

ATRIAL FIBRILLATION: SURVEILLANCE, CONCORDANCE AND  
HEALTHCARE UTILIZATION

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## **DEDICATION**

This dissertation is dedicated to my parents, Gerald and Claire Smith. From an early age you instilled in me the value of education, demonstrated the power of persistence and encouraged me to find my calling.

## ABSTRACT

Background information on the epidemiology of atrial fibrillation (AF), including descriptive data and risk factors, pathophysiology, clinical aspects and outcomes, as well as three original manuscripts that together form the basis of this doctoral dissertation, are presented. The objectives of this dissertation were to assess temporal trends in the occurrence and prognosis of AF among acute myocardial infarction (MI) patients, to determine the usefulness of administrative data to identify incident AF, and to describe the impact of AF on healthcare utilization.

AF in the setting of MI occurs frequently and is associated with increased mortality. Nonetheless, temporal trends in the occurrence of AF complicating MI and in the prognosis of these patients are not well described. In a population-based sample of 20,049 validated first incident nonfatal hospitalized MIs from the Atherosclerosis Risk in Communities (ARIC) Study, prevalence of AF in MI increased from 11% to 15% (adjusted odds ratio [OR] for prevalent AF: 1.11; 95% confidence interval [CI]: 1.04 – 1.19 per five-year increment) from 1987 through 2009. In patients with MI, AF was associated with increased 1-year mortality (adjusted OR 1.47, 95% CI 1.07-2.01) compared to those without AF. However, there was no evidence that the impact of AF on MI survival changed over time or differed over time by sex, race or MI classification. In the setting of MI, co-occurrence of AF should be considered a critical clinical event and treatment needs unique to this population should be explored further.

Increasingly, epidemiologic studies use administrative data to identify AF. Capture of *incident* AF is not well documented. ARIC cohort participants without prevalent AF enrolled in fee-for-service Medicare, Parts A and B, for at least 12 continuous months between 1991 and 2009 were included. Of 10,134 eligible participants, 738 developed AF according to both ARIC and Centers for Medicare and Medicaid Services (CMS); an additional 93 and 288 incident cases were identified using only ARIC and CMS data, respectively. Incidence rates per 1,000 person-years were 10.8 (95% CI: 10.1–11.6) and 13.6 (95% CI: 12.8–14.4) in ARIC and CMS, respectively; agreement was 96%; the kappa statistic was 0.77 (95% CI: 0.75–0.80). Additional CMS events did not alter observed associations between risk factors and AF. Drawbacks of CMS are its inapplicability to those <65 years and inability to capture AF for those with Medicare Advantage.

AF is associated with increased risk of hospitalizations. However, little is known about the impact of AF on non-inpatient healthcare utilization or about sex or race differences in AF-related utilization. ARIC cohort participants with incident AF (n=944) enrolled in fee-for-service Medicare, Parts A and B, for at least 12 continuous months between 1991 and 2009 were matched on age, sex, race and center to up to three participants without AF (n=2,761). The average annual days hospitalized were 13.1 (95% CI: 11.5-15.0) and 2.8 (95% CI: 2.5-3.1) for those with and without AF, respectively; the annual numbers of outpatient claims were 53.2 (95% CI: 50.4-56.1) and 23.0 (95% CI: 22.2-23.8) for those with and without AF, respectively. Most utilization in AF patients was attributable to non-AF conditions, particularly other- cardiovascular disease-related

reasons. There was suggestive evidence that sex modified the association between AF and inpatient utilization, with AF related to greater utilization in women than men. The association between AF and healthcare utilization was similar in whites and blacks. In addition to rate or rhythm treatment, management of AF also should focus on the accompanying cardiovascular comorbidities.

Overall, the results from this dissertation indicate that co-occurrence of AF in MI is a critical clinical event, that administrative data can be useful in AF epidemiologic research, and AF patients have substantial healthcare utilization, especially for other-cardiovascular disease-related reasons.

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## 2.0 INTRODUCTION

Atrial fibrillation (AF) was first reported to affect humans in 1906 when two publications reported that “auricular fibrillation” was common in heart disease patients and that it could be identified by a new instrument, the electrocardiograph.<sup>1</sup> Subsequent to its discovery, AF has become the most common sustained cardiac arrhythmia; the estimated prevalence in the United States (US) in 2010 was between 2.7 and 6.1 million and it is expected to increase to between 5.6 and 12 million by 2050.<sup>2,3</sup> Overall, prevalence is 1% in the general adult population but increases dramatically with age from less than 1% among those less than 60 years of age to 9% among octogenarians.<sup>2,4</sup> A number of important risk factors for developing AF have been identified and include advancing age,<sup>2,5,6</sup> male sex,<sup>3,5</sup> white race,<sup>7</sup> hypertension,<sup>5,8</sup> diabetes,<sup>9,10</sup> obesity,<sup>11</sup> metabolic syndrome,<sup>12</sup> hyperthyroidism,<sup>13</sup> acute myocardial infarction (MI),<sup>5,14</sup> heart failure (HF),<sup>5,15</sup> valvular heart disease,<sup>5</sup> sleep apnea<sup>16,17</sup> and structural cardiac abnormalities.<sup>5</sup> AF is a major cause of morbidity, especially stroke,<sup>18,19</sup> HF,<sup>20,21</sup> acute MI<sup>22,23</sup> and dementia<sup>24,25</sup> as well as mortality.<sup>15,26,27</sup> The primary treatment objectives are correction of rhythm disturbance, prevention of thromboembolism and heart rate control.<sup>28</sup> However, the preferred treatment strategy has yet to be determined.<sup>29</sup> Healthcare costs associated with AF are substantial. The total incremental cost of AF in the first year after diagnosis in the US in 2008 dollars was \$26 billion, of which \$6 billion was attributed to AF.<sup>30</sup> AF is a major public health concern as it is associated with significant morbidity and mortality as well as with substantial healthcare costs. The

burden of AF is expected to increase, as AF is increasing in prevalence, due in part to the aging population and increasing prevalence of chronic heart disease.

### **3.0 DESCRIPTIVE EPIDEMIOLOGY**

#### **3.1 INCIDENCE AND PREVALENCE**

AF is the most common sustained cardiac arrhythmia. Both the incidence and prevalence of AF have been increasing steadily. In 2010 AF affected between 2.7 and 6.1 million Americans; the prevalence is estimated to increase to between 5.6 and 12.1 million by 2050.<sup>2,3,31</sup> The lifetime risk of developing AF among whites is one in four.<sup>32</sup> Among blacks the lifetime risk is lower; at age 80, one in nine will develop AF.<sup>7</sup>

Several population-based cohort studies have estimated the incidence of AF. In Olmsted County, Minnesota, a predominately white population, the age- and sex-adjusted incidence of AF per 1,000 person-years increased from 3.04 (95% confidence interval [CI]: 2.78 – 3.31) in 1980 to 3.68 (95% CI: 3.42 – 3.95) in 2000 or a significant relative increase of 12.6% (95% CI: 2.1 – 23.1),  $p = 0.014$ .<sup>3</sup> Age is a particularly strong risk factor for AF and the Cardiovascular Health Study (CHS), a population-based study among adults aged  $\geq 65$  years, calculated an AF incidence rate of 19.2 per 1,000 person-years.<sup>8</sup> Onset of AF was strongly associated with age, male sex and cardiovascular disease (CVD); the incidence rate per 1,000 person-years among men aged 65 – 74 and 75 – 84 was 17.6 and 42.7, respectively, and the corresponding rates for women were 10.1 and 21.6, respectively.<sup>8</sup> The Atherosclerosis Risk in Communities (ARIC) study found that, compared to whites, blacks had a 41% (95% CI: 8% - 62%) lower age- and sex-adjusted risk of being diagnosed with AF.<sup>7</sup>

In addition to utilizing cohort studies to determine AF incidence, administrative data from Medicare have been used. In the Medicare population, those 65 years and older, the age- and sex-adjusted incidence rate of AF per 1,000 person-years was virtually unchanged from 1993 to 2007 at 27.3 and 28.3, respectively.<sup>27</sup> Similarly to population-based studies, incidence increased substantially with age and men and whites had consistently higher rates.<sup>27</sup>

There is an increasing prevalence of AF; advancing age, male sex and white race are associated with prevalent AF.<sup>2</sup> The prevalence of AF increases dramatically with age from 0.1% among adults < 55 years of age to 9.0% among those 80 years and older.<sup>2</sup> In the CHS 4.8% of women and 6.2% of men had AF at baseline.<sup>14</sup> The prevalence varied based on presence of CVD; the prevalence among those with clinical, subclinical and no evidence of CVD was 9.1%, 4.6% and 1.6%, respectively.<sup>14</sup> In the Framingham Heart Study (FHS) the age-adjusted prevalence from 1968-1970 to 1987-1989 increased from 3.2% to 9.1% among men and from 2.8% to 4.7% among women.<sup>33</sup>

Administrative data from Medicare indicate that the prevalence of AF has increased during the last several decades.<sup>27,34</sup> From 2003-2007 there was a 5% mean annual increase in prevalence; as of 2007, 85.8 per 1,000 Medicare beneficiaries had AF.<sup>27</sup> The magnitude of the increase was greatest among the oldest beneficiaries, those age 90 and older.<sup>27</sup> Based on data from the National Hospital Discharge Survey, hospitalizations for AF as the principle diagnosis increased 144.3% from 1985 to 1999; during this same time span, hospitalizations with any mention of AF increased 189.9%.<sup>35</sup>

From 1996-2001 there was a 34% increase in hospitalizations with AF as the primary diagnosis.<sup>36</sup>

Globally AF incidence and prevalence are increasing. Among Canadians, Europeans and Australians the incidence and prevalence are similar to the US.<sup>15,37-40</sup> The majority of published epidemiological studies have been conducted in predominately white populations in North America and Europe. However, there is a growing body of literature in nonwhite populations.<sup>41</sup> In Asian countries the incidence of AF is fairly similar; in Taiwan the incidence rate per 1,000 person-years in men and women was 0.76 and 1.68, respectively; in Japan the incidence rate was 2.2 per 1,000 person-years.<sup>41</sup> The prevalence of AF has been found to vary markedly between countries; in India the prevalence is very low at 0.1%, while in Japan the prevalence consistently ranges from 0.6% - 1.6%. Prevalence estimates in Japan are similar to those in Taiwan and Thailand.<sup>41</sup> Among Chinese living in Singapore, the prevalence of AF among those 80 and older is about half that observed in Western populations at 5.8%.<sup>42</sup> Few studies in South America have examined the incidence and/or prevalence of AF. A population-based study in Sao Paulo, Brazil, found 2.4% of the population 65 years and older had AF.<sup>43</sup> There is a shortage of studies in Africa and they are almost exclusively hospital-based, where prevalence is expected to be higher. In one recent study, 4.6% of cardiac patients that presented at the hospital had AF.<sup>44</sup> As in the US, risk factors for AF include increasing age, male sex and hypertension.<sup>15,38,39,41</sup>

### **3.2 MORTALITY**

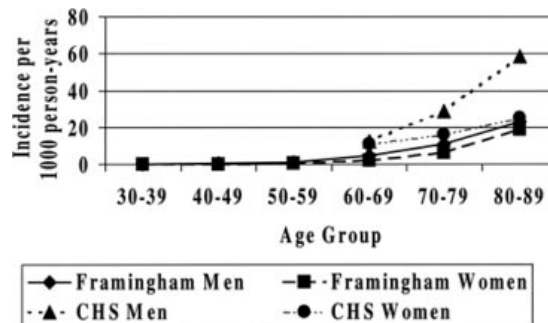
The risk of death among those with first-detected AF is particularly high during the months immediately following diagnosis. Among residents of Olmsted County, Minnesota, the age- and sex-matched hazard ratios (HR) for mortality among those with new-onset AF compared to those without AF were 9.62 (95% CI: 8.93 – 10.32) in the first four months and 1.66 (95% CI: 1.59 – 1.73) subsequently.<sup>45</sup> In the FHS the multivariable adjusted odds ratio (OR) for death among those with AF compared to those without AF was of 1.5 (95% CI: 1.2 – 1.8) in men and 1.9 (95% CI: 1.5 – 2.2) in women.<sup>26</sup> In addition, there was a significant age-sex interaction and AF was found to abate the female survival advantage.<sup>26</sup> The Women’s Health Study (WHS) corroborated these findings.<sup>46</sup> From 1980 to 2000 there was no trend in the age-, sex- and calendar year of diagnosis adjusted mortality.<sup>45</sup>

Hospital-based and administrative data are increasingly utilized to determine mortality following AF diagnosis. Among Medicare beneficiaries mortality following an AF diagnosis is 3.5 times higher than expected; 30-day and one-year mortality are 12.6% and 27.6%, respectively.<sup>27</sup> Hospital-based data have found no significant change in in-hospital mortality.<sup>36</sup> However, death certificate data indicate that deaths due to AF have been on the rise. The age-standardized mortality rate for AF, as the underlying or contributory cause of death, per 100,000 people increased from 27.6 in 1980 to 69.8 in 1998.<sup>47</sup>

## 4.0 RISK FACTORS

### 4.1 DEMOGRAPHIC

Demographic characteristics, including age, sex and race/ethnicity, are known to be associated with AF. Age is perhaps the most important nonmodifiable risk factor for AF. The incidence of AF doubles with each decade of life (Figure 4.1).<sup>5</sup> Consequently the prevalence of AF increases from 0.5% to 9% among 50-59 and 80-89 year olds, respectively.<sup>4</sup> As a result of the dramatic increase in AF incidence with advancing age, the lifetime risk of AF at 40 and 80 years is stable, approximately one in four.<sup>32</sup> The median age of patients with AF is 75.<sup>48,49</sup> About 70% of AF patients are between 65 and 85 years of age.<sup>49</sup>



**Figure 4.1:** Incidence of atrial fibrillation by age in two cohort studies. Framingham = Framingham Heart Study; CHS = Cardiovascular Health Study. From Fuster V, et al. *Circulation*. 2006;114(7):e257-354.

Male sex consistently has been associated with increased risk of developing AF.<sup>3,5,7,8</sup> Men had a 1.5-fold higher risk (95% CI: 1.3 – 1.8; p-value <0.0001) of developing AF than women, after adjustment for age and other risk factors, in the FHS.<sup>5</sup>



In Olmsted County, Minnesota, the incidence ratio for men compared to women was 1.86.<sup>3</sup> The overall and age-specific prevalence of AF is higher in men than in women.<sup>2</sup> However, the prevalence is high among both men and women at older ages.<sup>2,49</sup> In the CHS, among 65 – 69 year olds, AF prevalence was higher among men than women; however, among 70-79 year olds, the prevalence was indistinguishable.<sup>14</sup>

The majority of epidemiologic data on AF in the US is based on whites. Despite limited data on racial/ethnic differences, there is evidence that differences do exist. In the US, the burden of AF is lower among blacks even though they have a higher prevalence of risk factors for AF.<sup>12,50</sup> The age- and sex-adjusted incidence of AF in blacks was 41% lower (95% CI: 8% - 62%) compared to whites in the ARIC study.<sup>7</sup> The prevalence of AF among adults aged 50 and older was also significantly lower in blacks compared to whites in the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study.<sup>2</sup> A recent study sought to determine the role of genetic ancestry in the development of AF among blacks. European ancestry was a significant predictor of incident AF. After adjustment for potential confounders, every 10% increase in European ancestry increased the risk of incident AF by 17% (95% CI: 1.07 – 1.29; p<0.001).<sup>51</sup>

## **4.2 BEHAVIORAL**

The role of dietary habits, including alcohol and n-3 polyunsaturated fatty acid (PUFA) consumption, in the development of AF has been studied. Episodic heavy alcohol consumption, coined “holiday heart,” long has been known to be associated with the onset of AF.<sup>52</sup> Heavy alcohol consumption impacts maintenance of sinus rhythm

through several mechanisms, including electrophysiological changes in atrial cells,<sup>53,54</sup> direct impact on myocardial structure,<sup>55</sup> impaired vagal tone<sup>56</sup> and achievement of a hyperadrenergic state.<sup>57</sup> Habitual consumption of low to moderate amounts of alcohol are not thought to be associated with AF.<sup>58-61</sup> The FHS found an increased risk of AF among those who consumed more than 36 grams of alcohol/day (about three drinks/day) but no association at lower levels.<sup>61</sup> The CHS found no association between current moderate alcohol consumption and development of AF.<sup>58</sup> Despite these results, a recent meta-analysis reported a pooled estimate of 1.08 (95% CI: 1.05-1.10) for each 10 gram per day increment of alcohol.<sup>62</sup> In this analysis, a linear model showed a significant association between alcohol consumption and AF and there was no evidence of a J-shaped association or threshold effect.<sup>62</sup> Nevertheless, low to moderate alcohol consumption is not thought to increase the risk of AF.<sup>62,63</sup>

The association between fish-derived n-3 PUFAs and incident AF is unclear. The CHS found a protective effect of n-3 PUFAs; consumption of tuna or other broiled or baked fish, but not fried fish or fish sandwiches, was associated with a lower incidence of AF.<sup>64</sup> After adjustment for confounders, consumption of tuna or other broiled or baked fish 1-4 times per week and  $\geq 5$  times per week was associated with a 28% (95% CI: 0.58 – 0.91) and 31% (95% CI: 0.52-0.91) lower risk of incident AF, respectively, compared to consumption  $< 1$  time per month (p trend = 0.004).<sup>64</sup> However, five other large prospective cohort studies found no association.<sup>65-69</sup> There are several potential explanations for the inconsistent results, including that a larger proportion of the CHS participants consumed high amounts of fish compared to the other studies and total fish

consumption (fried, baked, broiled) was combined in some studies and fried fish may have adverse effects. Despite inconsistent results, there are biological mechanisms that support an inverse association between n-3 PUFAs and AF; n-3 PUFAs are protective against coronary heart disease<sup>70,71</sup> and might play a role in preventing inflammatory triggers from initiating ectopic activity resulting in AF.<sup>72</sup>

In addition to dietary habits, behaviors that might affect the development of AF have been studied, including exercise. Numerous studies have reported an increased risk of AF, particularly lone AF, among vigorous exercisers and elite athletes.<sup>73-77</sup> Among elderly adults,  $\geq 65$  years, exercise intensity had a U-shaped association with AF (interaction term  $p = 0.02$ ); light to moderate physical activity was associated with a reduced risk of AF.<sup>78</sup> However, in a middle-aged population, there was no association between work related physical activity and risk of AF.<sup>79</sup> In the WHS, increasing quintiles of physical activity were associated with reduced risk of AF (HR for extreme quintiles: 0.82; 95% CI: 0.66 – 1.01;  $p$  trend = 0.007). The association was attenuated after adjustment for body mass index (BMI) (HR for extreme quintiles: 0.99; 95% CI: 0.80 – 1.23;  $p$  trend = 0.22).<sup>80</sup>

