-year risk of developing AF in non-whites is uncertain. This is particularly relevant given the lower risk of AF among blacks.[53,204] Therefore, we aimed to develop a risk score for predicting AF incidence based on risk factors that can be easily assessed in clinical practice using a cohort of blacks and whites, the Atherosclerosis Risk in Communities (ARIC) study.

12.3 METHODS

Study Population

The ARIC study is a prospective cohort investigation aimed to identify risk factors for atherosclerosis and cardiovascular disease. ARIC recruited probability samples of adults aged 45-64 years from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis suburbs, Minnesota; and Washington County, Maryland.[174] Blacks and whites were recruited from Forsyth County, only blacks from Jackson, Mississippi, and predominantly whites from the other two communities. A total of 15,792 participants (8710 women, 4266 blacks) were enrolled from 1987 to 1989, and completed a home interview and clinic visit. Three triennial follow-up clinic visits were conducted (1990-92, 1993-95, 1996-98). In addition, participants are followed-up by annual telephone interviews and active surveillance of the ARIC community hospitals. The ARIC study was approved by institutional review boards at each participating center, and informed consent was obtained from participants at every clinic visit.

Atrial Fibrillation Ascertainment

Electrocardiograms (ECGs) during the baseline visit were used to identify individuals with prevalent AF or atrial flutter for exclusion. Incident AF diagnoses within 10 years of the baseline exam were identified from 3 sources: ECGs performed during study follow-up visits through 1998, and hospital discharge records and death certificates through 10 years of follow-up.

All ARIC examination ECGs were recorded using MAC PC Personal Cardiographs (Marquette Electronics, Inc., Milwaukee, WI). A standard supine 12-lead resting ECG was recorded at least one hour after smoking tobacco or ingestion of caffeine at each clinic visit. ECGs were then transmitted by modem to the ARIC ECG Reading Center for computer coding. ECG recordings during follow-up that were computer coded as AF were visually re-checked by a cardiologist to confirm the diagnosis.[176]

Annual follow-up telephone calls were placed to cohort participants in order to identify hospitalizations and deaths. In addition, local hospitals were surveyed for potential cardiovascular events. Hospital discharge ICD codes were recorded from all hospitalizations, and AF was identified by an ICD-9 discharge code of 427.31 or 427.32 among any of the discharge diagnoses. AF was also identified when any listed cause of death on a death certificate was coded as AF (ICD-9 code 427.3 or ICD-10 code I48). AF occurring simultaneously with heart revascularization surgery (ICD-9 code 36.X) or other cardiac surgery involving heart valves or septa (ICD-9 code 35.X) was not considered an incident event and follow-up was continued beyond that episode for incident AF not associated with cardiac surgery. Prior analysis within the ARIC cohort

to determine the validity of hospital discharge diagnoses for AF reported 84% sensitivity and 98% specificity for the ascertainment of AF.[53]

Baseline Measurements

Study participants were asked to fast for 12 hours before the clinic visit, during which a blood sample was obtained and a physical exam was performed. Blood collection and processing techniques for the ARIC study have been previously described.[177] Enzymatic methods were used to measure total cholesterol (TC) and triglycerides (TG).[178] High-density lipoprotein (HDL) cholesterol was measured enzymatically after dextran sulfate-Mg^{2+} precipitation of other lipoproteins.[179] Low-density lipoprotein (LDL) cholesterol levels were estimated with the Friedewald formula for individuals with TG levels <400 mg/dL.[205] In a scrub suit and without shoes, standing height and waist circumference (at the level of the umbilicus) were measured to the nearest centimeter. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared.

Race, smoking status, and drinking status were determined by self-report. The sports index for physical activity during leisure time ranged from 1 (low) to 5 (high), and was based on the questionnaire developed by Baecke et al.[181] Seated blood pressures were measured 3 times in the sitting position after 5 minutes of rest using a random-zero sphygmomanometer, and the last 2 blood pressure measurements were averaged. Participants were asked to bring all medications with them during clinic visits. A prescription bottle or self-report was used to determine cholesterol and blood pressure medication use.

The presence of a systolic or diastolic murmur was identified during the physical examination by a trained clinician using a stethoscope. A resting 12-lead ECG was used to define the P-R interval and presence of left ventricular hypertrophy (LVH). ECG-diagnosed left ventricular hypertrophy was considered present if the Cornell voltage was >28mm in men or >22mm in women.[206] A participant was categorized as diabetic if they had a fasting glucose $\geq$126 mg/dL (or non-fasting glucose of $\geq$200 mg/dL) or reported a physician diagnosis of diabetes or were currently taking medication for diabetes. Prevalent CHD at baseline included a history of myocardial infarction (MI), MI adjudicated from the baseline ECG, or history of coronary bypass or angioplasty. Prevalent HF was identified using the Gothenburg criteria[182] or self-report of HF medication use in the past 2 weeks.