Smoking is another behavior that increases the risk of coronary heart disease (CHD) but the association with AF is uncertain. Smoking affects several mechanisms involved in the etiology of AF;<sup>81</sup> smoking increases oxidative stress,<sup>82</sup> inflammation<sup>82</sup> and atrial fibrosis.<sup>83</sup> In ARIC, the multivariable-adjusted HRs for AF were 1.32 (95% CI: 1.10 – 1.57) in former smokers, 1.58 (95% CI: 1.35 – 1.85) in ever smokers and 2.05 (95% CI: 1.71 – 2.47) in current smokers, compared to never smokers.<sup>84</sup> These results

corroborate earlier findings in the Rotterdam Study<sup>85</sup> and the Manitoba Follow-Up Study.<sup>15</sup> In the FHS, smoking increased the odds of developing AF among women but not men,<sup>5</sup> while two other large population-based studies found no association.<sup>86,87</sup>

### **4.3 TRADITIONAL CARDIOVASCULAR DISEASE**

Of the traditional CVD risk factors, hypertension is consistently one of the most important contributors to the burden of AF. There is a linear trend in the association between increasing systolic and diastolic blood pressure and increasing AF risk.<sup>88</sup> Similarly, in the CHS, a positive association was reported; for each 10 mm Hg increment in systolic blood pressure, an 11% increased risk of AF was reported.<sup>8</sup> In the FHS, the multivariable adjusted OR for new-onset AF among hypertensive men and women was 1.5 (95% CI: 1.2 – 2.0) and 1.4 (95% CI: 1.1 – 1.8), respectively.<sup>5</sup> In ARIC, the population attributable fraction (%) for elevated blood pressure (systolic blood pressure  $\geq$  140 mm Hg, diastolic blood pressure  $\geq$  90 mm Hg, or antihypertensive medication) was 21.6% (95% CI: 16.8% – 26.7%).<sup>70</sup>

The association of type-2 diabetes mellitus and new-onset AF is inconsistent. A recent meta-analysis reported that patients with diabetes mellitus had a 34% greater risk of new-onset AF compared to non-diabetics (95% CI: 1.07 – 1.68) after correcting for publication bias.<sup>10</sup> Results from the ARIC study corroborate the meta-analysis; compared to non-diabetics, having type-2 diabetes mellitus was associated with a 35% increased risk of new-onset AF (95% CI: 1.14 – 1.60) after adjustment for confounders.<sup>9</sup> Additionally, in those with and without diabetes, there was a positive linear association

between HbA1c and the risk of AF.<sup>9</sup> However, other studies have found no association.<sup>89-</sup>  
<sup>91</sup> The mechanisms by which increased glucose levels and diabetes mellitus promote a proarrhythmic effect are not fully understood. Insulin resistance, a mechanism involved in the association of both hypertension and obesity with AF, is thought to play an important role.<sup>92</sup> Long-term inflammation has been suggested as a mediator in the link between diabetes mellitus and AF; higher levels of C-reactive protein, interleukin-6 and other inflammatory markers are found in atrial biopsies of patients with AF.<sup>93,94</sup>

Obesity consistently has been associated with an increased risk of developing AF. Five population-based cohort studies included in a meta-analysis each reported a significantly increased risk of AF among obese participants. The pooled results indicated a 49% increased risk (95% CI: 1.36 – 1.64) of developing AF in obese compared to nonobese adults.<sup>11</sup> There was a positive graded association between BMI and increased AF risk; compared to normal weight participants, overweight and obese participants had a 39% and 87% increased risk, respectively.<sup>11</sup> Obesity and overweight accounted for 17.9% of all incident AF cases in the ARIC study.<sup>70</sup> Despite the consistent association, the mechanisms by which obesity increases the risk of AF are not fully understood. Obesity often clusters with other risk factors for AF, such as hypertension, diabetes and obstructive sleep apnea (OSA), all of which increase the risk of AF.<sup>16,95,96</sup> Obesity might act as an indirect cause through hemodynamic (increased heart rate, blood pressure and stroke volume) and/or metabolic changes.<sup>96-98</sup> Additionally, left ventricular hypertrophy with subsequent atrial dilation may have a role in the development of AF.<sup>97</sup>

While the clinical significance of metabolic syndrome as an entity has not been firmly established, research has found an association between this disorder and development of AF. Metabolic syndrome is defined as the clustering of three or more of the following: elevated blood pressure, abdominal obesity, impaired glucose tolerance, low high-density lipoprotein cholesterol and elevated triglycerides.<sup>99</sup> In a prospective community-based cohort in Japan, there was a 61% increased risk of AF among individuals with metabolic syndrome (95% CI: 1.21 – 2.15; p = 0.001).<sup>100</sup> Each component of the metabolic syndrome, except elevated triglycerides, increased the risk of incident AF.<sup>100</sup> Another smaller study in Japan corroborates these results.<sup>101</sup> In ARIC, participants with, compared to those without, metabolic syndrome had a 67% increased risk of incident AF (95% CI: 1.49 – 1.87).<sup>12</sup> Once again, elevated blood pressure, abdominal obesity, impaired glucose tolerance and low high-density lipoprotein cholesterol, but not elevated triglycerides, were independently associated with an increased risk of AF (Table 4.1).<sup>12</sup> Additionally, there was a monotonically increased risk of AF with the increasing number of metabolic syndrome components present (5 components versus 0 components: HR: 4.40; 95% CI: 3.25 – 5.94).<sup>12</sup> The mechanisms underlying the association between metabolic syndrome and AF are likely due to the pathophysiological effects that occur as a result of each individual component of metabolic syndrome as well as the cumulative effect that might increase the risk of AF through development of CHD or HF.

	Overall	Blacks	Whites
<b>MetSyn components*</b>			
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)
<b>No. of components<sup>†</sup></b>			
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 MetSyn components. Overall model additionally adjusted for race.

†Multivariate model among individuals without any missing values for MetSyn 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.

**Table 4.1:** 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. From Chamberlain AM, et al. *Am Heart J.* 2010;159(5):850-856.

Over the past decade accumulating evidence indicates that inflammation is involved in the initiation and maintenance of AF.<sup>102,103</sup> Inflammatory markers were known to be elevated in AF patients, but it was unclear if inflammation was a cause or a consequence of AF.<sup>93</sup> However, in CHS, C-reactive protein (CRP) was found to be associated with the presence of AF at baseline and with incidence of AF. Among participants with AF at baseline, the prevalence of AF was significantly higher among those in the highest quartile of CRP compared to the lowest.<sup>104</sup> Furthermore, the risk of incident AF was 31% greater in participants in the highest CRP quartile compared to the lowest (95% CI: 1.08 – 1.58; p = 0.005).<sup>104</sup>

#### 4.4 MAJOR COMORBIDITIES

Individuals with major cardiovascular comorbidities, such as acute MI, HF and valvular heart disease, are at an increased risk of developing AF. In the FHS, history of MI was associated with a multivariable adjusted OR of developing AF of 1.4 (95% CI: 1.0 – 2.0;  $p < 0.05$ ) and 1.2 (95% CI: 0.8 – 1.8) in men and women, respectively.<sup>5</sup> Other population-based cohort studies have found similar increased risk.<sup>14,15</sup> HF is consistently associated with an increased risk of new-onset AF.<sup>5,14,15</sup> Among men, the odds of developing AF were 4.5 times greater (95% CI: 3.1 – 6.6;  $p < 0.0001$ ) in those with concomitant HF compared to those without; among women, the odds were 5.9 times greater (95% CI: 4.2 – 8.4;  $P < 0.0001$ ).<sup>5</sup> Women were significantly more likely to have valvular heart disease,<sup>5</sup> but the associated increased risk of developing AF occurred among both men and women.<sup>14,15</sup> In the Manitoba Follow-Up Study, the risk of incident AF was significantly higher among those with a history of MI (HR: 3.62; 95% CI: 2.59 – 5.07), HF (HR: 3.37; 95% CI: 2.29 – 4.96) and valvular heart disease (HR: 3.15; 95% CI: 1.99 – 5.00).<sup>15</sup> In addition to increasing risk on a population level, each of these comorbid conditions is predicative of a person's individual risk of developing AF.<sup>6,105</sup> AF following cardiac surgery is a common complication and the incidence has increased continuously over the past decades.<sup>106</sup> The incidence of post-operative AF is about 30% following coronary artery bypass grafting.<sup>106,107</sup> The incidence is even higher after valve replacement or repair at 40% and nearly 50% following combined procedures.<sup>106</sup>

In addition to cardiovascular comorbidities, there are several noncardiovascular conditions that have a strong association with development of AF, including OSA, reduced lung function and hyperthyroidism. OSA is highly prevalent in AF patients.



Among AF patients undergoing electrocardioversion, 49% had OSA compared with 32% of general cardiology patients ( $p = 0.0004$ ).<sup>108</sup> The multivariable-adjusted odds of AF were four times higher in patients with sleep-disordered breathing compared to those without sleep-disordered breathing (95% CI: 1.03 – 15.74).<sup>17</sup> In a retrospective cohort study, OSA was an independent predictor of incident AF among individuals <65 years of age but not among older adults.<sup>16</sup> The association was independent of the effect of obesity on risk of AF.<sup>16</sup> A case-crossover design was utilized to determine if an apnea episode acts as a trigger for paroxysmal AF. While the absolute rate of AF associated with respiratory disturbances was low, the odds of AF after a respiratory disturbance were nearly 18 times higher than (95% CI: 5.3 – 58.4) the odds of AF after normal breathing.<sup>109</sup> Among AF patients who had cardioversion, recurrence of AF at one year was nearly double among those not using continuous positive airway pressure (CPAP) therapy compared to those using CPAP ( $p = 0.01$ ).<sup>110</sup>

The few studies that have examined the association of forced expiratory volume in one second (FEV<sub>1</sub>) with AF development report contradictory results. The multivariable adjusted OR of incident AF among individuals with a FEV<sub>1</sub> between 60-80% compared to those with a normal FEV<sub>1</sub> ( $\geq 80\%$ ) was 1.8 (95% CI: 1.01 – 3.05).<sup>111</sup> However, results from the multivariable adjusted analysis in the FHS indicate that FEV<sub>1</sub> is not an independent predictor of AF.<sup>5</sup> Case-control studies have found that AF patients have a higher prevalence of reduced lung function than control patients, irrespective of risk factors.<sup>112,113</sup> The mechanisms that connect reduced lung function and AF have not been clearly elucidated, but there are several potential explanations including ectopic

beats originating in the pulmonary veins, deterioration of the blood gas composition, hypoxia, hemodynamic changes due to pulmonary hypertension, stress on the right atrium and inflammation.<sup>114,115</sup>

Clinical and subclinical hyperthyroidism are established risk factors for AF. In a recent meta-analysis, subclinical hyperthyroidism was associated with a 71% increased risk of incident AF (95% CI: 1.18 – 2.48) compared to euthyroidism, after multivariable adjustment.<sup>13</sup> There was an inverse association between thyrotropin level and AF; compared to 0.45 – 4.99 mIU/L (normal) the multivariable adjusted risk of AF was 1.70 (95% CI: 1.15 – 2.53) and 2.34 (95% CI: 0.98 – 5.58) with thyrotropin levels of 0.10 – 0.44 mIU/L (subclinical) and <0.10 mIU/L (clinical), respectively (p trend = 0.06).<sup>13</sup> Individual studies not included in the meta-analysis found similar associations.<sup>116-119</sup> In totality, the data indicate there is a graded inverse association.

#### **4.5 STRUCTURAL CARDIAC ABNORMALITIES**

Structural cardiac abnormalities often are found in patients with AF, but the echocardiographic precursors of AF were unknown until the FHS report in 1994 (Table 4.2).<sup>120</sup> After adjustment for age, sex and other risk factors, left atrial size, left ventricular fractional shortening and the sum of septal and left ventricular posterior wall thickness were independent echocardiographic predictors of AF (Table 4.2).<sup>4,120</sup>

Echocardiographic Variable	Variable Increment	Hazard Ratio (95% CI)	P
Left atrial dimension, mm	5	1.39 (1.14-1.68)	.001
Fractional shortening, %	-5	1.34 (1.08-1.66)	.007
Sum of wall thickness, mm	4	1.28 (1.03-1.60)	.028

CI indicates confidence interval. Model is adjusted for age, sex, coronary heart disease, valvular heart disease, congestive heart failure, diabetes, and hypertension.

**Table 4.2:** Multivariable adjusted hazard ratios for echocardiographic variables

significantly associated with risk of atrial fibrillation. From Vaziri SM, et al. *Circulation*. Feb 1994;89(2):724-730.

Left ventricular diastolic dysfunction is independently predictive of AF. There is a graded association of risk based on the severity of diastolic dysfunction.<sup>121</sup> Additionally, there is some evidence that mitral annular calcification is associated with risk of developing AF.<sup>50,120</sup>

#### 4.6 GENETIC PREDISPOSITION

In the past decade, a genetic component to AF in the general population has been established.<sup>122-124</sup> In the FHS, having at least one parent with AF was associated with a 1.85-fold higher odds of AF in the adult offspring (95% CI: 1.12 – 2.06; p = 0.02).<sup>122</sup> Also from the FHS, after multivariable adjustment, the risk of incident AF was greater if the first-degree relative's age of onset was  $\leq 65$  years (HR: 2.01; 95% CI: 1.49 – 2.71; p < 0.001).<sup>125</sup> The risk of new-onset AF increased by 24% for each additional affected first-degree relative (95% CI: 1.05 – 1.46; p = 0.01).<sup>125</sup> In a large study of Icelanders, the risk of developing AF, compared to the general population, was nearly double among those with a first-degree relative with AF; in patients diagnosed with AF before age 60, the risk

among first-degree relatives was almost fivefold greater.<sup>124</sup> Mutations in sodium and potassium gene coding channels, somatic myocardial mutations in gap junction proteins and signaling alterations have been identified in lone AF or familial AF series. However, they are not a major contributor to AF in the community.<sup>126</sup>

Recent genome-wide association studies have identified several single-nucleotide polymorphisms (SNPs) associated with AF. Two sequence variants on chromosome 4q25 had a strong association with AF. These variants are adjacent, upstream, of the PITX2 gene, which has a critical function in left-right asymmetry of the heart.<sup>127</sup> SNP rs2106261 on chromosome 16q22, which is near gene ZFHX3, was significantly associated with AF in a meta-analysis of five community-based cohort studies and replicated in an independent cohort.<sup>128</sup> ZFHX3 is thought to regulate myogenic and neuronal differentiation; however, the role in cardiac tissue is not known.<sup>128</sup> The causative SNPs and the functional basis of these associations are still under investigation. A GWAS among individuals of European descent corroborated previously identified susceptibility loci on chromosomes 4q25 and ZFHX3 and identified six new AF susceptibility loci.<sup>129</sup> SNP rs3903239 on chromosome 1q24 in PRRX1, which encodes a homeodomain transcription factor that is highly expressed in the developing heart, especially in connective tissue, was the most significant new association.<sup>129</sup> Other susceptibility loci included chromosome 7q31, SNP rs3807989, in CAV1; chromosome 14q23, rs1152591 located in an intron of SYNE2; chromosome 9q22, rs10821415 located in an ORF on chromosome 9; chromosome 15q24 rs7164883, in the first intron of HCN4 and chromosome 10q22 rs10824026 located 5 kb upstream of SYNPO2L and 20 kb upstream

of MYOZ1.<sup>129</sup> These loci are located on genes that encode transcription factors related to cardiopulmonary development, cardiac-expressed ion channels and cell signaling molecules.<sup>129</sup>

## **5.0 PATHOPHYSIOLOGY**

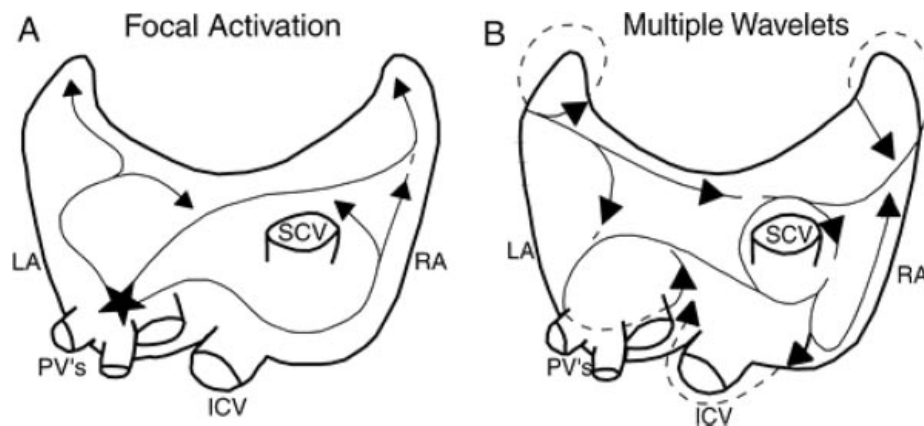
### **5.1 NATURAL HISTORY**

AF is an uncoordinated atrial tachyarrhythmia caused by rapid and irregular atrial depolarization which results in ineffective atrial contraction.<sup>130,131</sup> AF is characterized by the absence of distinct P-waves before each QRS complex, the presence of rapid atrial oscillations (F-waves) and variable RR intervals on electrocardiogram (ECG).<sup>131</sup> Initiation of AF requires a trigger and, in order for AF to persist, the trigger must remain or electrical remodeling that promotes AF in the absence of the trigger must occur.<sup>28,131</sup>

Underlying atrial pathology can result in AF. Atrial fibrosis and loss of atrial muscle mass are the most common pathoanatomic changes.<sup>28,132</sup> Atrial fibrosis can be triggered by many factors including inflammation<sup>133</sup> and atrial dilation caused by any type of CVD associated with AF, including hypertension, HF and atherosclerosis.<sup>134</sup> Histological changes also have been identified. Heterogeneity of conduction is caused, at least in part, by fibrotic atrial fibers juxtaposed with healthy atrial tissue.<sup>135</sup> In addition to atrial pathology resulting in AF, AF causes numerous changes in the atrial architecture and function that result in remodeling and persistence of the arrhythmia. AF can cause loss of contractility and increased compliance that result in atrial dilation.<sup>135</sup> Atrial stretch and fibrosis also can cause pathologic changes.<sup>28</sup>

The two main pathophysiologic mechanisms thought to underlie AF are a focal mechanism and multiple reentrant wavelets (Figure 5.1).<sup>28</sup> With a focal initiation of AF, one or more rapidly depolarizing atrial impulses, most commonly originating in the

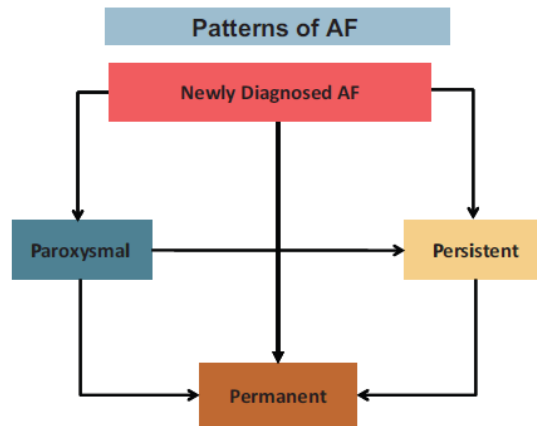
pulmonary veins, is the trigger. This mechanism is supported by a study that demonstrated that identification and ablation of a focal source of AF terminated the arrhythmia.<sup>136</sup> Histologically, AF patients have atrial tissue on the pulmonary veins with shorter refractory periods compared to control patients.<sup>137</sup> It is also possible for AF to begin as a result of rapid depolarization from the pulmonary veins and the subsequent electrical remodeling to promote multiple reentry wavelets.<sup>138</sup> With multiple reentry wavelets, one or more circuits is involved and fractionation of wavefronts through the atria results in self-perpetuating “daughter wavelets.”<sup>28</sup> The refractory period, mass and conduction velocity in various parts of the atria determine the number of wavelets at a given time.<sup>28,139</sup> An increased number of wavelets, caused by a large atrial mass, short refractory period and delayed conduction, fosters sustained AF.<sup>28</sup> Electrophysiologic mapping in humans supports this theory.<sup>140</sup> These mechanisms are not mutually exclusive and can and do coexist within a patient.<sup>28,131</sup>



**Figure 5.1:** Posterior view of principal electrophysiological mechanisms of atrial fibrillation. From Fuster V, et al. *Circulation*. 2006;114(7):e257-354.

## 5.2 CLASSIFICATION

The American College of Cardiology, American Heart Association and European Society of Cardiology recommend the following consensus classification scheme developed with an emphasis on simplicity and clinical relevance.<sup>28</sup> AF can be classified as either the first-detected episode or recurrent (Figure 5.2). If a patient has two or more episodes of AF, it is classified as recurrent and can be further subclassified based on duration and response to treatment; both paroxysmal and persistent AF can be recurrent.<sup>28</sup> An AF episode that spontaneously terminates within seven days is classified as paroxysmal. AF is classified as persistent if an episode lasts more than seven days, regardless of if the episode self-terminates or requires pharmacological therapy or direct current cardioversion.<sup>28</sup> Longstanding AF (greater than one year) in which cardioversion was not successful or not attempted is classified as permanent.<sup>28</sup> These categories are not mutually exclusive within a patient. For example, a patient might have episodes of paroxysmal and persistent AF.<sup>28</sup>



**Figure 5.2:** Patterns of atrial fibrillation. From Gillis AM, et al. *Can J Cardiol.* 2011;27(1):47-59.



In addition to the above classifications, AF in individuals under 60 years of age without evidence of cardiopulmonary disease, including hypertension or diabetes, is classified as lone AF.<sup>28,141</sup> Nonvalvular AF is defined as AF in individuals without rheumatic mitral valve disease, a prosthetic heart valve or mitral valve repair.<sup>28</sup>

### **5.3 RECURRENCE AND PROGRESSION**

Among patients with first detected AF, approximately 54% experienced a recurrent event within one year of diagnosis.<sup>142</sup> During one year of follow-up, one-third of general practice patients in France with a diagnosis of paroxysmal AF had recurrence.<sup>143</sup> By five years, 63.2% of patients with paroxysmal AF experienced recurrence.<sup>144</sup> Recurrence is likely underestimated as many episodes go undiagnosed, in part because they often are asymptomatic.

In addition to being recurrent, AF is a progressive disease. The rate of progression from paroxysmal to a more advanced disease state (either persistent or permanent) is highest in the first year after diagnosis.<sup>144,145</sup> Among patients with paroxysmal AF, 8.6% progressed to permanent AF within the first year and 24.7% progressed to permanent AF within five-years.<sup>144</sup> A similar probability of progression to permanent AF was found when paroxysmal and persistent AF were combined.<sup>146</sup> The progression rate from paroxysmal to persistent or permanent AF was 13.6 per 100 person-years during the first year of follow-up and 6.2 per 100 person-years during a mean follow-up of 2.7 years.<sup>145</sup>

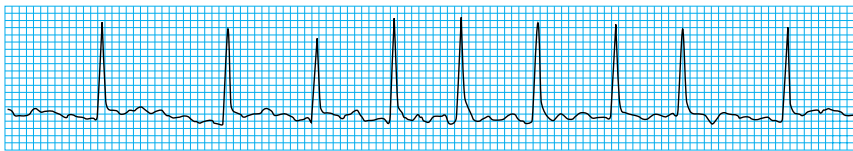
In multivariable analysis independent predictors of progression of AF from paroxysmal to persistent or permanent included history of HF, hypertension, chronic

obstructive pulmonary disease, history of stroke or transient ischemia attack and age > 75 years.<sup>147</sup> Diagnosis of cardiomyopathy, aortic stenosis, mitral regurgitation and left atrial enlargement also have been found to be independent predictors of progression in multivariable analysis.<sup>144</sup>

#### 5.4 ATRIAL FIBRILLATION VERSUS ATRIAL FLUTTER

AF and atrial flutter (AFL) are both tachyarrhythmias, but historically have been viewed as two separate conditions with distinct *International Classification of Diseases, ninth revision*, (ICD-9) codes of 427.31 for AF and 427.32 for AFL.<sup>28,131</sup>

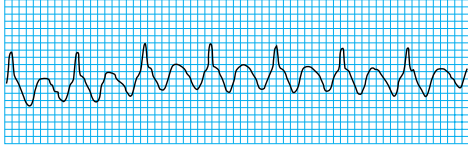
During AF the atrial rate ranges from 350 to 600 beats per minute (BPM).<sup>28,131</sup> As a consequence of concealed atrioventricular (AV) nodal penetration and subsequent AV block of varying degrees, the classic characteristic of irregularly irregular ventricular rate ranges between 100 to 160 bpm.<sup>131</sup> On ECG, the absence of distinct P-waves before each QRS complex, rapid atrial oscillations (F waves) and variable RR intervals indicate AF (Figure 5.3).<sup>28,131</sup>



**Figure 5.3:** Rhythm strip of AF. From Goodacre S, Irons R. *BMJ*. 2002;324(7337):594-597.

AFL is defined by a single reentrant circuit confined to the right atrium.<sup>131</sup> AFL is characterized by an atrial rate between 250 and 350 bpm, a regular ventricular rhythm and a 2:1 AV conduction which results in a ventricular rate of about 150 bpm.<sup>131</sup> On

ECG, regular, broad, saw-toothed F-waves (flutter waves) are seen, especially in the inferior leads (Figure 5.4).<sup>28,131</sup>



**Figure 5.4:** Rhythm strip of AFL. From Goodacre S, Irons R. *BMJ*. 2002;324(7337):594-597.

It is increasingly documented that AF and AFL can occur in isolation or in combination. AFL can precede or coexist with AF and AFL frequently degenerates into AF.<sup>28</sup> In addition, the increased risk of thromboembolism is present in both AF and AFL, which has resulted in identical antithrombotic clinical performance measures.<sup>148</sup> Also, the *tenth revision* of the ICD codes (ICD-10) combines AF and AFL into one code, I48.

## **6.0 CLINICAL ASPECTS**

### **6.1 DIAGNOSIS**

AF is often asymptomatic and consequently undiagnosed.<sup>149</sup> Individuals with AF may have no, episodic or severe symptoms.<sup>149</sup> When symptoms are present they include palpitations, fatigue, lightheadedness and dyspnea on exertion.<sup>149</sup>

Given that AF often occurs without symptoms, it frequently is diagnosed during a routine ECG examination, based on data from an implanted pacemaker, during ambulatory ECG monitoring or during the course of treatment for MI or stroke.<sup>149</sup> In the CHS, 12% of AF cases were diagnosed incidentally during annual study ECGs.<sup>8</sup> On ECG, AF is characterized by the absence of distinct P-waves prior to each QRS complex, the presence of rapid atrial oscillations (F-waves) varying in amplitude, shape and timing and irregular RR intervals.<sup>131</sup>

The initial evaluation of a patient with suspected or proved AF focuses on characterizing the arrhythmia as paroxysmal or persistent, pinpointing its cause and identifying associated cardiac and extracardiac factors relevant to the etiology, tolerability and management.<sup>28</sup> A diagnosis of AF requires supporting ECG documentation with a minimum of a single-lead recording during the arrhythmia. Additionally, all patients with AF should have 2-dimensional Doppler echocardiography to assess left atrium and left ventricle dimensions and left ventricle wall thickness and function.<sup>28</sup> A thorough history and diagnostic workup (Table 6.1) are used to guide therapy and usually can occur during a single outpatient appointment.<sup>28</sup>

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**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, or permanent)
  - Onset of the 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)
  - LV hypertrophy
  - P-wave duration and morphology of fibrillatory waves
  - Preexcitation
  - Bundle-branch block
  - Prior MI
  - Other atrial arrhythmias
  - To measure and follow the R-R, QRS, and QT intervals in conjunction with antiarrhythmic drug therapy
3. *Transthoracic echocardiogram, to identify*
  - Valvular heart disease
  - LA and RA size
  - LV size and function
  - Peak RV pressure (pulmonary hypertension)
  - LV hypertrophy
  - LA thrombus (low sensitivity)
  - 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 (One or several tests may be necessary)**

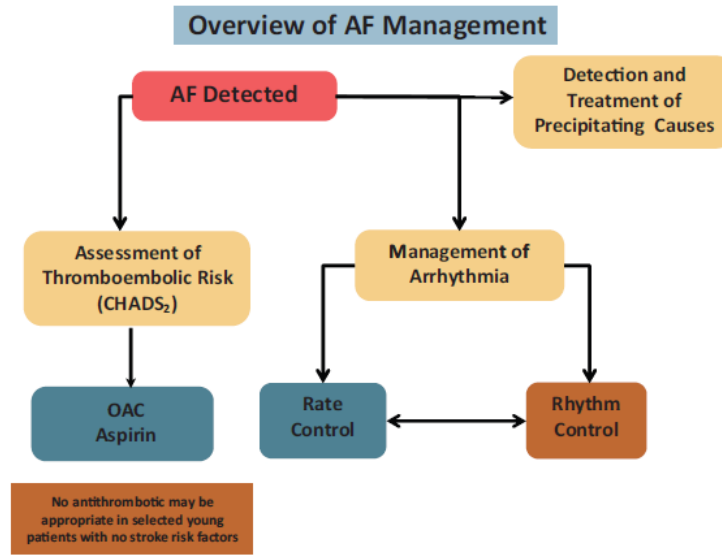
1. *Six-minute walk test*
  - If the adequacy of rate control is in question
2. *Exercise testing*
  - If the adequacy of rate control is in question (permanent AF)
  - To reproduce exercise-induced AF
  - To exclude ischemia before treatment of selected patients with a type Ic antiarrhythmic drug
3. *Holter monitoring or event recording*
  - If diagnosis of the type of arrhythmia is in question
  - As a means of evaluating rate control
4. *Transesophageal echocardiography*

- To identify LA thrombus (in the LA appendage)
  - To guide cardioversion
  - 5. *Electrophysiological study*
    - To clarify the mechanism of wide-QRS-complex tachycardia
    - To identify a predisposing arrhythmia such as atrial flutter or paroxysmal supraventricular tachycardia
    - To seek sites for curative ablation or AV conduction block/modification
  - 6. *Chest radiograph, to evaluate*
    - Lung parenchyma, when clinical findings suggest an abnormality
    - Pulmonary vasculature, when clinical findings suggest an abnormality
- 

**Table 6.1:** Clinical evaluation in patients with AF. Type IC refers to the Vaughan Williams classification of antiarrhythmic drugs; AV indicates atrioventricular; LA, left atrial; LV, left ventricular; MI, myocardial infarction; RA, right atrial; RV, right ventricular. Reproduced from Fuster V, et al. *Circulation*. 2006;114(7):e257-354.

## 6.2 TREATMENT

The primary treatment objectives of AF patients are correction of rhythm disturbance, heart rate control and prevention of thromboembolism (Figure 6.1). The initial treatment decision is focused on selecting a rhythm control or rate control strategy.<sup>28</sup> The rhythm-control strategy focuses on reestablishing and maintaining sinus rhythm and the rate-control strategy focuses on controlling the ventricular rate. Regardless of the strategy selected, antithrombotic therapy is necessary for the prevention of thromboembolism.<sup>28</sup>



**Figure 6.1:** Overview of atrial fibrillation management. From Gillis AM, et al. *Can J Cardiol.* 2011;27(1):47-59.

Rhythm control treatment options include pharmacological therapy, electrical cardioversion, catheter ablation, the maze procedure, atrial pacing and implantation of an internal atrial defibrillator. The potential benefits of a rhythm control strategy include fewer symptoms, increased exercise capacity, improved hemodynamic function and prevention of tachycardia-induced cardiomyopathy as a result of AF.<sup>28</sup> However, antiarrhythmic medication often is unsuccessful in maintaining sinus rhythm and can have serious adverse effects.<sup>28</sup> Pharmacological therapy is the first line of treatment with a rhythm control strategy. The primary medications used for pharmacologic cardioversion are class Ia, Ic and III antiarrhythmics.<sup>150</sup> Flecainide and propafenone, class Ic agents, are commonly used and have similar efficacy.<sup>150</sup> Class Ic drugs have the highest efficacy for recent-onset AF while class III drugs are best for persistent AF.<sup>150</sup> Electrical cardioversion involves ECG monitoring and delivery of an electrical shock

synchronized with the intrinsic activity of the heart; the ECG monitors the R wave to prevent stimulation during the vulnerable phase of the cardiac cycle.<sup>28</sup> Cardioversion can be performed with or without the use of antiarrhythmic drugs.<sup>28</sup> Electrical cardioversion is successful in 70% to 90% of patients; short duration of AF, presence of AFL and younger age are predictors of successful cardioversion.<sup>150</sup> In patients with a structurally normal heart, catheter-based radiofrequency ablation, pulmonary vein isolation or linear ablation to compartmentalize the atrium can be used to target the arrhythmogenic foci in the pulmonary veins, the atria, superior vena cava or the coronary sinus.<sup>150</sup> These procedures have a success rate up to 80% in patients with a single focus of AF who had limited ablation or in healthy patients who underwent complete pulmonary vein isolation for paroxysmal or persistent AF.<sup>151</sup> The procedural success decreases to 50-60% in patients with permanent AF and significant structural heart disease.<sup>151</sup> Recurrent AF following successful ablation occurs in up to 40% of patients.<sup>151,152</sup> The maze procedure, indicated for highly symptomatic, drug-resistant AF patients or patients who experience thromboembolism while on warfarin, is effective in more than 90% of cases.<sup>150</sup> While highly effective, the procedure is not widely utilized, in part because it requires the use of cardiopulmonary bypass.<sup>28</sup> In the maze procedure surgical scars are created in the left atrium and the pulmonary veins are isolated.<sup>150</sup> By creating conduction barriers in the atrium, this procedure prevents the propagation of reentry wavefronts.<sup>150</sup> Atrial pacing, either in the right atria or in multiple locations, works by altering the pattern of atrial depolarization and suppression of premature atrial beats.<sup>28,150</sup> However, the usefulness of this approach has yet to be proved.<sup>28,150</sup> Patients with recurrent, drug-resistant, highly



symptomatic AF are potential candidates for implantation of an internal atrial defibrillator.<sup>150</sup> Delivery of a synchronous shock between the high right atrium and coronary sinus is known to effectively terminate an episode of AF.<sup>153</sup> Implantable cardiac defibrillator (ICD) technology has made great progress and now ICD devices can detect, treat and prevent AF.<sup>150</sup> Despite the efficacy of ICDs, patients find the shock uncomfortable and therefore this device has limited clinical use.<sup>28,150</sup>

Rate control treatment modalities include pharmacological therapy, ablation and pacemaker implantation. Benefits of a rate control strategy include a simplified treatment plan and use of less toxic medication, with fewer side effects, than antiarrhythmic medication.<sup>28</sup> Current guidelines for rate control are a ventricular rate of 60-80 BPM at rest and 90-115 BPM during moderate exercise.<sup>28</sup> The main determinants of ventricular rate are the intrinsic conduction characteristics, refractoriness of the AV node and sympathetic and parasympathetic tone.<sup>28</sup> Pharmacological therapy is the primary treatment choice and medications that prolong the refractory period are generally effective for rate control because of the inverse correlation between the functional refractory period of the AV node and the ventricular rate.<sup>28</sup> Beta blockers, calcium channel antagonists and digitalis are used individually or in combination to achieve rate control.<sup>28</sup> If pharmacological therapy is unsuccessful, AV nodal ablation and permanent pacemaker implantation is an effective method to control the heart rate and improve symptoms.<sup>131,154</sup>

Consensus has not been reached on the preferred treatment strategy, rhythm or rate control, for AF patients. Historically, rhythm control was considered the best

treatment approach.<sup>155</sup> However, since the publication of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial results in 2002, either strategy has been considered acceptable.<sup>28,152</sup> In the AFFIRM trial there was no difference in the primary endpoint of all-cause mortality between rhythm and rate control strategies (HR: 1.15; 95% CI: 0.99 – 1.34; p = 0.08); rates of the composite end point of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, or cardiac arrest were also similar between the two groups.<sup>155</sup> More patients in the rhythm control group were hospitalized during following-up.<sup>155</sup> Similar results were reported from four smaller randomized controlled trials, published around the same time as AFFIRM; in each of the studies there was no difference in all-cause mortality between rate and rhythm control.<sup>156-159</sup> A meta-analysis of these five trials reported a pooled OR for all-cause mortality comparing rate and rhythm control groups of 0.87 (95% CI: 0.74 – 1.02; p = 0.09).<sup>160</sup> Additionally, there was no difference in the odds of ischemic stroke between the rate and rhythm control groups in any of the three individual trials<sup>155-157</sup> or in the pooled estimate (OR: 0.50; 95% CI: 0.14 – 1.83; p = 0.30).<sup>160</sup> Despite evidence that the rate and rhythm treatment strategies result in similar patient outcomes, the generalizability of the trial results to the general AF patient population has been questioned. A recent population-based study with a mean follow-up duration of 3.1 years (standard deviation 2.3 years) found the effect of rate versus rhythm control drugs changed over time; in the first six months, mortality was slight higher among patients treated with rhythm control drugs, mortality was similar between groups until year four and then mortality among those treated with rhythm control decreased (5-year HR: 0.89; 95% CI: 0.81 – 0.96; 8-year HR:

0.77; 95% CI: 0.62 – 0.95).<sup>161</sup> In analyses that accounted for treatment crossovers, the long-term mortality reduction was even greater for patients who initiated and maintained rhythm control therapy compared to those who initiated and maintained rate control therapy.<sup>161</sup>

Regardless of the treatment strategy, antithrombotic therapy currently is recommended for AF patients, except those with lone AF or contraindications, to prevent thromboembolism (Table 6.2).<sup>28</sup> Several stroke risk classification schemes have been developed in order to stratify the risk of ischemic stroke in AF patients. The CHADS<sub>2</sub> classification scheme (congestive HF, hypertension, age, diabetes, stroke [doubled]) incorporates elements from the Atrial Fibrillation Investigators (AFI) and Stroke Prevention and Atrial Fibrillation (SPAF) schemes to quantify stroke risk and select the appropriate antithrombotic therapy.<sup>162</sup> The American Heart Association and the American Stroke Association recently published a science advisory on the use of oral antithrombotic agents for the prevention of stroke; warfarin, dabigatran, apixaban and rivaroxaban are all recommended for the prevention of first and recurrent stroke in patients with nonvalvular AF.<sup>163</sup> Antithrombotic therapy is recommended for patients at high stroke risk<sup>163</sup> and aspirin for patients at low stroke risk.<sup>164,165</sup>

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

\*If mechanical valve, target international normalized ratio (INR) greater than 2.5.