Statistical Analysis

All analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC). For the development of this risk score, we considered the following variables at baseline: age (45 to <50 (reference), 50 to <55, 55 to <60, and 60 to 64 years), gender (male, female (reference)), race (black, white (reference)), BMI (<20, 20 to <25 (reference), 25 to <30, $\geq$30 kg/m^2), height (<164 (reference), 164 to <173, $\geq$173 cm), waist circumference (<88/<102 (reference), $\geq$88/102 cm in men/women), sports score (<2.0, 2.0 to <3.0, 3.0 to <4.0, $\geq$4.0 (reference)), smoking status (current, former, never (reference)), drinking status (current, former, never (reference)), systolic blood pressure (<100, 100 to <120 (reference), 120 to <140, 140 to <160, $\geq$160 mmHg), diastolic blood pressure (<70, 70 to <80 (reference), 80 to <90, 90 to <100, $\geq$100 mmHg), hypertension

medication usage (no (reference), yes), total cholesterol (<200 (reference), 200 to <240, ≥240 mg/dL), LDL cholesterol (<100 (reference), 100 to <130, 130 to <160, 160 to <190, ≥190 mg/dL), HDL cholesterol (<40, 40 to <60, ≥60 mg/dL (reference)), triglycerides (<150 (reference), 150 to <200, ≥200 mg/dL), cholesterol medication usage (no (reference), yes), heart murmur (no (reference), yes), heart rate (<60, 60 to <90 (reference), ≥90 beats per minute (bpm)), P-R interval (<160 (reference), 160 to <200, ≥200 ms), LVH by ECG (no (reference), yes), diabetes (no (reference), yes), CHD (no (reference), yes), and HF (no (reference), yes).

Of the 15,792 ARIC participants, we excluded those who were not of black or white race (N=48), blacks from Minneapolis and Washington County (N=55), prevalent AF (N=37) or missing AF status (N=244) at baseline, those with unreadable ECGs (N=85), and those with missing values for any variable in our final risk score (N=799). Person-years of follow-up were computed from the baseline exam date until a first AF diagnosis, death, lost to follow-up, or a follow-up of 10 years, whichever came first. Univariate associations of AF with potential risk factors were run first using Cox proportional hazards models. Significant ($p<0.05$) risk factors from the univariate models were then pooled into 1 multivariate Cox model and a backwards stepwise elimination was used to identify significant predictors in our multivariate model, using $p<0.10$ as our significance cut-off level. All possible interactions of risk factors with age and race were then tested to determine whether the association of a risk factor differed by age group or race. Interaction tests between risk factors identified in our multivariate model and log of follow-up time confirmed the proportional hazards assumption was met for our model.

Once the final Cox model was determined, we followed the method used by the Framingham Heart Study[207] to calculate points associated with each level of our risk factors and to determine the 10-year probability of developing AF by point total. We calculated a score for all participants in our dataset by calculating a point total based on our risk score. The discrimination of both our Cox regression model and the actual point-based risk score was estimated using the area under the receiver-operating characteristics curve (AUC).[208] The calibration, an estimation of the extent of bias, was assessed by calculating a chi-square statistic comparing observed and predicted number of AF events in deciles of predicted risk. We additionally calculated a point-based score for participants using the Framingham Heart Study's AF,[203] CHD,[209] and hard CHD[175] risk scores, as well as ARIC's CHD risk score,[210,211] in order to estimate how well these risk scores predict AF in comparison to our newly developed AF risk score.

Finally, 1000 bootstrap samples were generated, sampling individuals with replacement, in order to compare our Cox regression model to the point-based score and to conduct an internal validation of our risk score. To determine if the Cox regression model provided better discrimination than the point-based score, we calculated the difference between the 1000 pairs of AUC's obtained from the bootstrap samples and ranked these differences to get a confidence interval for the difference between the two methods. Bootstrapping methods provide more stable estimates with lower bias compared to other methods of internal validation.[212] However, since we used the same cohort to generate the 1000 bootstrap samples for validation of our risk score as we used to develop the risk score, we adjusted our AUC obtained for the internal validation for optimism.[213]

12.4 RESULTS

After exclusions, 14,544 individuals remained at risk of AF. During 10 years of follow-up, 514 incident AF events occurred. The baseline characteristics of the study sample, along with age-, race-, and sex-adjusted hazard ratios for AF by potential risk factor category, are presented in Table 12.1. The risk of developing AF increased monotonically with increasing age, systolic and diastolic blood pressure, and was greater among males and whites. An increased risk of AF was also seen among smokers, those with obesity, a heart murmur, LVH, diabetes, CHD, and HF, and in those in the tallest tertile of height, the highest heart rate category, and the longest P-R interval category. Plasma lipids, except for very low HDL and very high TG, sports exercise, and drinking status did not appear to be associated with AF risk.