INR indicates international normalized ratio; LV, left ventricular; and TIA, transient ischemic attack.

**Table 6.2:** Antithrombotic therapy for patients with atrial fibrillation. From Fuster V, et al. *Circulation*. 2006;114(7):e257-354.

## **7.0 CONCOMITANT CLINICAL EVENTS**

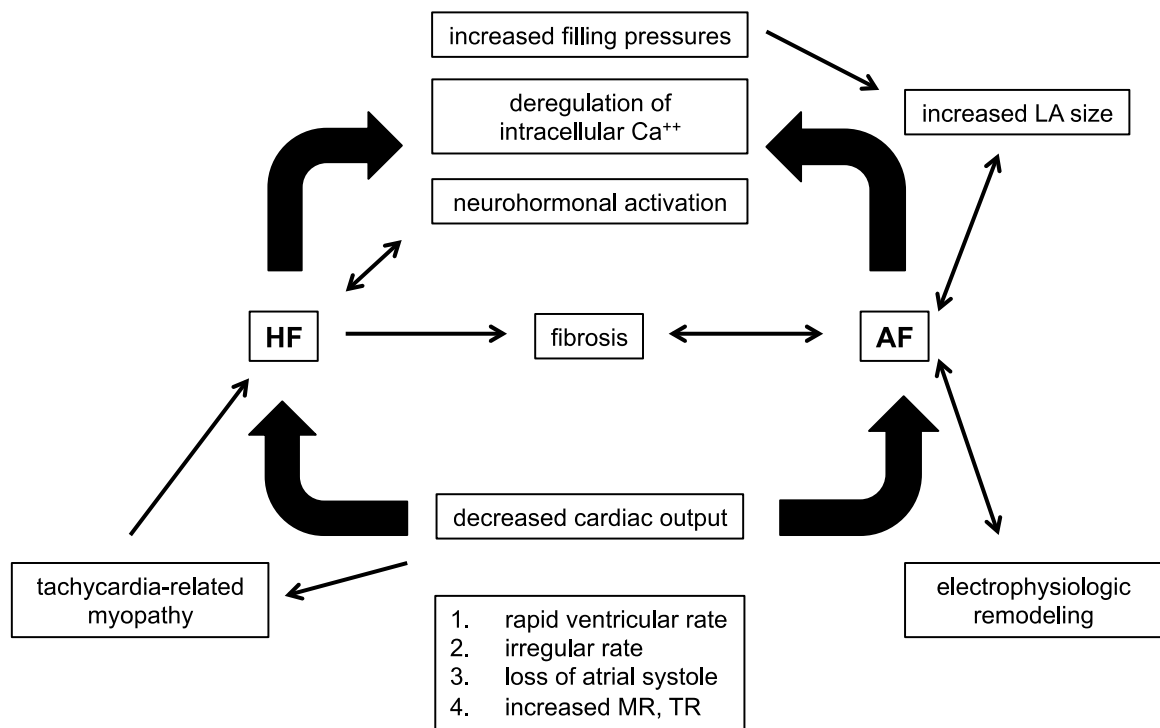
### **7.1 ACUTE MYOCARDIAL INFARCTION**

AF frequently complicates acute MI. The incidence of AF among MI patients varies between 6% and 22%.<sup>166</sup> In Olmsted County residents who experienced a first MI, 10% had AF prior to MI and 23% developed AF after the event.<sup>22</sup> A recent systematic review and meta-analysis reported that among MI patients roughly one in 10 had concomitant AF.<sup>23</sup> Both conditions dramatically increase in frequency with advancing age. Among elderly Medicare beneficiaries, MI patients who presented with AF were older, had a higher heart rate, had more advanced HF and were more like to have a history of coronary artery bypass graft surgery, previous MI and cerebrovascular disease compared to MI patients who developed AF during MI hospitalization.<sup>167</sup> The biological mechanisms involved in the development of AF during MI have not been fully elucidated. Potential mechanisms include pericarditis, atrial ischemia or infarction, increased catecholamines, metabolic abnormalities and increased atrial pressures.<sup>167</sup> Patient prognosis is worse for those who experience both MI and AF compared to those who have either condition individually.<sup>22,23,167,168</sup>

### **7.2 HEART FAILURE**

AF and HF frequently coexist, partly because of shared risk factors and partly because they predispose to each other. Age, hypertension, MI, diabetes, obesity and valvular heart disease are risk factors for both AF and HF.<sup>169</sup> AF may influence the

development and progression of HF in a number of ways (Figure 7.1). During AF, an increase in resting heart rate as well as an exaggerated heart rate response to exercise shorten the diastolic filling time which in turn results in lower cardiac output. In addition, irregular ventricular contraction reduces overall cardiac output because the reduction in left ventricular filling during short cycles is not fully compensated for by the increased filling during longer cycles. Reduced contractile function of the atrium also plays an important role in the reduction of cardiac output.<sup>169</sup> Likewise, HF increases the risk of AF in multiple ways, including elevation of cardiac filling pressures, deregulation of intracellular calcium and autonomic and neuroendocrine dysfunction.<sup>169</sup>



LA = left atrial; MR = mitral regurgitation; TR = tricuspid regurgitation

**Figure 7.1:** Atrial fibrillation and heart failure: a vicious pathophysiological cycle.

Reproduced from Anter E, Jessup M, Callans DJ. *Circulation*. 2009;119(18):2516-2525.

In the FHS, 1470 participants developed incident AF or HF between 1948 and 1995; a quarter (n = 382) developed both AF and HF.<sup>21</sup> AF preceded HF approximately as often as HF preceded AF, 38% and 41%, respectively, and 21% had both diagnosed on the same day.<sup>21</sup> The unadjusted incidence of HF following incident AF was slightly higher in Olmsted County at 44 per 1,000 person-years,<sup>20</sup> compared to the FHS at 33 per 1,000 person-years.<sup>21</sup>

### **7.3 STROKE**

AF was associated with a five-fold increased risk of ischemic stroke in the FHS.<sup>19</sup> Among Olmsted County residents diagnosed with incident AF, 11% had a first ischemic stroke over a mean follow-up of 5.5 years.<sup>18</sup> A collaborative analysis of five randomized controlled trials identified advanced age, history of hypertension, previous transient ischemic attack or stroke and diabetes as independent risk factors for stroke among AF patients.<sup>170</sup> The relative risk of stroke associated with AF was fairly stable across age groups; however, the attributable risk increased significantly with age, from 1.5% to 23.5% among 50-59 and 80-89 year olds, respectively.<sup>19</sup> Ischemic stroke and systemic arterial occlusion in AF are primarily attributed to embolism of a thrombus as a result of blood stasis in the left atrium.<sup>28</sup> Nevertheless, up to 25% of strokes in AF patients might be a result of intrinsic cerebrovascular diseases, other cardiac sources of embolism or atherosclerotic pathology in the proximal aorta.<sup>171,172</sup> Treatment with warfarin reduced the risk of stroke by 68% (95% CI: 50% 79%).<sup>170</sup>

## **7.4 COGNITIVE IMPAIRMENT**

There is increasing evidence that AF is a risk factor for cognitive impairment. Several cross-sectional studies found that after adjustment for cardiovascular risk factors, AF was associated with cognitive dysfunction, independent of stroke.<sup>173-175</sup> In the cross-sectional portion of the Rotterdam Study, participants with AF had an adjusted 2-fold increased prevalence of dementia.<sup>175</sup> A prospective cohort study among residents of Olmsted County with incident AF and without stroke found the cumulative rate of dementia was 2.7% and 10.5% at one and five years, respectively.<sup>25</sup> A meta-analysis restricted to studies conducted among non-stroke AF patients reported a pooled OR of dementia of 1.64 (95% CI: 1.00 – 2.71;  $p = 0.05$ ) comparing those with and without AF.<sup>24</sup>

## **7.5 DEATH**

AF is associated with an increased risk of death. Among newly diagnosed AF patients, the risk of death is extremely high; within the first four months of diagnosis, the HR for death among those with AF compared to those without AF was 9.62 (95% CI: 8.93 – 10.32).<sup>45</sup> The risk of death for the remainder of the 21-year follow-up was 1.66 (95% CI: 1.59 – 1.73).<sup>45</sup> The most common causes of cardiovascular death were coronary artery disease, HF and ischemic stroke, accounting for 22%, 14% and 10%, respectively, of deaths within 4 months of AF diagnosis and 15%, 16% and 7%, respectively of later deaths.<sup>45</sup> In the FHS, the adjusted odds of death in men with AF were 1.5-fold greater (95% CI: 1.2 – 1.8;  $p = 0.0001$ ) compared to men without AF; among women the odds of



death were 1.9-fold greater (95% CI: 1.6 – 2.3;  $p = 0.0001$ ) in those with AF.<sup>26</sup> The death rate per 1,000 person-years among initially healthy women with and without new-onset AF was 10.8 (95% CI: 8.1 – 13.5) and 3.1 (95% CI: 2.9 – 3.2), respectively.<sup>46</sup> Among elderly Medicare beneficiaries, mortality following AF diagnosis declined slightly over time but remained high.<sup>27</sup> In 2007, the age- and sex-adjusted mortality at 30 days and 1-year were 10.8% and 24.7%, respectively.<sup>27</sup> Mortality following an inpatient diagnosis of AF was significantly higher than mortality following an outpatient diagnosis; in 2007 the one-year mortality following an inpatient diagnosis was 32.3% compared to 10.2% following an outpatient diagnosis.<sup>27</sup>

## **8.0 ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY**

### **8.1 OVERVIEW**

The ARIC study is a prospective epidemiologic study of CVD conducted in four US communities: Forsyth County, NC; the city of Jackson, MS; eight northwestern suburbs of Minneapolis, MN; and Washington County, MD. The ARIC study has both cohort and community surveillance components and was designed to investigate the etiology and natural history of atherosclerosis, the etiology of clinical atherosclerotic disease and differences in cardiovascular risk factors, medical care and disease by race, sex, location and date.<sup>176,177</sup>

### **8.2 ATHEROSCLEROSIS RISK IN COMMUNITIES SURVEILLANCE COMPONENT**

#### **8.2.1 STUDY OBJECTIVES**

The community surveillance component of ARIC was designed to provide knowledge about the burden of and trends in CHD morbidity and mortality in four US communities. The specific objectives of the community surveillance component are to estimate CHD incidence, case fatality and mortality using standardized criteria and methods and to elucidate the availability and use of medical care in four US communities.<sup>177</sup>

## **8.2.2 STUDY DESIGN AND POPULATION**

Continuous retrospective surveillance of hospitalized acute MI and in- or out-of hospital death due to CHD was initiated in 1987 in the four ARIC communities. Hospitalized MI and deaths due to CHD in residents of the ARIC communities age 35 – 74 years were eligible for inclusion;<sup>177</sup> beginning in 2005 residents aged 75 – 84 years were eligible. Community boundaries were defined by county lines in Forsyth County, NC, and Washington County, MD, and by metropolitan boundaries in Jackson, MS, and the suburbs of Minneapolis, MN.<sup>177</sup> In order to calculate rates, age, sex and race-specific population estimates were calculated from U.S. censuses; in 1987 the total population of each community was as follows: Forsyth County, NC, 108,815 (22,236 black), Jackson, MS, 71,000 (30,398 black), suburbs of Minneapolis, MN, 85,134 and Washington County, MD, 50,631.<sup>177</sup>

## **8.2.3 DATA COLLECTION**

Fatal CHD events in Forsyth County, NC, Jackson, MS, and the suburbs of Minneapolis, MN, were identified monthly from state vital statistics files containing a list of deaths and the corresponding death certificates that met age, residence and cause of death eligibility criteria. State nosologists used the rules of the ICD-9 to code the cause of death and the underlying cause of death was assigned by the Automated Classification of Medical Entities (ACME). In Washington County, MD, death certificates were obtained directly from the county health department and the ACME underlying cause of death was determined in conjunction with the National Center for Health Statistics. A systematic

sampling fraction was used to reduce the number of abstracted death certificates that did not lead to a valid CHD death. Deaths that occurred out of the state of residence or within the state of residence but at a hospital not part of the community catchment area were not captured. Death certificates were reviewed by trained abstractors and classified into one of five categories.<sup>177</sup>

Hospitalized MIs were ascertained through annual lists of selected discharge diagnosis codes from hospitals located within the ARIC community and those outside the community where six or more community residents had deaths coded as ICD-9 410 – 414 in 1984 – 1985. The hospital list of discharge diagnosis codes also included information on age, date of birth, address, zip code, vital status at discharge and date of discharge that were used to determine study eligibility. All hospitalizations that met eligibility criteria and had an ICD-9 discharge diagnosis for MI (410.x) were abstracted. A sample of discharge codes potentially related to CHD was abstracted. Sampling probabilities were adjusted periodically and differed by sex, race, field center and discharge code group.<sup>178,179</sup> Trained and certified abstractors reviewed hospital records for cases meeting age, residence and discharge diagnosis code eligibility and recorded clinical data onto standardized collection forms. Data included presenting symptoms, including chest pain, history of CVD, timing and onset of symptoms, medications on admission, during hospitalization or at discharge, diagnostic and therapeutic procedures, cardiac enzyme levels and ECGs. A computerized diagnostic algorithm was applied to each hospitalization and classified the event into one of four categories: definite, probable,

suspect or no MI.<sup>177</sup> Additionally, the ARIC Mortality and Morbidity Classification Committee adjudicated MI diagnoses.<sup>177</sup>

#### **8.2.4 ATRIAL FIBRILLATION ASCERTAINMENT**

Presence of AF during the MI hospitalization was identified by the presence of AF ICD-9 hospital discharge diagnosis codes of 427.3x in any position. The ARIC Mortality and Morbidity Classification Committee did not adjudicate AF diagnosis. Validity of ICD codes for the identification of AF has been described elsewhere.<sup>180</sup>

### **8.3 ATHEROSCLEROSIS RISK IN COMMUNITIES COHORT COMPONENT**

#### **8.3.1 STUDY OBJECTIVES**

The cohort component of the ARIC Study was designed to identify characteristics associated with the development and progression of clinical atherosclerosis as measured by carotid B-mode ultrasonography, to identify risk factors associated with incident atherosclerotic events and to measure variation in risk factors over time.<sup>177</sup>

#### **8.3.2 STUDY DESIGN AND POPULATION**

The ARIC Study recruited a prospective cohort of white and black adults between 45 and 64 years of age at baseline, 1987 – 1989, from four U.S. communities: Forsyth County, NC, the city of Jackson, MS, eight northwest suburbs of Minneapolis, MN, and

Washington County, MD.<sup>176</sup> Approximately 4,000 participants were selected from each community using community specific probability sampling; households were identified by area sampling in Forsyth County, NC, driver's licenses or state identification cards were used in Jackson, MS, eligibility for jury duty (with driver's license, voter registration cards or identification cards) were applied in Minneapolis, MN, and driver's licenses or inclusion in a 1975 private county health census were utilized in Washington County, MD. Regardless of the community, all age-eligible residents of an identified household were selected as potential participants. Only blacks were recruited from the city of Jackson, MS; the other sites included both whites and blacks although < 5% of the population in Minneapolis, MN, and Washington County, MD, were black. A total of 15,792 participants enrolled at baseline (8710 women, 4314 blacks). Participants had a clinical exam at baseline and were reexamined every three years, 1990-92, 1993-95 and 1996-98. The response rates for visits 2 (1990 – 1992), 3 (1993 – 1995) and 4 (1996 – 1998) were 93%, 86% and 81%, respectively. A fifth follow-up clinical exam started in May 2011 and was completed in 2013. Annual telephone calls are used to maintain contact with participants and identify medical events and death.<sup>176</sup> Follow-up is complete through December 31, 2010.

### **8.3.3 DATA COLLECTION**

Between 1987 and 1989 baseline data were collected; the baseline exam consisted of a home interview comprised of questionnaires about cardiovascular risk factors, socioeconomic status, and family medical history as well as a clinical examination. The

baseline clinical exam and each of the three triennial follow-up exams consisted of anthropometry, sitting blood pressure, venipuncture, ECG, ultrasound, physical exam and interviewer-administered questionnaires on medical history, health behaviors (alcohol and tobacco use) and social characteristics. Additional data were collected at some exams; for example, interview-administered questionnaires on physical activity and diet were conducted at baseline and exam 3 while pulmonary function was measured at baseline and exam 2. In addition, annual telephone calls continue to maintain contact with participants and to identify any cardiovascular events, hospitalizations and death. It is of particular important to this proposal that only the baseline ECG included a two-minute rhythm strip. Each center's institution review board approved the study and all participants provided written informed consent.<sup>176</sup>

#### **8.3.4 MEDICARE LINKAGE**

The ARIC study has an Interagency Agreement with the Centers for Medicare and Medicaid Services (CMS) to obtain Medicare data on ARIC cohort participants. The Collaborative Studies Coordinating Center provides ARIC participants' social security number, sex, and date of birth to Medicare and by referencing this information ARIC participants are linked to CMS data. Of the 15,738 ARIC participants alive as of January 1, 1991, 14,530 (92.3%) were matched successfully and linked to CMS Medicare claims. Matched participants are linked to the following Medicare files: the Master Beneficiary Summary File, Medicare Provider Analysis and Review (MedPAR), Carrier, Outpatient and Prescription Drug Event (PDE). The Master Beneficiary Summary File contains four

segments: the beneficiary summary file, chronic conditions, cost and utilization and National Death Index information. The MedPAR file contains claims for inpatient services covered under Medicare Part A. The outpatient files contain claims for services covered under Medicare Part B, including institutional claims (Outpatient file) for outpatient services and noninstitutional physician claims (Carrier file). The PDE file contains information on outpatient prescription drugs. CMS claims for inpatient and outpatient services have been available for research since 1991, while prescription drug information has been available since 2006 when Part D commenced. ARIC has enrollment, inpatient and outpatient claims data from 1991 through 2010 and prescription drug information from 2006 through 2010. The annual beneficiary summary file identifies Medicare enrollment periods for Parts A, B, C and D for ARIC participants.

Analyses for Manuscript 2, Part 10.0, and Manuscript 3, Part 11.0, will be restricted to ARIC participants who enrolled in fee-for-service (FFS) Medicare, both Parts A and B, because Medicare Advantage plans are not required to submit claims for their beneficiaries and incomplete claims data are available for those enrolled in only Part A.

### **8.3.5 ATRIAL FIBRILLATION ASCERTAINMENT**

Utilizing ARIC data, prevalent AF was identified by baseline ECG. Incident AF was identified by ECG during follow-up study visits, hospital discharge codes and death certificates.<sup>7</sup>



Standard supine 12-lead resting ECGs were recorded at least one hour after consumption of caffeine or tobacco and transmitted to the ARIC ECG Reading Center for coding and interpretation. The baseline ECG had a two-minute rhythm strip and subsequent ECGs had a 10-second reading. ECGs automatically coded as AF were visually checked by a trained cardiologist to confirm the diagnosis.<sup>181</sup> All ECGs were recorded using MAC PC Personal Cardiographs (Marquette Electronics, Inc., Milwaukee, WI).

Hospitalizations were identified by annual telephone calls to participants and through surveillance of local hospital discharges in each of the ARIC communities.<sup>176,177</sup> A hospital discharge code, ICD-9 code of 427.3, 427.31 or 427.32, in any position, indicates AF.

AF was identified through death certificates with an ICD-10 code I48 or ICD-9 code 427.3x as the underlying cause of death. The AF incidence date was defined as the first documented occurrence of AF on ECG, hospital discharge diagnosis or death certificate. In ARIC, two analyses were performed to determine the validity of the diagnosis of incident AF based on hospital discharge diagnosis codes.<sup>7</sup> First, a sample of 125 hospital discharge summaries with a first ICD-9 code for AF and ECGs performed during that hospitalization were reviewed by a study physician; the positive predictive value (PPV) for AF was 89% and for incident AF was 62%.<sup>7</sup> Second, a trained abstractor used information routinely collected for stroke ascertainment to complete a form with data from the complete medical record. The form includes information on the presence of AF during four weeks prior to the stroke hospitalization. Of 161 participants with AF

recorded in the stroke abstraction form, 135 had an ICD code for AF (sensitivity = 84%) and of 1385 participants without AF in the abstraction form, 34 had an ICD code for AF (specificity = 98%).<sup>7</sup> The sensitivity of using hospital discharge codes to identify AF was similar in the CHS; hospital discharge diagnoses codes (ICD-9 code of 427.3x) correctly identified 29 (70.7%) of the 41 participants with AF or AFL on at least one ECG.<sup>8</sup> A recent systematic review of algorithms used in administrative data to identify AF patients reported a median PPV of 89% (range: 70% - 96%) and a median sensitivity of 79% (range: 57% - 95%).<sup>180</sup>

Utilizing CMS data, incident AF was defined as an AF discharge diagnosis (ICD-9 code 427.3, 427.31 or 427.32), in any position, on a single inpatient (MedPAR) claim or as a diagnostic code on two outpatient claims within 7 – 365 days. A minimum of two outpatient claims at least 7 days apart were required to reduce the likelihood of including “rule out” diagnoses and to improve algorithm specificity.<sup>27,182,183</sup> Additionally, requiring at least two outpatient or physician claims can be used to define the presence of chronic disease in Medicare claims data.<sup>184</sup> The incidence date of AF was defined as the discharge date for a MedPAR short-stay claim or the date of the second qualifying outpatient claim, whichever occurred earlier. Secondary CMS definitions of AF were restricted to only MedPAR claims criteria and only outpatient claims criteria.

## **9.0 MANUSCRIPT 1 – TEMPORAL TRENDS IN THE OCCURRENCE AND OUTCOMES OF ATRIAL FIBRILLATION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION: THE ATHEROSCLEROSIS RISK IN COMMUNITIES SURVEILLANCE STUDY**

### **9.1 OVERVIEW**

**Background:** AF frequently coexists in the setting of MI, being associated with increased mortality. Nonetheless, temporal trends in the occurrence of AF complicating MI and in the prognosis of these patients are not well described. We examined temporal trends in prevalence of AF in the setting of MI and the impact of AF on prognosis in the community.

**Methods and Results:** We studied a population-based sample of 20,049 validated first incident nonfatal hospitalized MIs among 35- to 74-year old residents of four communities in the ARIC Study from 1987 through 2009. Prevalence of AF in the setting of MI increased during the 23-year study period, from 11% to 15% (multivariable adjusted OR for prevalent AF: 1.11 (95% CI: 1.04 – 1.19) per five-year increment). Overall, in patients with MI AF was associated with increased 1-year mortality (OR 1.47, 95% CI 1.07-2.01), compared to those with no AF. However, there was no evidence that the impact of AF on MI survival changed over time or differed over time by sex, race or MI classification (all p-values > 0.10).

**Conclusions:** Co-occurrence of AF in MI slightly increased between 1987 and 2009. The adverse impact of AF on survival in the setting of MI was consistent throughout. In the

setting of MI, co-occurrence of AF should be viewed as a critical clinical event, and treatment needs unique to this population should be explored further.

## 9.2 INTRODUCTION

Despite the significant decline in the incidence rate of MI since the end of the 20<sup>th</sup> century,<sup>185-187</sup> the estimated annual incidence of MI in the US remains high at 525,000 cases.<sup>31</sup> AF, the most common sustained cardiac arrhythmia, often coexists with MI.<sup>166</sup> A recent systematic review and meta-analysis reported that among MI patients approximately one in 10 had concomitant AF.<sup>23</sup> The presence of AF was associated with a significantly increased risk of death among MI patients; the pooled mortality OR associated with AF was 1.46 (95% CI: 1.35 – 1.58).<sup>23</sup>

Notwithstanding the frequent co-occurrence of AF with MI and the adverse impact on survival, little is known about the temporal trends related to the association of AF with prognosis of MI patients. In the Worcester Heart Attack Study, from 1990 through 2005, the mortality rate in-hospital, at 30-days and at 1-year post-discharge, was significantly higher among MI patients who developed AF compared to those who did not, after controlling for potential confounders.<sup>168</sup> In-hospital mortality among MI patients without AF decreased steadily from 1990 to 2005 (12.8% in 1990 to 5.9% in 2005), but decreased only slightly among those with AF (24.6% in 1990 to 21.3% in 2005).<sup>168</sup> Among patients hospitalized with incident MI from 1983 through 2007, in Olmsted County, MN, concomitant AF, regardless of its timing, was associated with an increased risk of death (unadjusted HR: 3.77; 95% CI: 3.37 – 4.21).<sup>22</sup> There was no

evidence of a clinically meaningful improvement in survival during the study period among those with coexisting AF and MI.<sup>22,168</sup>

Understanding temporal trends in the occurrence and outcomes of AF in the setting of MI is important given the common co-occurrence of these conditions. Better understanding of the temporal trends could facilitate identification of a more vulnerable population or of unmet treatment needs. Prior studies, which examined trends in coexisting AF with MI, were relatively small and lacked precision in trend analyses.<sup>22,168</sup> In addition, the previous epidemiologic studies on prognosis of patients with co-occurring AF and MI have been conducted in predominately white communities, which is a limitation because the decline in incidence and mortality rates for MI have been slower among blacks compared to whites, especially among men,<sup>185</sup> and blacks have a lower risk of AF compared to whites.<sup>7</sup>

We sought to address the lack of precision in trend analyses and the scarce data in nonwhite populations utilizing a large community-based biracial study for our analyses. Our aims were to estimate the prevalence of AF in the setting of MI over time as well as by sex, race and MI classification; to describe the impact of AF on mortality; and to assess the temporal trends in mortality among MI patients with and without concomitant AF overall and among subgroups defined by sex, race and MI classification.

### **9.3 METHODS**

#### **Study population / data source**

The community surveillance component of the ARIC Study, described previously, was designed to provide knowledge about the burden of and trends in CHD morbidity and mortality in four US communities.<sup>176,177</sup> Briefly, since 1987, the ARIC Study has conducted continuous surveillance of hospitalized nonfatal MIs and in- and out-of-hospital deaths due to CHD among residents aged 35 – 74 in the four ARIC communities: Forsyth County, North Carolina; Jackson, Mississippi; northwest suburbs of Minneapolis, Minnesota; and Washington County, Maryland.

Hospitalized MIs were ascertained through annual electronic discharge lists from all hospitals serving the ARIC Study communities. Trained abstractors reviewed hospital records randomly sampled from annual discharge lists from each hospital on the basis of age, residence, and ICD-9 discharge diagnosis codes, including 402, 410 – 414, 427, 428 and 518.4, for possible events. Sampling probabilities differed by sex, race, field center and discharge code group and periodically were adjusted.<sup>178,179</sup> Hospitalizations for community residents that occurred outside the study catchment area were not included unless the patients were transferred to and discharged from a hospital within the surveillance area. The following clinical information is abstracted from hospital records onto standardized forms: demographic characteristics; presenting symptoms, including presence of chest pain; timing of symptom onset; history of MI or other cardiovascular-related conditions; medications during hospitalization or at discharge; cardiac biomarkers (total creatinine phosphokinase [CK], CKMB, lactate dehydrogenase, and troponin); diagnostic and therapeutic procedures; and up to three copies of 12-lead ECGs were sent

to the Electrocardiographic Reading Center at the University of Minnesota for classification according to the Minnesota code.<sup>188</sup>

### **MI Classification**

A standardized computerized diagnostic algorithm, based on cardiac pain, ECG characteristics, and cardiac biomarkers, was applied to each sampled hospitalization and provided the computer diagnosis as definite, probable, suspect, or no MI.<sup>177</sup> Criteria for each of the three algorithm elements remained constant throughout the study period, details of which have been described.<sup>178</sup> Physicians on the ARIC Mortality and Morbidity Classification Committee reviewed events with discordant classification between the computerized diagnosis and discharge diagnosis codes and determined the final classification.<sup>177</sup> Events with abnormal or equivocal biomarker levels were further classified, based on Minnesota-coded ECGs<sup>188</sup> and chest pain as ST-Elevation MI (STEMI) or non-ST-Elevation MI (NSTEMI). MI was defined as a first incident event if the patient's medical record either specified no history of MI or did not include a history of MI. Hospitalizations occurring within 28 days were combined and considered one event.

### **Definition of atrial fibrillation**

Presence of AF during the MI hospitalization was defined by the presence of AF ICD-9 hospital discharge diagnosis codes of 427.3x in any position. Validity of ICD codes for the identification of AF has been described elsewhere.<sup>180</sup> We did not distinguish between AF that started before vs. after MI.

### **All-cause mortality**

All-cause mortality, at 28-days and one-year, was determined by medical record review, state death records linkage, and linkage with the National Death Index. Deaths were classified based on the duration from date of hospital admission until date of death.

### **Assessment of covariates**

Patient characteristics, including age, sex, and race, were abstracted from medical records by trained and certified study staff as were data on cardiovascular-related comorbidities, including a history of hypertension, stroke and diabetes. Prescription medications at admission, during hospitalization or at discharge and procedures were classified as yes or no. New therapies have been introduced during the study period and the impact of these therapies was estimated beginning in the year for which complete treatment information was available: ACE or angiotensin II inhibitors, 1992; Antiplatelet agents other than aspirin, 1997; and lipid-lowering agents, 1999.

Adjustment for disease severity and clinical comorbidities was performed with a modified Predicting Risk of Death in Cardiac Disease Tool (PREDICT) score.<sup>189</sup> The PREDICT score, developed in a community-based study, utilizes information routinely collected during a hospitalization with MI, including cardiogenic shock, clinical history (cardiac events and procedures), age, severity of ECG changes, congestive HF, kidney function, and the Charlson Comorbidity Index, to determine mortality risk. Data on renal function has not always been collected in ARIC community surveillance, so a modified PREDICT score, ranging from 0 to 21, was used,<sup>190</sup> the modified score has been validated.<sup>191</sup>

### **Study sample**



Hospitalized non-fatal first incident definite and probable MIs were eligible for inclusion. Patients whose race was not white or black as well as nonwhites from the Minneapolis and Washington County field centers were excluded (n = 442) due to insufficient sample size. Patients with unknown mortality status at 28-days or one-year (n = 342) or with incomplete covariate data (n = 91) were also excluded.

### **Statistical analysis**

The temporal trend in prevalence of coexisting AF among MI patients was assessed with a logistic regression model using year (continuous) as the main independent variable adjusted for age (5-year groups), sex, a composite race and field center variable, number of ICD-9 diagnosis codes, MI classification (STEMI/NSTEMI/Unclassified) and severity (PREDICT). The impact of AF on survival overall and within subgroups defined by sex, race, and MI classification were assessed with logistic regression models adjusted for age, sex, race, field center, MI classification, number of ICD-9 codes, severity (PREDICT), presentation characteristics (first systolic blood pressure and first pulse), medications, and therapeutic procedures. Trends in the association of AF with one-year mortality among MI patients were examined with multivariable logistic regression models. Pre-specified 2-way multiplicative interactions of trends in prevalence and mortality with sex, race, and MI classification were examined. A  $p < 0.10$  was considered evidence of effect modification.

All analyses were weighted by the inverse of the sampling fraction and standard errors were computed with stratified random sample methodology to account for the complex sampling scheme, which was adjusted periodically to improve efficiency.<sup>178,179</sup>

All statistical analyses were performed using survey procedures in SAS (version 9.2; SAS Institute, Inc, Cary, NC).

#### **9.4 RESULTS**

Our final analytic sample included 13,155 definite and probable first incident MIs, for a weighted sample of 20,049. Baseline patient characteristics over time, in four-year intervals, are shown in Table 9.1. The age and sex distributions of the sample were stable over the study period, with an overall mean age of 59 years at the time of hospitalization; women accounted for 36 percent of the sample. The prevalence of AF accompanying MI increased slightly over the 23-year study period, from 11 percent during 1987—1990 to 15 percent during 2007—2009. The proportion of MIs classified as NSTEMI increased during the study period. The percent of patients receiving aspirin,  $\beta$  blockers, ACE or angiotensin II inhibitors, lipid-lowering medications, antiplatelet agents other than aspirin, or percutaneous coronary interventions, increased during the study period (Table 9.2).

The prevalence of coexisting AF in the setting of MI increased over the study period; the OR for concomitant AF and MI compared to MI without AF was 1.11 (95% CI: 1.04 – 1.19) per five-year increment, after adjustment for age group, sex, race, field center, MI classification, severity of MI and number of ICD-9 diagnosis codes. After adjustment there was no evidence that the time trend in prevalence of co-occurring AF and MI differed by sex ( $p$  for interaction = 0.43) or race ( $p$  for interaction = 0.69); however, there was evidence of a different AF time trend by MI classification ( $p$  for

interaction = 0.005) (Figure 9.1). The prevalence of AF in patients with NSTEMI or unclassified MI increased during the study period, while among STEMI patients the prevalence of AF decreased.

Overall, the presence (versus absence) of AF complicating MI was associated with more than a 2-fold increased odds of post-MI death at 28-days and one-year, after adjustment for age group, sex, race, field center and year (Table 9.3). After further adjustment for MI classification, number of ICD-9 diagnosis codes, presentation characteristics, medications and therapeutic procedures, the association between AF and 28-day mortality was attenuated, but the odds of one-year mortality were 1.47 times greater (95% CI: 1.07 – 2.01) among MI patients with AF compared to those without. This association did not differ by sex, race or MI classification.

Among those with AF and MI, there was no evidence of improved one-year survival over time: after adjustment for age, sex, race by field center, MI classification, number of ICD-9 codes, presentation characteristics, medications and therapeutic procedures, the OR for one-year mortality was 0.86 (95% CI: 0.60 – 1.21) per 5-year increment (Table 9.4). Conversely, among those without AF, the adjusted OR for one-year mortality was 0.74 (95% CI: 0.62 – 0.88) per 5-year increment of time. There was no statistical evidence that the trend in one-year MI survival differed for those with versus without AF (p for interaction = 0.45). The impact of AF on one-year mortality did not differ by sex, race or MI classification. Within strata defined by AF status as well as sex, race or MI classification, respectively, temporal trends in survival were similar; the

point estimates suggested improved survival among all strata, except men with AF, over the study period.

A sensitivity analysis, excluding those who had a cardiac operative procedure performed during the index hospitalization, was performed and results were consistent with the primary analysis.

## **9.5 DISCUSSION**

In this population-based sample of validated MI hospitalizations, the prevalence of concomitant AF in MI increased slightly from 1987 to 2009 and was approximately 15% in the most recent years. The secular trend in the prevalence of AF in the setting of MI differed by MI classification; the prevalence of coexisting AF increased over time among NSTEMI and unclassified MIs and decreased among STEMIs. Co-occurrence of AF in the setting of MI was associated with an increased risk of death and this association did not differ by sex, race or MI classification. Finally, improvements in 1-year survival among MI patients were greater in those without AF compared to those with AF, but this difference was not statistically significant.

The percent of patients with co-occurring AF increased over time among those with NSTEMI and unclassified MIs, while simultaneously decreasing among STEMIs. It is not surprising that AF was more common among NSTEMIs as these patients tend to be older and have more comorbidities.<sup>192-194</sup> However, we adjusted for age group, sex, race, field center, MI classification, severity of MI and number of ICD-9 diagnosis codes. This is not the first study to report an increasing prevalence of AF complicating NSTEMI; in

the Worcester Heart Attack Study, the adjusted OR of having AF in the setting of NSTEMI was 1.96 (95% CI: 1.38 – 2.79) in 2005 compared to 1997, while in STEMI the corresponding OR was 1.53 (95% CI: 0.97 – 2.44).<sup>186</sup> The reasons for this difference between STEMI and NSTEMI have not been fully elucidated. Potential explanations include that changes in patient characteristics over the study period led to more AF in NSTEMI than in STEMI patients, that changes in treatment strategies resulted in STEMI patients going directly to the catheterization lab for treatment and subsequently they were less likely to develop AF, or that AF impacts the ST segments on ECG which makes it more difficult to classify an event as STEMI in the presence of AF.

Regardless of the temporal trends, AF complicating MI is consistently associated with worse survival,<sup>22,23,29,166,168</sup> in a meta-analysis of 23 studies that provided multivariable adjusted analyses, the pooled mortality OR associated with AF in MI patients was 1.46 (95% CI 1.35 – 1.58).<sup>23</sup> Our results are consistent with previous studies. Given the independent negative impact of AF on survival following MI, the occurrence of AF in MI should not be viewed as a minor event relative to more severe complications like ventricular tachycardia, but should be recognized as a critical condition. To date, prognostic risk scores for MI ignore AF in determining the risk of death and therapeutic decisions.<sup>195,196</sup> Further consideration of AF in prognostic scores is warranted, especially because prevalence of AF in the community is estimated to increase as the population ages,<sup>2,3</sup> and because AF often complicates MI.<sup>23,166</sup>

Moreover, patients with AF complicating MI have unique treatment needs that are not fully understood. Aspirin is a cornerstone of acute MI therapy and dual antiplatelet

therapy (aspirin and clopidogrel) is considered the gold standard following percutaneous coronary intervention.<sup>197</sup> However, the combination of oral anti-coagulants and antiplatelets is associated with a high frequency of major bleeding.<sup>198</sup> Thus, the optimal treatment strategy is unclear when the risks of thromboembolism and bleeding are considered. The introduction of new oral anticoagulant agents, including dabigatran, rivaroxaban, and apixaban, for the prevention of thromboembolic complications in AF as well as for the treatment of acute coronary syndromes raise additional questions about the optimal treatment strategy.<sup>199,200</sup>

There are several limitations of this study. The diagnosis of AF relied on ICD-9 hospital discharge codes and is not otherwise adjudicated. Nonetheless, this method has been found to have acceptable validity within the cohort component of the ARIC Study, which uses identical methods to ascertain hospitalized AF events; in a sample of 125 hospital discharge summaries with a first ICD-9 code for AF, 89% were confirmed based on ECGs performed during that hospitalization.<sup>7</sup> Temporal trends in co-occurrence of AF and MI are based on the proportion of MIs in a given time with documented AF. It is possible that the trends would change if this analysis were based on rates of co-occurrence, which would scale the results to account for changes in the size of the population. The onset of AF was unknown and we included both AF occurring before and during the MI hospitalization. However, in a prior study the occurrence of AF before or after MI was associated with an increase in mortality over no AF in MI patients.<sup>22</sup> In our study, patients who developed AF after hospital discharge were not identified and would be misclassified. Nevertheless, there is a positive association between time from

incident MI to first-detected AF and risk of death;<sup>22</sup> consequently, our reported association likely was underestimated. Coding practices likely have changed over time. In an effort to account for these changes, analyses were adjusted for the number of ICD-9 codes.