The final risk score model included the following variables: age, race, BMI, height, systolic blood pressure, hypertension medication use, smoking status, heart murmur, LVH by ECG, diabetes, CHD, and HF. In addition, we found an interaction with race and LVH, along with interactions of diabetes and CHD with age. Table 12.2 lists all risk factors in our risk score, along with points derived for each category. The oldest age group (60-64) had the highest points assigned of any risk factor category. Blacks were given a point value of -5, indicating a lower risk of developing AF compared to whites. In addition, the association of LVH with AF incidence differed by race; the presence of ECG-diagnosed LVH increased the probability of developing AF in whites, but not blacks. Also, diabetes and CHD were associated with AF in younger individuals, but not among the oldest individuals in our cohort. Based on our risk score, a person's total score for predicting AF may range from -9 to 48. The 10-year predicted probability

of developing AF by total risk score is presented in Table 12.3. Individuals scoring 5 points or less had a 10-year predicted probability of developing AF of less than 5%, whereas those scoring 15 points or more had greater than 25% predicted probability of developing AF in 10 years. As the majority of participants in our study scored less than 17 points (89%), 10-year predicted risks of AF for individual scores above 17 were not reported.

The final Cox regression model had an AUC of 0.78, indicating good discrimination. The predicted number of AF events in the 10-year risk deciles were similar to the observed events (χ^2=6.84, p>0.10). The point-based score developed from the Cox regression model had an AUC of 0.76, which was statistically significantly lower than the Cox regression model. However, the calibration of the point-based score was not good (χ^2=42.93, p<0.001). Figure 12.1 depicts the observed and expected AF events by decile of predicted risk for both the Cox regression model and the point-based score. The 7th and 9th deciles of predicted risk appeared to contribute most to the poor calibration for the point-based score, followed by the 6th and 10th deciles; in the remaining deciles, the expected number of AF events were similar to the observed number of events. The internal validation of our risk score, based on 1000 bootstrap samples adjusted for optimism, revealed an AUC of 0.77 (95% CI, 0.75-0.79) for the Cox regression model and an AUC of 0.76 (95% CI, 0.74-0.78) for the point-based score, indicating that our score would perform well in individuals from populations similar to the ARIC cohort.

In addition to developing a risk score for AF in the ARIC cohort, we also calculated scores for all participants based on the Framingham Heart Study's AF,[203]

CHD,[209] and hard CHD[175] risk scores, as well as ARIC's CHD risk score,[210,211] to determine whether these previously published risk scores predict 10-year risk of AF as well as our AF risk score (Table 12.4). The Framingham AF risk score predicted AF in the ARIC cohort, with an AUC of 0.68. The Framingham AF risk score had better discrimination for AF in whites (AUC=0.69) compared to blacks (AUC=0.65). Finally, the 10-year probability of developing AF was not predicted well by the Framingham CHD (AUC=0.63) or hard CHD (AUC=0.59) risk scores, or the ARIC CHD (AUC=0.58) risk score.

12.5 DISCUSSION

We developed a 10-year risk score for incidence of AF using risk factors commonly measured in clinical practice in a prospective community-based cohort of blacks and whites. The risk score had good discrimination, with AUC's of 0.78 for the Cox regression model and 0.76 for the point-based score calculated based on the Cox regression model. As expected, in comparison to the Framingham AF risk score,[203] our risk score better predicted who would develop AF in the ARIC cohort. In addition, the prediction of AF using the Framingham[175,209] and ARIC[210,211] CHD risk scores was not good, suggesting an AF-specific score is necessary to predict individual risk of AF.

We developed our AF risk score in a cohort that included both blacks and whites. AF has been reported to be less common among blacks compared to whites, with prevalence of AF in blacks almost half that of whites.[5,51,84-87] We found a similar difference in AF risk by race. Yet, most other risk factors predicted AF similarly by race.

Unlike the Framingham AF score, we did not find P-R interval to predict AF risk. In addition to the other variables in the Framingham AF score, we found height, smoking status, ECG-diagnosed LVH, diabetes, and CHD to predict incidence of AF. ECG-diagnosed LVH increased the risk of AF in whites, but did not appear to contribute to 10-year incidence of AF in blacks. A clear explanation for this racial difference is not evident; however, it is possible that the diagnosis of LVH by ECG results in more false positives in blacks.[214] It also appeared that diabetes and CHD contributed more to AF risk in younger individuals. This may reflect more serious disease among individuals diagnosed at younger ages or fewer competing risk factors, resulting in a greater proportion of AF risk attributed to diabetes or CHD among young individuals.

The Framingham 10-year risk score for CHD is widely used clinically and has been shown to predict CHD well in other cohorts within the US, Australia, and New Zealand.[215] However, we have shown that CHD risk scores are not effective at predicting AF risk. CHD and AF share some common risk factors, such as hypertension, diabetes, and obesity, but others, such as lipids, seem important in the development of CHD only. This highlights the importance of a separate risk score to predict AF and, potentially, the need to develop different preventive interventions.

A recent workshop on prevention of atrial fibrillation recommended the development and validation of incident AF risk prediction models across cohorts to enhance the understanding of the epidemiology of AF and to advance AF prevention research.[216] A risk score for AF, such as our risk score developed using the ARIC cohort, may prove useful for identification of high risk patients to include in primary preventive trials of AF. In turn, the results of these preventive trials may provide insight into what

interventions are most effective in preventing AF and may help influence treatment guidelines for the primary prevention of AF.

We developed a risk score for AF using clinical risk factors that are easily and readily available. We acknowledge that the addition of genetic variants or biomarkers may have improved the ability of our risk score to correctly classify those at greatest risk of developing AF; however, we did not include these variables because they are less likely to be consistently measured in primary care. Other possible candidates for inclusion in an AF prediction model include single nucleotide polymorphisms (SNPs) on chromosome 4q25, which carry an approximately 1.4 to 1.7-fold increased risk of AF per variant copy,[17,50] or inflammatory[51,52] or neurohormonal[53] biomarkers. Compared to the lowest quartile, the highest quartile of C-reactive protein (CRP)[108] and fibrinogen[217] increase the risk of incident AF approximately 30%, and 2-fold, respectively. In addition, B-type natriuretic peptide (BNP) and plasma N-terminal pro-atrial natriuretic peptide (N-ANP) levels predict AF risk, with values above the 80th percentile corresponding to twice the risk of incident AF compared to values below the 80th percentile.[218] The addition of several biomarkers to the traditional risk factors has been shown to increase the predictability of CHD risk scores;[210,211,219] however, the addition of any one biomarker to these risk scores had less impact. Although it is likely that genetic factors and biomarkers may increase the predictability of our risk score for AF, the addition of these variables may not increase the predictability enough to be considered a useful and cost-effective addition to this AF risk score.

Our study has several strengths, specifically the large, population-based cohort of blacks and whites; however, we also acknowledge several limitations. First, it is possible

that some incident AF events were missed because the majority of AF events were ascertained by hospital discharge records. However, since incidence rates of AF in ARIC are similar to those from other cohorts[53] and associations of genetic risk factors and AF in ARIC are similar to those found in cohorts relying more on study exam ECGs for identification of AF events,[141] we believe the underascertainment of AF events in ARIC was likely minimal. Second, our risk score was developed in a bi-racial cohort, and although our risk score may be useful for black and white patients, it may not be useful for individuals of other racial or ethnic backgrounds. For example, AF appears to be less prevalent in Asians[68-70] compared to whites. The development of an AF risk score in a multi-racial cohort would have been preferable because it would have further improved the generalizability of our risk prediction score. Also, the majority of studies on AF have been in primarily white cohorts from the U.S. and Europe. Thus, the development of a risk score in a multi-racial cohort would also provide some insight into racial differences in AF. For example, AF appears to be less prevalent in Asians,[68-70] Hispanics,[84] and blacks[5,51,84-87] compared to whites, but information on racial differences in AF is limited. Third, the limited age range of our population at baseline, 45-64 years, limits the generalizability of our risk score to older individuals. Fourth, only 1 measure of AF risk factors was used to develop our risk score. Therefore, misclassification of exposure as risk factors change over follow-up may result in poorer prediction of AF, and a risk score that accounts for changes in risk factors over time may better predict AF risk. Finally, the external validation of our risk score using other cohorts may have provided better information on the generalizability of our risk score and whether it predicts well in other populations.

AF is an important public health problem, and an estimated 10 million Americans will have AF by the year 2050.[48] Prevention of AF is important, particularly because it carries an increased risk of stroke,[2,3] HF,[3] and death.[3,4] The different physiopathologies of AF and CHD limit the usefulness of a CHD risk score at identifying individuals at higher risk of AF. Therefore, a risk score developed specifically to predict AF may be useful in the risk stratification of patients and in the identification of high risk patients for enrollment in primary prevention trials of AF.

12.6 TABLES AND FIGURES

Table 12.1: Baseline Prevalences of Potential Atrial Fibrillation Risk Factors and Hazard Ratios for Atrial Fibrillation, ARIC 10-Year Follow-Up.