In conclusion, this study provides evidence that the co-occurrence of AF in the setting of MI has increased over time. The presence of AF was consistently associated with worse survival after MI throughout the study. The results highlight that temporal trends in MI survival in those with AF have been similar among groups defined by sex, race and MI classification.

## 9.6 TABLES

**Table 9.1: Baseline characteristics of patients hospitalized with incident definite or probable myocardial infarction by event year groups in the Community Surveillance component of the Atherosclerosis Risk in Communities Study, 1987 – 2009**

	1987 - 1990 (n = 3330)	1991 - 1994 (n = 3735)	1995 - 1998 (n = 3770)	1999 - 2002 (n = 3501)	2003 - 2006 (n = 3215)	2007- 2009 (n = 2499)
Age, years	59.8	59.9	59.6	59.0	58.9	58.8
Female, %	1140 (34)	1313 (35)	1380 (37)	1276 (36)	1144 (36)	955 (38)
Community and race groups, %						
Forsyth County, NC blacks	271 (8)	325 (9)	459 (12)	364 (10)	369 (11)	420 (17)
Forsyth County, NC whites	966 (29)	1124 (30)	1174 (31)	975 (28)	899 (28)	763 (31)
Jackson, MS blacks	286 (9)	388 (10)	432 (11)	579 (17)	582 (18)	397 (16)
Jackson, MS whites	496 (15)	537 (14)	367 (10)	289 (8)	181 (6)	151 (6)
Minneapolis, MN whites	701 (21)	724 (19)	668 (18)	743 (21)	749 (23)	433 (17)
Washington County, MD whites	610 (18)	637 (17)	670 (18)	551 (16)	435 (14)	336 (13)
Comorbidities, %						
Hypertension	1807 (54)	2138 (57)	2215 (59)	2240 (64)	2053 (64)	1855 (74)
Stroke	155 (5)	259 (7)	301 (8)	280 (8)	219 (7)	198 (8)
Diabetes	--	641 (17)	1076 (29)	1043 (30)	1139 (35)	946 (38)
PREDICT score*	6.2	6.5	6.5	5.7	5.7	6.8
Presentation characteristics						
Hospital arrival < 2 hours, %	995 (30)	1113 (30)	1143 (30)	1064 (30)	798 (25)	623 (25)



First systolic blood pressure, mm Hg	144.2	148.3	147.4	149.2	145.5	148.0
First pulse rate, bpm	84.1	85.3	85.8	86.9	87.6	89.5
Atrial fibrillation, %	351 (11)	489 (13)	513 (14)	471 (13)	527 (16)	366 (15)
Myocardial infarction classification						
ST-elevation myocardial infarction	793 (24)	1071 (29)	1038 (28)	689 (20)	512 (16)	517 (21)
Non ST-elevation myocardial infarction	2214 (66)	2157 (58)	2221 (59)	2373 (68)	2326 (72)	1789 (72)
Unclassified	323 (10)	506 (14)	510 (14)	438 (13)	377 (12)	194 (8)

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Continuous variables presented as mean

Categorical variables presented as count (%)

History of diabetes not routinely collected until 1991 (29) / 1992 (270)

\*Modified PREDICT score did not include kidney function

Hospital arrival < 2 hours was determined based on duration from earliest symptom onset time to hospital arrival time

**Table 9.2: Medication\* and therapeutic procedures during hospitalization with incident definite or probable myocardial infarction by event year groups in the Community Surveillance component of the Atherosclerosis Risk in Communities Study, 1987 – 2009**

	1987 - 1990 (n = 3330)	1991 - 1994 (n = 3735)	1995 - 1998 (n = 3770)	1999 - 2002 (n = 3501)	2003 - 2006 (n = 3215)	2007- 2009 (n = 2499)
Medication, %						
Aspirin	2251 (68)	3233 (87)	3358 (89)	3173 (91)	2846 (89)	2280 (91)
β blockers	1549 (47)	2252 (60)	2671 (71)	2832 (81)	2796 (87)	2236 (89)
Calcium channel blockers	2151 (65)	2197 (59)	1497 (40)	852 (24)	702 (22)	634 (25)
ACE or angiotensin II inhibitors	--	664 (18)	1724 (46)	2162 (62)	2115 (66)	1624 (65)
Warfarin	302 (9)	545 (15)	635 (17)	476 (14)	430 (13)	338 (14)
Lipid-lowering medications	--	--	248 (7)	2047 (58)	2284 (71)	1829 (73)
Antiplatelet agents other than aspirin	--	--	823 (22)	1992 (57)	2011 (63)	1504 (60)
Procedures, %						
Thrombolytic agents	737 (22)	998 (27)	708 (19)	366 (10)	52 (2)	52 (2)
PCI	538 (16)	855 (23)	999 (27)	1202 (34)	1325 (41)	1020 (41)
CABG	466 (14)	478 (13)	577 (15)	438 (13)	301 (9)	189 (8)

\*On admission, during hospitalization, or at discharge

Thrombolytic agents include intracoronary and intravenous

The following medications were not routinely collected until the year indicated in parentheses: ACE or angiotensin II inhibitors (1992), antiplatelet agents other than aspirin (1997) and lipid-lowering agents (1999)

**Table 9.3: Odds ratios for 28-day and one-year all-cause mortality comparing patients with versus without atrial fibrillation in the setting of hospitalized incident definite or probable myocardial infarction in the Community Surveillance component of the Atherosclerosis Risk in Communities Study, 1987 – 2009**

	28-Day Mortality	One-Year Mortality
	OR* (95% CI)	OR (95% CI)
Number of deaths, (%)	204 (1.0)	1431 (7.1)
Model 1: Age, sex, race, field center and year	2.23 (1.13 - 4.42)	2.15 (1.63 - 2.83)
Model 2: Model 1 + MI classification <sup>†</sup> and # ICD-9	2.13 (1.06 - 4.29)	1.93 (1.45 - 2.58)
Model 3: Model 2 + presentation characteristics	1.92 (0.92 - 4.02)	1.72 (1.26 - 2.35)
Model 4: Model 3 + Medication	2.20 (0.97 - 4.99)	1.55 (1.12 - 2.12)
Model 5: Model 3 + therapeutic procedures	1.71 (0.84 - 3.49)	1.56 (1.15 - 2.12)
Model 6: Model 2 + presentation characteristics, medications and procedures	2.10 (0.94 - 4.70)	1.47 (1.07 – 2.01)

\*OR = odds ratio; Comparison of co-occurring atrial fibrillation and myocardial infarction (MI) to MI

<sup>†</sup>MI classification = ST-Elevation MI, non ST-Elevation MI and unclassified

Presentation characteristics = first systolic blood pressure, first pulse and the modified PREDICT score

Medications = aspirin,  $\beta$  blockers, Calcium channel blockers, ACE or angiotensin II inhibitors, warfarin, lipid-lowering medications and antiplatelet agents other than aspirin

Therapeutic procedures = percutaneous coronary intervention and coronary artery bypass graft

**Table 9.4: Temporal trends in 1-year all-cause mortality stratified by atrial fibrillation status among those hospitalized with incident definite or probable myocardial infarction in the Community Surveillance component of the Atherosclerosis Risk in Communities Study, 1987 – 2009. Results presented as odds ratios (OR)\* of mortality per 5-year increment**

	Atrial Fibrillation			No Atrial Fibrillation		
	n / N	OR per 5-year Increment	Interaction p-value (subgroup*year)	n / N	OR per 5-year Increment	Interaction p-value (subgroup*year)
Overall	367 / 2717	0.86 (0.60 - 1.21)	--	1063 / 17332	0.74 (0.62 - 0.88)	--
Men	229 / 1731	1.05 (0.64 - 1.70)	0.32	630 / 11110	0.72 (0.57 - 0.92)	0.21
Women	139 / 986	0.71 (0.43 - 1.19)		433 / 6222	0.82 (0.63 - 1.06)	
Whites	249 / 2140	0.98 (0.68 - 1.41)	0.33	621 / 13036	0.84 (0.66 - 1.05)	0.40
Blacks	119 / 577	0.79 (0.42 - 1.45)		442 / 4296	0.63 (0.48 - 0.82)	
STEMI	45 / 391	0.68 (0.32 - 1.44)	0.63	173 / 4228	0.71 (0.50 - 1.00)	0.13
NSTEMI	245 / 1945	0.84 (0.57 - 1.24)		726 / 11136	0.73 (0.58 - 0.90)	
Unclassified	77 / 381	0.68 (0.32 - 1.44)		165 / 1968	0.59 (0.35 - 1.00)	

Overall, there was no statistical evidence that one-year survival over time differed between those with or without AF (p for interaction = 0.45)

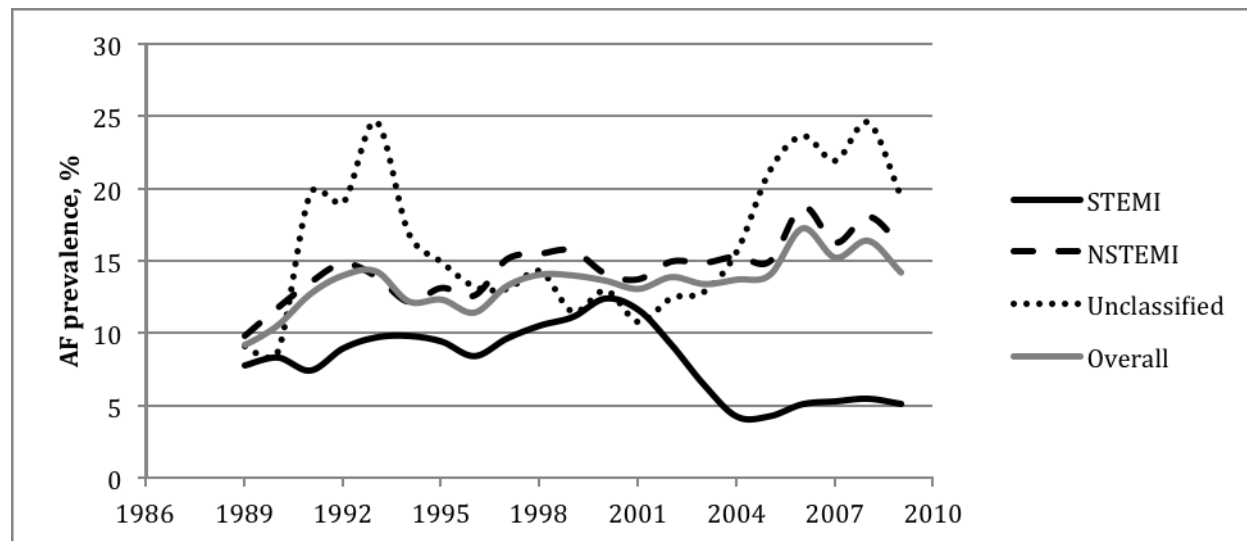
AF = atrial fibrillation

\*Adjusted for age, sex, race, field center, MI classification (STEMI/NSTEMI/Unclassified), number of ICD-9 codes, presentation characteristics (first systolic blood pressure, first pulse and MI severity), medications (aspirin,  $\beta$  blockers, Calcium channel blockers,

ACE or angiotensin II inhibitors, warfarin, lipid-lowering medications and antiplatelet agents other than aspirin), and therapeutic procedures (percutaneous coronary intervention and coronary artery bypass graft)

## 9.7 FIGURES

**Figure 9.1: Three-year mean AF prevalence in hospitalizations with incident definite or probable myocardial infarction overall and by subtypes (ST-Elevation myocardial infarction, non-ST-Elevation myocardial infarction, and unclassified) in the Community Surveillance component of the Atherosclerosis Risk in Communities Study, 1987 – 2009**



## **10.0 MANUSCRIPT 2 – ASCERTAINMENT OF NEWLY-DIAGNOSED ATRIAL FIBRILLATION USING ACTIVE COHORT FOLLOW-UP VERSUS SURVEILLANCE OF CENTERS FOR MEDICARE AND MEDICAID SERVICES IN THE ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY**

### **10.1 OVERVIEW**

**Background:** Increasingly, epidemiologic studies use administrative data to identify AF. Capture of *incident* AF is not well documented. We examined incidence rates and concordance of AF diagnosis based on active cohort follow-up versus surveillance of CMS data in the ARIC study.

**Methods and Results:** ARIC cohort participants without prevalent AF enrolled in FFS Medicare, Parts A and B, for at least 12 continuous months between 1991 and 2009 were included. In ARIC cohort follow-up, annual telephone calls captured hospitalizations and deaths with incident AF diagnosis codes. For CMS claims, incident AF was defined by billed inpatient and outpatient diagnoses. Of 10,134 eligible participants, 738 developed AF according to both ARIC and CMS; an additional 93 and 288 incident cases were identified using only ARIC and CMS data, respectively. Incidence rates per 1,000 person-years were 10.8 (95% CI: 10.1–11.6) and 13.6 (95% CI: 12.8–14.4) in ARIC and CMS, respectively; agreement was 96%; the kappa statistic was 0.77 (95% CI: 0.75–0.80). Yet, the additional CMS events did not alter observed associations between risk factors and AF.

**Conclusions:** Among those enrolled in FFS Medicare, AF incidence rates were slightly lower via active cohort follow-up versus CMS surveillance, because the latter included outpatient AF. Concordance of incident AF was high and associations without CMS were not biased. Drawbacks of CMS are its inapplicability to those <65 years and inability to capture AF for those with Medicare Advantage.

## 10.2 INTRODUCTION

Increasingly, administrative data are used for research purposes, including epidemiologic studies to identify patients with CVDs<sup>201-205</sup> such as AF.<sup>27</sup> The ability to efficiently and inexpensively access information on a large number of people makes administrative claims an appealing source of outcomes for epidemiologic research. However, the usefulness of this approach varies by numerous factors, including the disease algorithm chosen and the population studied. Medicare data are often used but are limited to those  $\geq 65$  and not having supplemental health maintenance organization (HMO) coverage. High-performing algorithms have been developed to identify major CVDs.<sup>201-205</sup> A recent systematic review of algorithms used to identify AF in administrative data, compared most often to medical records or physician review of records, reported a median PPV of 89% (range: 70% - 96%) and a median sensitivity of 79% (range: 57% - 95%).<sup>180</sup>

Despite performance measures that indicate that administrative data could be a promising source for identifying AF patients, gaps exist concerning the appropriateness of this approach. A systematic review of 16 unique studies found that only one examined



the ability of administrative data to identify *incident* AF. In this single study, a physician reviewed a sample of 125 hospital discharge summaries with a first ICD-9 code for AF and ECGs performed during that hospitalization to determine the validity of using hospital discharge codes; the PPV for any AF was 89% and for incident AF was 62%.<sup>7</sup> Additionally, no study has compared the incidence or prevalence of AF using only inpatient or only outpatient claims compared to using both inpatient and outpatient claims. An important limitation of some cohort studies, including the ARIC and CHS cohorts, is reliance exclusively on inpatient claims to identify AF,<sup>7,8</sup> which could result in under-ascertainment of AF. Furthermore, the majority of studies were performed in predominately white populations. The validity of utilizing administrative data also may vary by race/ethnicity, as one study performed a subgroup analysis among stroke patients and reported a lower sensitivity of AF ascertainment from ICD-9 codes compared to medical record review for blacks compared to whites.<sup>7</sup>

In the present study we sought to address the limited knowledge regarding the usefulness of administrative data to determine AF incidence, the lack of inpatient and outpatient claims comparison, and the paucity of data in nonwhite populations. We compared overall and race-specific incidence rates of AF using the active ARIC cohort follow-up method with surveillance of CMS administrative Medicare claims data (inpatient only, outpatient only and both inpatient and outpatient claims). Additionally, we assessed concordance of AF diagnosis between the data sources and performed a descriptive analysis to identify factors associated with earlier diagnosis as well as concordance.

## **10.3 METHODS**

### **Data sources**

The ARIC study is a population-based prospective study of CVD in a predominantly biracial cohort of 15,792 participants between 45 and 64 years of age at enrollment.<sup>176</sup> From 1987 – 1989, participants were sampled from four US communities: Forsyth County, North Carolina; Jackson, Mississippi; northwest suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Additional study exams occurred during three follow-up visits as well as annual telephone contact to obtain information about all hospitalizations and vital status, details of which have been reported previously.<sup>7</sup>

The ARIC study has an Interagency Agreement with the CMS to obtain Medicare data for ARIC cohort participants. Participants are matched on social security number, sex, and date of birth. Of the 15,738 ARIC participants alive as of January 1, 1991, 14,530 (92.3%) were matched successfully and linked to CMS Medicare claims. Matched participants are linked to inpatient, outpatient, and carrier files. The MedPAR file contains claims for inpatient services covered under Medicare Part A. The outpatient files contain claims for services covered under Medicare Part B, including institutional claims (Outpatient file) for outpatient services and noninstitutional physician claims (Carrier file). CMS claims for inpatient and outpatient services have been available for research since 1991.

### **Study sample**

For this analysis, ARIC cohort participants enrolled in FFS Medicare, both Parts A and B, for at least 12 continuous months between January 1, 1991, and December 31, 2009, were eligible for inclusion (Figure 10. 1). Enrollment in FFS Medicare was necessary because Medicare Advantage insurance plans are not required to submit claims for beneficiaries and those enrolled in only Part A are known to have incomplete claims data. Participants whose race was not white or black and nonwhites from the Minneapolis and Washington County field centers were excluded due to small numbers. Additionally, those at the initial ARIC study exam with missing or unreadable ECG or prevalent AF were excluded. Furthermore, because we are interested in incident AF and CMS data were available for research beginning January 1, 1991, participants diagnosed with AF based on ARIC data before January 1, 1992 were excluded. In order to ascertain incident diagnoses, participants with AF diagnosed during the first year of FFS enrollment, from either ARIC or CMS data, were excluded. Participants enrolled in Medicare due to disability or certain covered medical conditions were not included in the study unless they met eligibility criteria after becoming age eligible (aged  $\geq 65$  years). Each center's institutional review board approved the study and all participants provided informed consent.

### **Definition of atrial fibrillation**

Active ARIC cohort follow-up identifies AF cases through study visit ECGs, hospital discharge codes, and death certificates.<sup>7</sup> However, for this analysis, AF cases obtained exclusively from study ECGs (n=4) were not included as AF events due to their subclinical nature and to ensure consistent methods of ascertainment between data

sources. Incident cases of AF were ascertained through hospital discharge codes, ICD-9 codes 427.3, 427.31 or 427.32, in any position, and death certificates with ICD-10 code I48 or ICD-9 code 427.3x as the underlying cause of death. The date of AF incidence was defined as the date of first hospital discharge with an AF or AFL diagnosis, or death by AF, whichever occurred earlier.