Risk Factor	N(%)	AF cases (N)	Hazard Ratio (95% CI)*
Age, years			
45 to <50	3897 (26.8)	46	1.00 (ref)
50 to <55	3770 (25.9)	95	2.09 (1.47-2.97)
55 to <60	3556 (24.5)	129	2.91 (2.08-4.07)
60 to 64	3321 (22.8)	244	5.92 (4.32-8.11)
Race			
Black	3861 (26.5)	82	0.59 (0.47-0.75)
White	10638 (73.5)	432	1.00 (ref)
Gender			
Male	6505 (44.7)	324	1.91 (1.60-2.29)
Female	8039 (55.3)	190	1.00 (ref)
BMI, kg/m^2			
<20	469 (3.2)	14	1.22 (0.70-2.13)
20 to <25	4318 (29.7)	121	1.00 (ref)
25 to <30	5731 (39.4)	200	1.12 (0.89-1.40)
≥30	4026 (27.7)	179	1.78 (1.41-2.25)
Height, cm			
<164	4891 (33.6)	114	1.00 (ref)
164 to <173	4673 (32.1)	142	1.28 (0.97-1.69)
≥173	4980 (34.3)	258	1.92 (1.38-2.66)
Waist, cm			
<88/102 (women/men)	6795 (46.7)	209	1.00 (ref)
≥88/102 (women/men)	7746 (53.3)	304	1.54 (1.29-1.85)
Systolic blood pressure, mmHg			
<100	1317 (9.1)	23	0.82 (0.53-1.27)
100 to <120	6180 (42.5)	153	1.00 (ref)
120 to <140	4849 (33.3)	196	1.42 (1.15-1.76)
140 to <160	1647 (11.3)	103	2.16 (1.68-2.80)
≥160	551 (3.8)	39	2.64 (1.84-3.80)

Diastolic blood pressure, mmHg			
<70	5327 (36.6)	173	0.93 (0.75-1.15)
70 to <80	5227 (35.9)	178	1.00 (ref)
80 to <90	2888 (19.9)	113	1.23 (0.97-1.56)
90 to <100	790 (5.4)	34	1.54 (1.06-2.23)
≥100	311 (2.2)	16	2.04 (1.21-3.44)
Hypertension medication use			
No	10100 (69.4)	239	1.00 (ref)
Yes	4444 (30.6)	275	2.54 (2.13-3.03)
Total cholesterol, mg/dL			
<200	5409 (37.5)	181	1.00 (ref)
200 to <240	5430 (37.7)	205	1.02 (0.84-1.25)
≥ 240	3576 (24.8)	127	0.95 (0.76-1.20)
LDL cholesterol, mg/dL			
<100	2257 (15.9)	63	1.00 (ref)
100 to <130	4045 (28.5)	137	1.05 (0.78-1.41)
130 to <160	4236 (29.8)	160	1.06 (0.79-1.42)
160 to <190	2377 (16.7)	94	1.04 (0.76-1.44)
≥190	1291 (9.1)	40	0.89 (0.60-1.33)
HDL cholesterol, mg/dL			
<40	3862 (26.8)	215	1.78 (1.36-2.34)
40 to <60	6727 (46.7)	212	1.17 (0.90-1.51)
≥60	3828 (26.5)	86	1.00 (ref)
Triglycerides, mg/dL			
<150	14051 (97.4)	488	1.00 (ref)
150 to <200	228 (1.6)	12	1.27 (0.72-2.26)
≥200	139 (1.0)	13	2.62 (1.51-4.54)
Cholesterol medication use			
No	14044 (97.1)	488	1.00 (ref)
Yes	422 (2.9)	22	1.20 (0.78-1.84)
Sports Exercise			
<2.0	4102 (28.3)	143	1.22 (0.80-1.86)
2.0 to <3.0	6295 (43.4)	222	1.11 (0.73-1.66)
3.0 to <4.0	3407 (23.5)	122	0.96 (0.63-1.46)
≥4.0	695 (4.8)	26	1.00 (ref)
Smoking status			
Never	6058 (41.6)	150	1.00 (ref)
Former	4691 (32.3)	202	1.28 (1.02-1.60)
Current	3795 (26.1)	162	1.68 (1.35-2.11)

Drinking status			
Never	3617 (25.0)	101	1.00 (ref)
Former	2740 (18.9)	126	1.25 (0.95-1.63)
Current	8134 (56.1)	284	0.97 (0.76-1.23)
Heart rate, bpm			
<60	3603 (24.8)	136	1.00 (0.82-1.23)
60 to <90	10584 (72.7)	354	1.00 (ref)
≥90	357 (2.5)	24	2.03 (1.34-3.07)
P-R Interval, ms			
<160	6299 (43.3)	200	1.00 (ref)
160 to <200	6894 (47.4)	246	1.03 (0.86-1.25)
≥200	1350 (9.3)	68	1.41 (1.07-1.87)
Left ventricular hypertrophy			
No	14219 (97.7)	487	1.00 (ref)
Yes	325 (2.3)	27	2.75 (1.85-4.09)
Murmur			
No	13461 (92.5)	445	1.00 (ref)
Yes	1083 (7.5)	69	1.92 (1.49-2.48)
Diabetes			
No	12807 (88.1)	405	1.00 (ref)
Yes	1737 (11.9)	109	1.86 (1.50-2.31)
Coronary heart disease			
No	13856 (95.3)	440	1.00 (ref)
Yes	688 (4.7)	74	2.21 (1.72-2.85)
Heart failure			
No	13875 (95.4)	450	1.00 (ref)
Yes	669 (4.6)	64	3.05 (2.34-3.97)

* Hazard ratios are adjusted for sex, race, and continuous age.

Table 12.2: Points Assigned to Atrial Fibrillation Risk Factor Categories, ARIC.

Risk Factor	Points	Risk Factor	Points
Age, years		Smoking status	
45 to <50	0	Never	0
50 to <55	3	Former	1
55 to <60	5	Current	3
60 to 64	9	Heart murmur	
Race		No	0
Black	-5	Yes	2
White	0	Left ventricular hypertrophy	
BMI, kg/m^2		No	0
<20	-1	Yes, white race	6
20 to <25	0	Yes, black race	0
25 to <30	1	Diabetes	
≥30	3	No	0
Height, cm		Yes, age 45 to <50	4
<164	0	Yes, age 50 to <55	5
164 to <173	2	Yes, age 55 to <60	1
≥173	5	Yes, age 60 to 64	-2
Systolic blood pressure, mmHg		Heart failure	
<100	-1	No	0
100 to <120	0	Yes	2
120 to <140	1	Coronary heart disease	
140 to <160	3	No	0
≥160	4	Yes, age 45 to <50	6
Hypertension medication use		Yes, age 50 to <55	3
No	0	Yes, age 55 to <60	4
Yes	3	Yes, age 60 to 64	0

Table 12.3: Predicted 10-Year Risk of Atrial Fibrillation by Risk Score, ARIC.

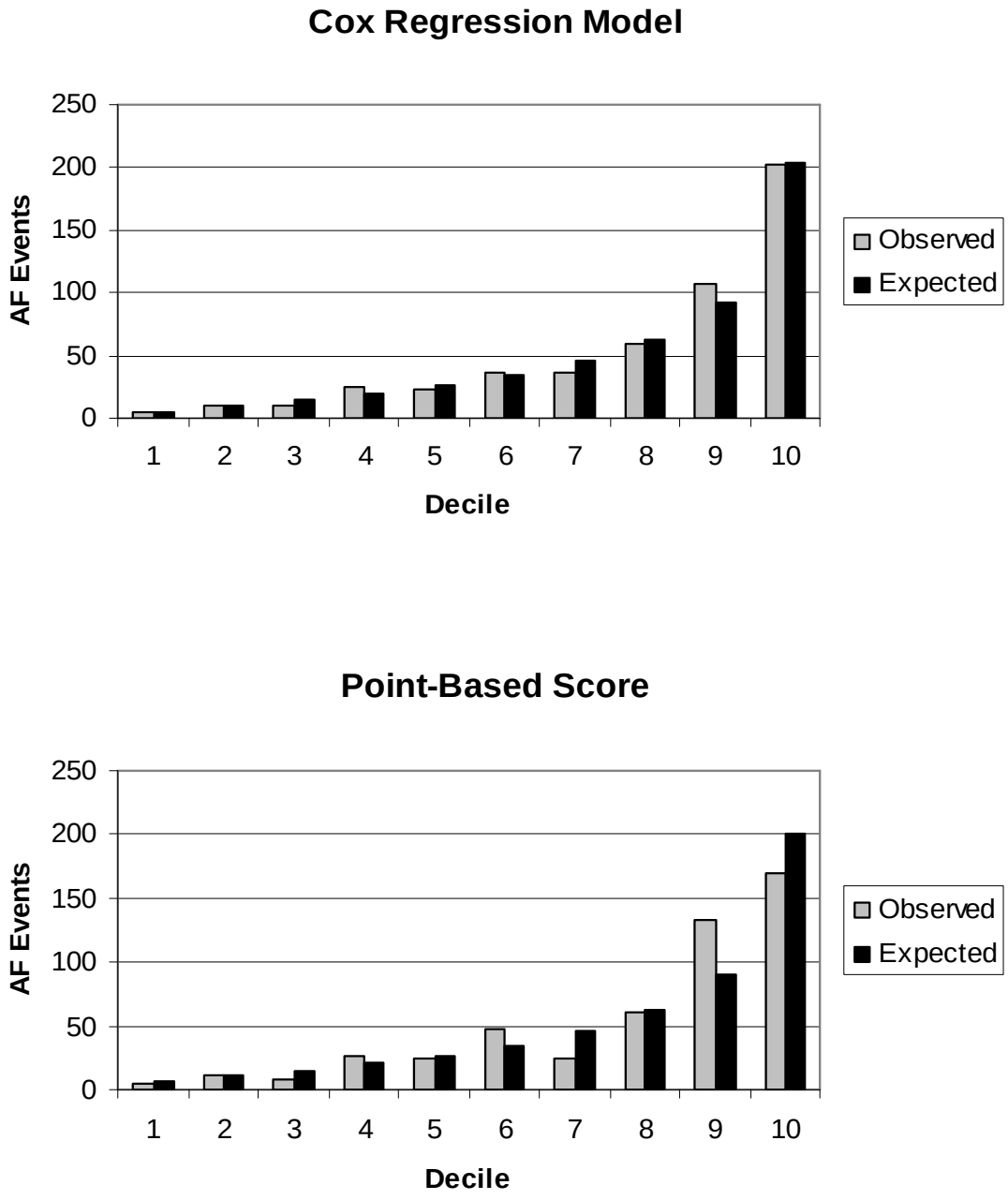
Score	Predicted Risk
-9 to -7	0%
-6 to -1	1%
0 to 1	2%
2 to 3	3%
4 to 5	4%
6	5%
7	6%
8	8%
9	9%
10	11%
11	13%
12	16%
13	18%
14	22%
15	26%
16	30%
≥17	>35%