For MedPAR and outpatient CMS claims, incident AF was defined as an AF discharge diagnosis (ICD-9 code 427.3, 427.31 or 427.32), in any position, on a single inpatient claim or as a diagnostic code on two outpatient claims within 7 – 365 days. A minimum of two outpatient claims at least 7 days apart were required to reduce the likelihood of including “rule out” diagnoses and to improve algorithm specificity.<sup>27,182</sup> The incidence date of AF was defined as the discharge date for a MedPAR short-stay claim or the date of the second qualifying outpatient claim, whichever occurred earlier. Secondary CMS definitions of AF were restricted to only MedPAR claims criteria and only outpatient claims criteria.

AF following cardiac operative procedures is fairly common.<sup>206</sup> Therefore, in both active cohort follow-up and surveillance of CMS, an AF diagnosis occurring simultaneously with cardiac revascularization (ICD-9 code 36.31, 36.1) or other cardiac surgery involving heart valves or septa (ICD-9 code 35.32, 35.33, 35.39, 35.95, 35.1X, 35.2X, 35.7X) during the index hospitalization, without a subsequent diagnosis of AF, was not considered an AF diagnosis.

### **Assessment of covariates**

During the baseline ARIC study exam, standardized methods were used to collect data on age, race, sex, educational achievement, cigarette smoking, ethanol consumption, height, weight, blood pressure, antihypertensive medication use, diabetes mellitus, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and previous myocardial infarction, HF or coronary heart disease.<sup>176</sup> An ECG Cornell voltage score  $>28$  mm in men or  $>22$  mm in women was considered evidence of left ventricular hypertrophy.<sup>207</sup>

### **Statistical analysis**

We calculated person-years of follow-up as the date of study eligibility, following 12 months of continuous enrollment in FFS Medicare without an AF diagnosis, to the date of AF diagnosis, death, loss to follow-up, cessation of FFS enrollment, or December 31, 2009, whichever occurred earliest. Person-years of follow-up were attributed to age- (5 year age groups), sex- and race- (whites and blacks) specific groups. Age-, sex- and race-specific rates were calculated dividing the number of incident AF cases by the corresponding person-years of follow-up. In addition, age- and sex-standardized rates of incident AF for whites and blacks separately were calculated using the sex and age (65–69 years, 70–74 years, 75–79 years and 80 years and older) person-time distribution of the eligible cohort.

Concordance of incident AF events between ARIC follow-up and CMS surveillance was assessed with Cohen’s Kappa (K) statistic, a chance-adjusted measure of agreement.<sup>208</sup> Due to inherent limitations of Kappa, percent agreement, overall, as well as

positive and negative agreement, were calculated to provide a more complete assessment of concordance.<sup>209-211</sup>

A descriptive analysis, restricted to participants with incident AF ascertained in both ARIC and CMS, and with complete covariate data, was performed to determine the mean difference in incident date. Subsequently, linear regression was used to determine predictors of earlier diagnosis. Additionally, log-binomial regression, restricted to participants with AF ascertained from at least one data source, ARIC or CMS, and with complete covariate data was used to identify demographic and clinical factors associated with concordance. Age, sex and a composite race and center variable were retained in the linear and log-binomial regression models regardless of statistical significance. Cox proportional hazards regression was used to determine the association between established risk factors and incident AF based exclusively on active ARIC cohort follow-up; subsequently, cases of incident AF ascertained only from surveillance of CMS data were included to determine the impact of these additional events on the associations. All statistical analyses were performed with SAS, version 9.2 (SAS Institute, Cary, NC).

#### **10.4 RESULTS**

Of the original 15,792 ARIC participants, our final analytic sample included 10,134 participants who were initially free of AF and enrolled in FFS for at least 12 continuous months between January 1, 1991 and December 31, 2009. It was notable that 18,194 person-years available to ARIC had to be omitted because those participants were in Medicare Advantage and therefore had incomplete CMS claims. To ensure

participants were free of AF, those diagnosed with AF within the first 12 continuous months of enrollment were excluded (Figure 10.1). A total of 831 incident AF diagnoses during 76,754 person-years of follow-up were ascertained from active ARIC follow-up. The corresponding figures from CMS surveillance were 1,026 (736 inpatient [MedPAR] and 827 outpatient) AF diagnoses during 75,596 (76,887 inpatient [MedPAR] and 76,293 outpatient) person-years of follow-up. Baseline characteristics of the study sample stratified by source of AF diagnosis are shown in Table 10.1. Overall, the mean age at baseline, date of study eligibility, was 66.4 years (standard deviation 1.5 years) and women accounted for slightly over half and blacks for a quarter of the study sample. Among AF diagnoses ascertained only by active ARIC follow-up, 32% were among blacks, while among those ascertained only in surveillance of CMS, 13% were among blacks. Participants with AF diagnosed from both data sources had a higher prevalence of prior MI and HF compared to those with AF ascertained from only one source.

AF incidence increased with age and was consistently higher among men and whites compared to women and blacks, respectively, regardless of the source of diagnosis (Figure 10.2). The age-, sex- and race-specific incidence rates were slightly higher based on CMS ascertainment of AF but followed a pattern similar to the rates based on active ARIC follow-up. Among participants with AF diagnosed in both data sources, 63% had identical dates of AF diagnosis from ARIC and CMS and nearly 75% had diagnoses within  $\pm 30$  days, based on a linear regression model with time between diagnosis dates in ARIC and CMS. Earlier ascertainment of AF by one system versus the other was not associated with any CVD risk factors, after accounting for sociodemographic factors.

After accounting for differences in the age and sex distribution of whites and blacks by standardizing the rates to the study sample (Table 10.2), the AF incidence rate based on ARIC ascertainment, per 1,000 person years, was 11.4 (95% CI: 10.5 – 12.2) and 8.6 (95% CI: 7.1 – 10.0) among whites and blacks, respectively. The comparable rates from CMS surveillance of AF were 14.8 (95% CI: 13.8 – 15.8) and 8.9 (95% CI: 7.5 – 10.4) for whites and blacks, respectively. Using secondary CMS definitions of AF, restricted to only inpatient (MedPAR) claims criteria, the age- and sex-standardized rate per 1,000 person-years among whites was 10.3 (95% CI: 9.5 – 11.1) and among blacks was 6.6 (95% CI: 5.3 – 7.8); restricted to only outpatient claims criteria, the corresponding rates were 12.1 (95% CI: 11.2 – 13.0) and 6.4 (95% CI: 5.1 – 7.6) for whites and blacks, respectively. Utilizing the secondary CMS definition of AF, restricted to only inpatient (MedPAR) claims criteria, among participants with AF diagnosed in both sources, 90% of participants had AF diagnosed on the same day and 93% were within  $\pm 30$  days. When considering only outpatient claims criteria for CMS surveillance of AF compared to active ARIC follow-up, among participants with AF diagnosed in both sources, 61% of AF diagnoses occurred earlier in ARIC (hospital discharge date) compared to outpatient CMS surveillance.

Cohen's K for overall concordance of incident AF diagnosis between ARIC cohort follow-up and CMS data was 0.77 (95% CI: 0.75 – 0.80) (Table 10.3). Comparing hospital inpatient ascertainment of AF, the primary method of AF detection in ARIC, the K statistic improved to 0.85 (95% CI: 0.83 – 0.87). Race-specific K statistics were similar to the overall sample estimates (data not shown) for all CMS and inpatient (MedPAR)



comparisons. However, the K statistic for active ARIC follow-up versus CMS outpatient surveillance was lower among blacks, 0.56 (95% CI: 0.48 – 0.63). After accounting for age, sex and race/center, a descriptive analysis did not identify any factors associated with concordance between data sources.

To explore the impact of including incident AF cases ascertained only in surveillance of CMS data, an analysis of the association between incident AF and the primary risk factors (age, male sex, white race, BMI, hypertension, diabetes, current smoking and prior heart disease) was performed. The HRs were very similar in a model based exclusively on active ARIC cohort follow-up methods compared to a model with the addition of incident AF ascertained from surveillance of CMS (Table 10.4) suggesting the omission of CMS ascertained (mostly outpatient) AF events does not bias the associations derived from active ARIC follow-up alone.

## **10.5 DISCUSSION**

In this community-based prospective study, incidence rates of AF were slightly lower based on active ARIC follow-up compared to CMS surveillance. The rates by either method followed a similar pattern, increasing with age and consistently higher among whites and men compared to blacks and women, respectively. Concordance of incident AF between ARIC cohort follow-up and CMS data was very good,<sup>208</sup> although 19% more AF cases were identified from CMS largely due to outpatient ascertainment of AF. Furthermore, there appeared to be little bias in associations based only on active ARIC follow-up versus surveillance including CMS. To our knowledge, this is the first

study to compare AF rates as well as concordance of diagnosis between data sources using only inpatient data, only outpatient data, and combined inpatient and outpatient data.<sup>180</sup>

Overall, reliance exclusively on active ARIC cohort follow-up identified 831 incident cases of AF while CMS surveillance yielded 1,026 incident AF events. Concordance between the two data sources was good with a K statistic of 0.77 (95% CI: 0.75 – 0.80). As would be expected, because active ARIC follow-up relies exclusively on inpatient claims to identify AF, concordance improved when comparing only inpatient data. However, discrepancies persisted between the two data sources. Potential reasons for the discrepancies include that, among the 63 ARIC participants with AF ascertained from inpatient (MedPAR) CMS data but not ARIC data, some participants stopped participating in annual telephone follow-up for the ARIC study but continued to be followed by the ARIC study for fatal events. As a result, ARIC would not be able to identify hospitalizations for these participants occurring outside of the geographic catchment area of the four ARIC communities. Possible reasons for divergence in the opposite direction--AF obtained in ARIC data but not in CMS data--include that the participant was admitted at a Veterans Affairs Hospital where CMS does not have access to the claims and that ARIC data captures up to 26 diagnosis and procedure codes while CMS MedPAR data only include 10 diagnosis and 6 procedure codes.

There are advantages and disadvantages of both active cohort follow-up and surveillance of CMS to identify incident AF. Advantages of utilizing active cohort follow-up include ascertainment of AF at younger ages (prior to Medicare eligibility) and

ability to identify AF regardless of type of insurance; disadvantages of this approach include missing outpatient diagnoses of AF and reliance on participants to report hospitalizations that occur outside of the study catchment area. The benefits of surveillance of CMS data include that outpatient AF diagnoses are obtained as are diagnoses for participants who stopped participating in cohort follow-up; disadvantages include lack of information on those <65 years as well as lack of claims during Medicare Advantage enrollment.

Despite these opposing advantages and disadvantages, the results from the two methods were similar with comparable incidence rates, high concordance, and little evidence of bias of associations between AF and risk factors. These results can be interpreted several ways: supporting the exclusive use of active cohort follow-up, providing caution about the completeness of data from reliance on one method, and finding that two very different methods of AF ascertainment yielded similar results.

There are several limitations of this study. Medicare Advantage plans are not required to submit claims on their beneficiaries; therefore, claims for ARIC participants during enrollment in Medicare Advantage were not included in the analysis. A total of 18,194 person-years (19%) of follow-up were unobservable as a result of HMO enrollment (all other eligibility criteria were met) out of 97,740 total person-years. More importantly, person-years missed varied by center (Forsyth County, NC: 7,935, Jackson, MS: 1,640, Minneapolis, MN: 7,985, and Washington County, MD: 634). This makes use of CMS alone impractical for ARIC follow-up. Although exclusion of participants with Medicare Advantage limits the generalizability of the study findings, the

concordance data are applicable to the FFS CMS population. Another drawback of ARIC is that it involves whites and blacks from only three and two communities, respectively, and might not be generalizable to all whites and blacks in the US. In active ARIC follow-up, AF ascertainment relies primarily on hospital discharge codes and the diagnosis is not otherwise validated. However, this method has been found to have acceptable validity; in a sample of 125 hospital discharge summaries with a first ICD-9 code for AF, 111 cases (89%) were confirmed based on ECGs performed during that hospitalization.<sup>7</sup> Finally, neither data source identified AF using a gold standard and consequently high concordance between the two data sources supports, but does not prove, validity of these approaches to identify incident AF.

The present study also has several strengths. First, its large sample size, with a substantial black population, and long follow-up of study participants enabled race-specific calculations through 2009. Most previous studies have been conducted in predominately white populations which is a limitation because some measures of validity, including PPV, are highly influenced by the prevalence of the disease in the source population, and blacks are known to have a lower risk of AF.<sup>2,7,12,122</sup> This study afforded the opportunity to determine the usefulness of this approach in both whites and blacks. Second, only one prior study has assessed the ability of administrative data, compared to physician reviewed hospital discharge summaries with a first ICD-9 code for AF and ECGs, to identify incident AF events; the PPV for AF was 89% and for incident AF was 62%.<sup>7</sup> In the present study, concordance of prevalent AF diagnosis was similar to that of incident AF diagnosis (data not shown). The ability to identify incident AF events is

especially important for comparative effectiveness research, studies of healthcare utilization over the entire disease course of AF, and drug safety surveillance; for example, a comparative effectiveness research study might want to include only treatment-naïve participants in order to decrease biases associated with treatment effectiveness in observational studies. Third, claims data are limited with respect to clinical characteristics because their primary purpose is for reimbursement. In this study, the ARIC data were linked to CMS data and, as a result, information not available in claims data, such as detailed and validated demographic, behavioral and comorbid conditions measured using standardized methodology, were present and included in descriptive analyses.

In conclusion, this study provides support for the potential value of utilizing multiple data sources to identify incident AF and suggests the need for caution about completeness of each data source. Nonetheless, two very different approaches to identifying incident AF produced similar results. Each approach has unique strengths and limitations and, when combined, could provide a more complete picture of newly-diagnosed AF. Moving forward, the ARIC cohort and similar studies should evaluate how to incorporate Medicare and other administrative data in the ascertainment of outcomes, factoring in the data limitations regarding coverage and quality.

## 10.6 TABLES

**Table 10.1: Baseline\* (1987-89) characteristics of ARIC Study participants enrolled in Medicare fee-for-service, overall and by source of incident atrial fibrillation diagnosis**

	Total (n = 10,134)	ARIC Only (n = 93)	CMS Only (n = 288)	ARIC and CMS (n = 738)	No Incident AF Diagnosis (n = 9015)
Age, years	66.4 ± 1.5	66.7 ± 1.9	66.5 ± 1.6	66.6 ± 1.6	66.4 ± 1.5
Women, %	57.0	46.2	42.4	45.4	58.5
Black, %	26.0	32.3	13.2	15.3	27.2
High school graduate, %	76.8	62.4	76.4	71.5	77.4
Current smoker, %	23.2	30.1	22.2	29.3	22.6
Current drinker, %	55.3	46.7	57.6	55.0	55.3
BMI (kg/m <sup>2</sup> )	27.7 ± 5.2	28.8 ± 5.6	28.1 ± 5.1	28.6 ± 5.4	27.6 ± 5.2
Hypertension, %	34.2	39.8	40.0	49.0	32.8
Antihypertensive medication, %	25.0	25.0	31.9	37.1	23.8
Diabetes mellitus, %	10.6	18.3	12.9	16.4	10.0
Total cholesterol, mg/dL	216.6 ± 41.7	220.8 ± 49.6	217.2 ± 45.4	219.3 ± 39.5	216.3 ± 41.6
LDL-c, mg/dL	139.0 ± 39.2	143.6 ± 47.4	141.8 ± 44.0	142.8 ± 35.6	138.5 ± 39.2
HDL-c, mg/dL	52.1 ± 17.0	49.1 ± 14.5	49.4 ± 16.4	47.7 ± 15.6	52.5 ± 17.1
Triglycerides, mg/dL	130.7 ± 85.3	140.5 ± 71.5	136.2 ± 100.9	147.8 ± 92.0	129.0 ± 84.1
Left ventricular hypertrophy, %	1.8	2.2	2.9	3.7	1.6
Previous myocardial infarction, %	3.4	3.2	6.6	9.5	2.8
Heart failure, %	4.1	4.4	4.3	8.5	3.7

Coronary heart disease, %	4.1	3.3	9.1	11.4	3.4
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ARIC = Atherosclerosis Risk in Communities

CMS = Centers for Medicare and Medicaid Services

Continuous variables presented as mean  $\pm$  standard deviation (SD)

\*Baseline age is age upon meeting enrollment criteria for the present analysis. All other characteristics are from the initial ARIC study exam (1987 – 1989)

**Table 10.2: Race-specific incidence rates of atrial fibrillation among Atherosclerosis Risk in Communities Study participants enrolled in Medicare fee-for-service by source of diagnosis**

Source of Diagnosis	Whites (n = 7504)	Blacks (n = 2630)
<b>ARIC Data</b>		
Incident AF (n/person years)	688 / 58606.8	143 / 18146.7
Unadjusted incidence rate *	11.7 (10.9 - 12.7)	7.9 (6.7 - 9.3)
Age- and sex-standardized incidence rate *	11.4 (10.5 - 12.2)	8.6 (7.1 - 10.0)
<b>All CMS Data<sup>†</sup></b>		
Incident AF (n/person years)	875 / 57528.8	151 / 18067.6
Unadjusted incidence rate	15.2 (14.2 - 16.3)	8.4 (7.1 - 9.8)
Age- and sex-standardized incidence rate	14.8 (13.8 - 15.8)	8.9 (7.5 - 10.4)
<b>Inpatient (MedPAR) Data</b>		
Incident AF (n/person years)	623 / 58677.7	113 / 18209.6
Unadjusted incidence rate	10.6 (9.8 - 11.5)	6.2 (5.2 - 7.5)
Age- and sex-standardized incidence rate	10.3 (9.5 - 11.1)	6.6 (5.3 - 7.8)
<b>Outpatient CMS Data</b>		
Incident AF (n/person years)	721 / 58094.2	106 / 18198.5
Unadjusted incidence rate	12.4 (11.5 - 13.4)	5.8 (4.8 - 7.0)
Age- and sex-standardized incidence rate	12.1 (11.2 - 13.0)	6.4 (5.1 - 7.6)

\*Rates per 1,000 person years (95% confidence intervals)

<sup>†</sup>Includes inpatient (MedPAR) and outpatient diagnosis of atrial fibrillation



**Table 10.3: Overall concordance of incident atrial fibrillation diagnosis based on Atherosclerosis Risk in Communities (ARIC) data and Centers for Medicare and Medicaid Services (CMS) data**

		All CMS			Inpatient (MedPAR) CMS			Outpatient CMS		
		AF	No AF	Total	AF	No AF	Total	AF	No AF	Total
ARIC Cohort Follow-up	AF	738	93	831	673	158	831	563	268	831
	No AF	288	9015	9303	63	9240	9303	264	9039	9303
	Total	1026	9108	10134	736	9398	10134	827	9307	10134
Kappa		0.77			0.85			0.65		
95% confidence interval		(0.75 – 0.80)			(0.83 – 0.87)			(0.62 – 0.68)		
% agreement		96			98			95		
% positive agreement		66			75			51		
% negative agreement		96			98			94		

Data are limited to participants enrolled in Medicare fee-for-service

All CMS includes MedPAR and outpatient claims

Inpatient CMS includes MedPAR claims

Outpatient CMS includes outpatient and carrier claims

% agreement calculated as the number of participants with consistent classification of diagnosed AF from active ARIC cohort follow-up and surveillance of CMS divided by the total number of observations and converted to a percent

% positive agreement calculated as the number of participants classified as having AF based on both active ARIC cohort follow-up and surveillance of CMS, conditional on being classified as having AF from at least one source, and converted to a percent