Table 12.4: Comparison of Prediction of Atrial Fibrillation in the ARIC Cohort using Various Risk Scores from the ARIC study and the Framingham Heart Study.

Score	AUC	Risk Factors in Score
ARIC AF		age, race, BMI, height, systolic blood pressure, hypertension medication,
Cox model	0.78	smoking status, heart murmur, ECG-based left ventricular hypertrophy, diabetes,
Point-based score	0.76	heart failure, coronary heart disease
Framingham AF[203]		age, gender, BMI, systolic blood pressure, hypertension medication,
Overall	0.68	P-R interval, cardiac murmur, heart failure
Whites	0.69	
Blacks	0.65	
Framingham CHD[209]		age, gender, total or LDL cholesterol,* HDL cholesterol, systolic and diastolic
Overall	0.63	blood pressure, diabetes, current smoking
Whites	0.63	
Blacks	0.66	
Framingham Hard CHD[175]		age, gender, total cholesterol, HDL cholesterol, systolic blood pressure,
Overall	0.59	hypertension medication, current smoking
Whites	0.60	
Blacks	0.59	
ARIC CHD[210,211]	0.58	age, race, gender, total cholesterol, HDL cholesterol, systolic blood pressure, hypertension medication, current smoking

* The Framingham CHD score uses either total cholesterol or LDL cholesterol. In this table, we report AUC's using total cholesterol in our replication of the Framingham CHD score; AUC's were 0.62 overall, 0.62 in whites, and 0.66 in blacks when using LDL cholesterol.

Figure 12.1: Observed and Expected Atrial Fibrillation Events by Decile of Predicted Risk, ARIC.



13.0 SUMMARY

The objectives of this dissertation were to characterize associations of AF with smoking and the MetSyn, and also to develop a 10-year risk score for AF using factors commonly measured in clinical practice.

The first manuscript aimed to determine if an increased risk of AF was associated with the MetSyn and which components contributed most to AF risk. In addition, a racial difference in the association between the MetSyn and AF was tested because some studies have suggested that AF is less common in blacks than whites,[5,9,53] but blacks have a higher prevalence of the MetSyn and most of its components than do whites.[88] At baseline, 45.7% of blacks and 39.6% of whites had the MetSyn. Age- and sex-adjusted incidence rates for AF among those with the MetSyn were lower in blacks than whites (52 and 62 per 10,000 person-years, respectively); similarly, the incidence rates were lower in blacks compared to whites among those without the MetSyn. However, the multivariate-adjusted hazard ratios for AF did not differ by race. The MetSyn was associated with a 1.67-fold increased risk of incident AF compared to those without the MetSyn. All individual MetSyn components, except for elevated triglycerides, conferred an increased risk of AF, with elevated blood pressure corresponding to a 2-fold greater risk of AF, the greatest of all individual components. In addition, a greater number of MetSyn components corresponded to higher cumulative probabilities of AF over up to 19 years of follow-up. Among those with all 5 MetSyn components at baseline, a cumulative risk of AF of 20.4% was observed.

The second manuscript aimed to determine the association of smoking with incidence of AF in the ARIC study, and to conduct a systematic review of the literature in

attempt to further understand the relation between smoking and AF. An association between smoking and CHD has been clearly established;[185] however, few studies have characterized associations of smoking with AF. In ARIC, we observed age- and sex-adjusted incidence rates for AF of 28, 36, and 48 per 10,000 person-years in never, former, and current smokers, respectively. Ever smoking increased the risk of AF by approximately 50%, whereas current smoking corresponded to a doubling of AF risk compared to never smoking. The risk of incident AF increased with increasing cigarette-years of smoking, and among individuals with similar cigarette-years of smoking, the risk of AF appeared to be somewhat greater among current than former smokers. Associations did not differ by race.

We identified 5 prospective studies reporting associations of smoking and AF in our systematic review. Of these studies, 2 reported significantly increased risks of AF, 2 reported no associations, and the other reported a significantly increased risk of AF in women but not men, in relation to smoking. Although a clear association between smoking and AF is not evident from our systematic review, limitations in study design could have masked positive associations of smoking and AF among the 2 null studies. Therefore, smoking may be an important risk factor for AF, but additional prospective studies are needed to further examine the association of smoking with incidence of AF.

A 10-year clinical risk score for AF was developed for the third manuscript. The following variables were included in the risk score: age, race, BMI, height, systolic blood pressure, hypertension medication use, smoking status, heart murmur, LVH by ECG, diabetes, CHD, and HF. In addition, interactions with race and LVH, and of diabetes and CHD with age were identified in the risk score. ECG-diagnosed LVH

contributed to increased risk of AF in whites but not blacks, and diabetes and CHD contributed more to AF risk in younger individuals. The discrimination of the risk score was good, with AUC's of 0.78 for the Cox regression model and 0.76 for the point-based score derived from the Cox regression parameter estimates. Scores for ARIC participants using the Framingham Heart Study's AF,[203] CHD,[209] and hard CHD[175] risk scores, as well as ARIC's CHD risk score,[210,211] were also calculated in order to estimate how well these risk scores predict AF. Application of the CHD risk scores in the ARIC cohort did not predict well the 10-year risk of AF, suggesting an AF-specific score is required to predict individual risk of AF.

These three manuscripts have contributed to the literature on AF and have highlighted areas where further research is needed to fully understand the relationships between potential risk factors and AF. A recent AF workshop identified knowledge gaps in the prevalence, incidence, lifetime risk, risk factors, and prognosis of AF in most ethnic/racial minority groups, and also in the ability to predict AF onset in individuals.[216] In ARIC, blacks have a lower incidence of AF than whites; however, the lower incidence of AF in blacks compared to whites was not explained by different effects of smoking or of any of the individual components of the MetSyn on AF between race groups. Therefore, additional studies are needed to investigate reasons for the racial differences in AF incidence. In addition, it appears that smoking may be an important risk factor for AF, although few studies have investigated this association, and results of those studies were conflicting. This again highlights the importance of additional studies to further enhance our understanding of the relationship between smoking and AF. Finally, a risk score for AF, such as the one developed in manuscript 3, may be useful in the

identification of high risk patients to enroll in primary prevention trials of AF, an area of research that has received much less attention than treatment for AF. [216]

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APPENDIX: DICTIONARY OF ABBREVIATIONS

AF	atrial fibrillation
AFL	atrial flutter
AHA	American Heart Association
ANOVA	analysis of variance
ARIC	Atherosclerosis Risk in Communities
AUC	area under the receiver-operating characteristics curve
AV	atrioventricular
BMI	body mass index
BNP	B-type natriuretic peptide
CABG	coronary artery bypass graft
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
ECG	electrocardiogram
FEV_1	forced expiratory volume in 1 second
GWAS	genome-wide association study
HDL	high-density lipoprotein
HF	heart failure
HR	hazard ratio

ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
I_{to}	transient outward potassium current
LDL	low-density lipoprotein
LVH	left ventricular hypertrophy
MetSyn	metabolic syndrome
MI	myocardial infarction
N-ANP	N-terminal pro-atrial natriuretic peptide
NCEP-ATP III	National Cholesterol Education Program Third Adult Treatment Panel
NHDS	National Hospital Discharge Survey
NHLBI	National Heart, Lung, and Blood Institute
OR	odds ratio
OSA	obstructive sleep apnea
SNPs	single nucleotide polymorphisms
TC	total cholesterol
TG	triglycerides
TSH	thyroid-stimulating hormone