% negative agreement calculated as the number of participants classified as not having AF based on both active ARIC cohort follow-up and surveillance of CMS, conditional on being classified as not having AF from at least one source, and converted to a percent

**Table 10.4: Beta estimates for primary risk factors of the hazard of incident atrial fibrillation (AF) using active Atherosclerosis Risk in Communities (ARIC) follow-up compared to active ARIC follow-up plus surveillance of Centers for Medicare and Medicaid Services (CMS) data**

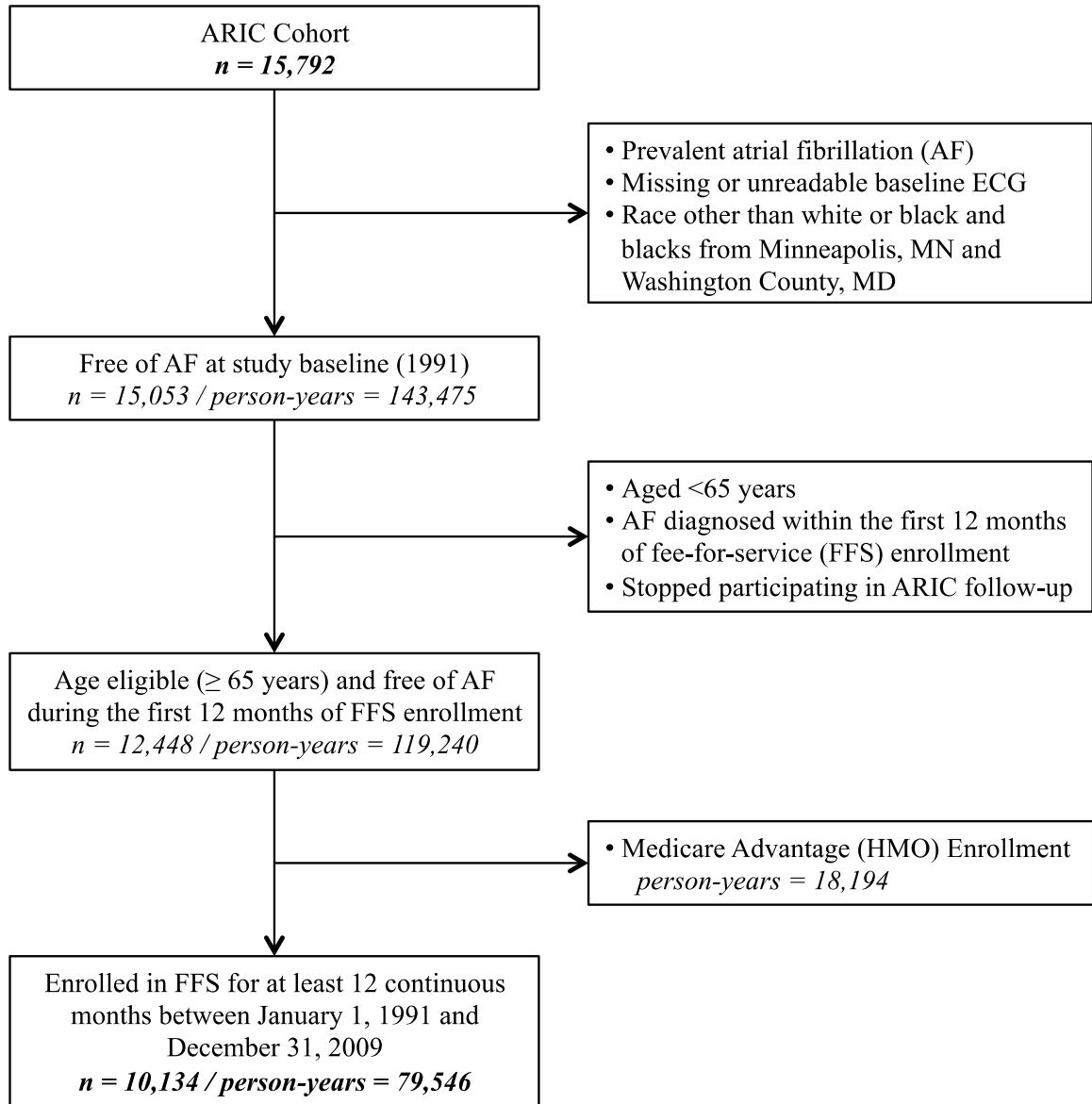
	Active ARIC Follow-Up		Active ARIC Follow-Up and CMS Surveillance	
	Beta Estimate	Standard Error	Beta Estimate	Standard Error
Age, years	0.10	0.004	0.10	0.004
Female (Male)	-0.45	0.05	-0.47	0.04
Black (White)	-0.53	0.06	-0.57	0.06
BMI, kg/m <sup>2</sup>	0.05	0.005	0.04	0.004
Hypertensive (Normotensive)	0.40	0.05	0.38	0.05
Diabetic (Non diabetic)	0.43	0.06	0.41	0.06
Current smoker (Ever, never smoker)	0.63	0.05	0.59	0.05
Prior heart disease (No prior heart disease)*	0.67	0.07	0.67	0.06

Exposed (Referent)

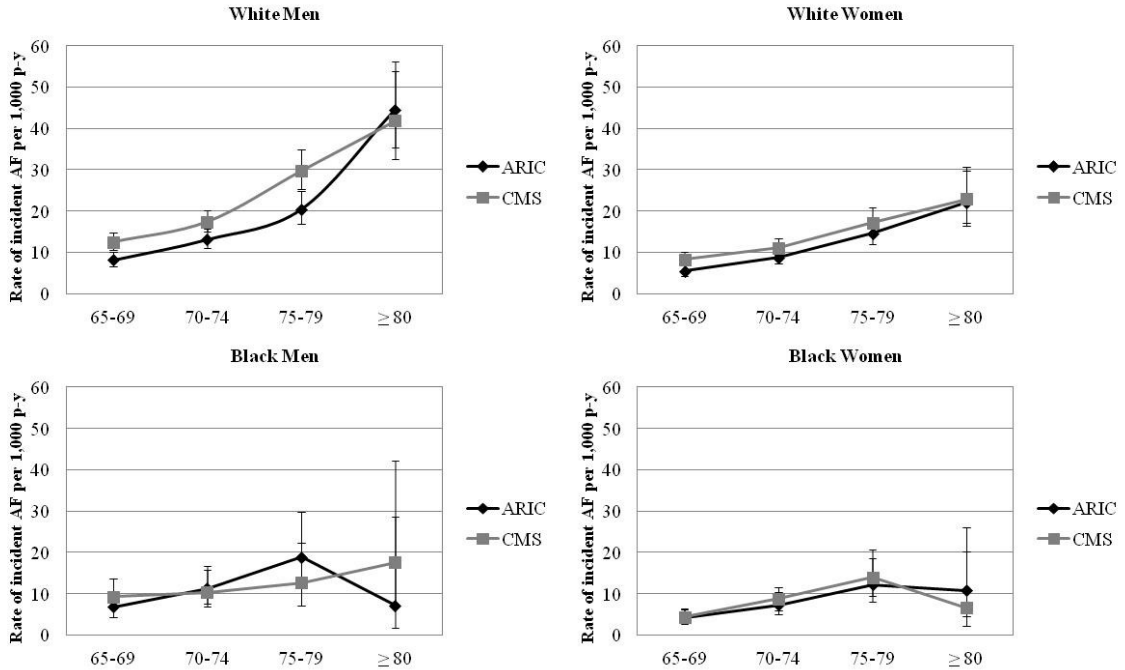
\*Prior heart disease defined as the presence of heart failure, myocardial infarction or coronary heart disease

## 10.7 FIGURES

**Figure 10.1: Derivation of study sample**



**Figure 10.2: Age-, sex- and race-specific incidence rates of atrial fibrillation by source of diagnosis**



CMS includes inpatient (MedPAR) or outpatient diagnosis of atrial fibrillation  
 1,000 p-y = 1,000 person-years  
 Vertical bars represent 95% confidence intervals

## **11.0 MANUSCRIPT 3 – IMPACT OF ATRIAL FIBRILLATION ON HEALTHCARE UTILIZATION IN THE COMMUNITY: THE ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY**

### **11.1 OVERVIEW**

**Background:** AF is associated with increased risk of hospitalizations. However, little is known about the impact of AF on non-inpatient healthcare utilization or about sex or race differences in AF-related utilization. We examined rates of inpatient and outpatient utilization by AF status in the ARIC study.

**Methods and Results:** ARIC cohort participants with incident AF enrolled in FFS Medicare, Parts A and B, for at least 12 continuous months between 1991 and 2009 were matched on age, sex, race and center to up to three participants without AF. Healthcare utilization was ascertained from inpatient and outpatient Medicare claims and classified based on primary ICD-9 code. The analysis included 944 AF and 2,761 non-AF participants. The average numbers of days hospitalized per year were 13.1 (95% CI: 11.5-15.0) and 2.8 (95% CI: 2.5-3.1) for those with and without AF, respectively. The corresponding numbers of outpatient claims per year were 53.2 (95% CI: 50.4-56.1) and 23.0 (95% CI: 22.2-23.8) for those with and without AF, respectively. Most utilization in AF patients was attributable to non-AF conditions, particularly other-CVD-related reasons; the adjusted rate ratio for days hospitalized per year for other-CVD-related reasons was 4.76 (95% CI: 3.51 – 6.44) for those with compared to those without AF. There was suggestive evidence that sex modified the association between AF and

inpatient utilization, with AF related to greater utilization in women than men. The association between AF and healthcare utilization was similar in whites and blacks.

**Conclusions:** This study highlights the considerably greater healthcare utilization (inpatient and outpatient) among those with AF; the differential in utilization due to other-CVD-related reasons was substantial. In addition to rate or rhythm treatment, management of AF should also focus on the accompanying cardiovascular comorbidities.

## 11.2 INTRODUCTION

In the US, the most recent annual national data reported 479,000 hospitalizations with AF as the primary diagnosis.<sup>31</sup> Hospitalizations with AF as the primary diagnosis increased by 34 percent from 1996 to 2001.<sup>36</sup> In addition to hospitalizations, outpatient burden is also high with five million physician office visits, 276,000 emergency department visits, and 234,000 hospital outpatient visits attributed to AF in the US in 2001.<sup>212</sup> AF patients are known to have many comorbidities: more than half of the AF burden can be explained by having at least one non-optimal risk factor, such as high blood pressure, elevated BMI, diabetes mellitus, cigarette smoking, or prior cardiac disease.<sup>70</sup> Furthermore, AF is a major cause of other cardiovascular morbidity, including stroke,<sup>18,19</sup> HF<sup>20,21</sup> and acute MI<sup>22,23</sup> as well as mortality.<sup>26</sup> Healthcare utilization among AF patients is clearly significant from both an economic and clinical perspective, however it is unknown whether this utilization is due to AF itself, or due to comorbidities which are common among AF patients.

Administrative claims data indicate that, compared to age- and sex- matched beneficiaries without AF, those with AF had twice as many hospitalizations during the 12-month period following initial AF diagnosis.<sup>30</sup> A more granular analysis of hospitalizations conducted among Olmsted County, MN, residents diagnosed with AF between 1980 and 2000 reported that the primary reasons for first hospitalization following AF diagnosis were due to AF (26.4%), HF (21.7%), coronary or peripheral arterial causes (21.6%), and thromboembolic events (10.5%).<sup>213</sup> In addition to hospitalizations, there is evidence of increased healthcare utilization in terms of surgery, clinic visits, phone contacts, specialist referrals, laboratory tests, and prescriptions among patients with AF compared to matched controls.<sup>214</sup>

While the overall clinical burden of AF is substantial, sex and race disparities in access to and quality of healthcare among AF patients exist. Data from the National Center for Health Statistics revealed that, even after adjustment for confounders, among AF patients, women were less likely to receive warfarin compared to men.<sup>215</sup> Among patients with atrial flutter, the odds of conversion therapy (procedure or medication) were 0.84 among women compared to men (95% CI: 0.79 – 0.90).<sup>216</sup> In the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study, a national population-based longitudinal study, the odds of blacks knowing they had AF were 0.33 compared to whites (95% CI: 0.20 – 0.52).<sup>217</sup> Moreover, among those who were aware of their AF, the odds of blacks being treated with warfarin were 0.25 that of whites (95% CI: 0.13 – 0.60).<sup>217</sup> Among elderly Medicare beneficiaries with AF, racial disparities in measures of

quality of care remained after adjustment for potential confounding factors; blacks had poorer quality of care compared to whites.<sup>218</sup>

Given the substantial and increasing burden of AF on healthcare utilization, the limited knowledge about inpatient and non-inpatient utilization, and the lack of sex- and race-specific data, we sought to heighten understanding of how AF patients utilize healthcare and to provide data that can be used to allocate adequate resources for the care of AF patients. Specifically, we compared healthcare utilization (inpatient or outpatient) and primary reason (AF-related, other-CVD-related, and non-CVD related) for seeking medical care among ARIC Study participants with AF to those without AF. We also described differences in utilization by sex and race.

### **11.3 METHODS**

#### **Data sources**

The ARIC study is a population-based prospective study of CVD in a cohort of 15,792 black and white participants between 45 and 64 years of age at enrollment in 1987-1989.<sup>176</sup> Participants were sampled from four US communities: Forsyth County, North Carolina; Jackson, Mississippi, northwest suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Additional participant contact has occurred through four follow-up clinic visits as well as annual telephone contact to obtain information regarding all hospitalizations and vital status, details of which have been reported previously.<sup>7</sup>

The ARIC study has an Interagency Agreement with the CMS to obtain Medicare data for ARIC cohort participants. Participants are matched on social security number,



sex, and date of birth. The finder file included 15,738 ARIC participants, of which 14,530 (92.3%) were matched successfully and linked to CMS Medicare claims. Data for participants whom matched successfully were linked to inpatient, outpatient and carrier files. The MedPAR file contains claims for inpatient services covered under Medicare Part A. The outpatient files contain claims for services covered under Medicare Part B, including institutional claims (Outpatient file) for outpatient services and noninstitutional physician claims (Carrier file). CMS claims for inpatient and outpatient services have been available for research since 1991.

### **Study sample**

For this analysis, ARIC cohort participants enrolled in FFS Medicare, both Parts A and B, for at least 12 continuous months between January 1, 1991, and December 31, 2009, were eligible for inclusion; for participants with multiple FFS enrollment periods (n = 647), only the first was included (Figure 11.1). Medicare FFS enrollment was a necessary requirement because Medicare Advantage insurance plans are not required to submit claims for beneficiaries. Additionally, those enrolled in only Part A (FFS) do not have claims data for Part B services (e.g., outpatient visits and physician visits).

Participants whose race was not white or black and nonwhites from the Minneapolis and Washington County field centers were excluded due to small numbers. Both active ARIC cohort follow-up and surveillance of CMS data were used to identify and exclude all participants with prevalent AF. As such, based on initial ARIC study exam, participants with missing or unreadable ECG and those with prevalent AF on the baseline ECG were excluded. We were interested in incident AF, therefore utilizing all available information

from ARIC and CMS we excluded participants diagnosed with AF prior to January 1, 1992 (CMS data were available for research from January 1, 1991, forward), participants with AF diagnosed prior to FFS enrollment or during the first year of FFS enrollment, and participants who stopped participating in ARIC follow-up. Participants enrolled in Medicare due to disability or certain covered medical conditions were not included in the study unless they met study eligibility criteria after becoming age eligible (aged  $\geq 65$  years). Participants who died on the date of AF diagnosis were excluded.

Participants with incident AF diagnosed based on CMS Medicare data during their initial FFS enrollment period were matched to up to three ARIC participants without AF based on age (within two years), sex, race and field center; matching was utilized to account for strong confounders and was performed with the SAS macro, *gmatch*, developed at the Mayo Clinic.<sup>219</sup> Three matches were found for 93 percent of participants with AF. Of the 3,737 participants, 3,705 (944 with AF and 2,761 without AF) had complete covariate information and comprised our final sample. Each center's institutional review board approved the study and all participants provided informed consent.

### **Definition of atrial fibrillation**

Incident cases of AF were ascertained through MedPAR and outpatient CMS claims; incident AF was defined as an AF discharge diagnosis, ICD-9 code of 427.3, 427.31 or 427.32, in any position, on a single short-stay inpatient (MedPAR) claim or on two outpatient claims within 7 – 365 days. A minimum of two outpatient claims at least 7 days apart were required to reduce the likelihood of including “rule out” diagnoses and to

improve the algorithm specificity.<sup>27,182</sup> The incidence date of AF was defined as the discharge date for a MedPAR short-stay claim or the date of the second qualifying outpatient claim, whichever occurred earliest. AF following cardiac operative procedures occurs frequently.<sup>206</sup> Accordingly, AF diagnosis occurring simultaneously with cardiac revascularization (ICD-9 code 36.31, 36.1) or other cardiac surgery involving heart valves or septa (ICD-9 code 35.32, 35.33, 35.39, 35.95, 35.1X, 35.2X, 35.7X) during the index hospitalization, without a subsequent AF diagnosis, was not included.

### **Definition of healthcare utilization**

Healthcare utilization was ascertained from short-stay inpatient (MedPAR) and outpatient (Outpatient and Carrier files) CMS Medicare claims. Each claim was classified based on the primary discharge diagnosis code as AF-related (ICD-9 code 427.3x), other-CVD-related (ICD-9 code 390 – 459) excluding AF, and non-CVD-related (all other valid ICD-9 codes). Claims with an invalid or missing primary diagnosis code were classified based on the first-listed usable diagnosis code. Length of hospitalization was taken into account for inpatient healthcare utilization by calculating length of stay (LOS). Multiple claims for the same date of service with identical diagnosis(es) code(s) were counted as one claim.

### **Assessment of covariates**

During the baseline ARIC study exam, standardized methods were used to collect data on age, race, sex, educational achievement, cigarette smoking, ethanol consumption, height, weight, blood pressure, antihypertensive medication use, diabetes mellitus, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol,

triglycerides, previous myocardial infarction, HF or coronary heart disease.<sup>176</sup> An ECG Cornell voltage >28 mm in men or >22 mm in women was considered evidence of left ventricular hypertrophy.<sup>207</sup> Data on these covariates were updated during additional ARIC study exams. Behavioral and clinical characteristics were updated to reflect closest values preceding AF diagnosis (for those with incident AF) or date of matching (for those without incident AF).

### **Statistical analysis**

Person-years of follow up were calculated as the date of incident AF diagnosis (for those with incident AF) or the date matched (for those without incident AF), until the date of disenrollment in FFS Medicare, death or December 31, 2009, whichever occurred earliest. The annualized rate of inpatient (MedPAR) utilization was calculated by dividing the total number of days hospitalized by the corresponding person-years of follow-up, which can be interpreted as the average annual number of days hospitalized per person. The annualized rate of outpatient utilization was calculated by dividing the total number of unique claims per date of service by the corresponding person-years of follow-up. Negative binomial regression models were used to calculate rates and rate ratios of inpatient (MedPAR) and outpatient utilization comparing those with and without AF; models include an offset of log follow-up time to account for differential follow-up. Covariate data were updated to reflect the closest ARIC exam preceding AF diagnosis or the matched reference date for those without AF. Sex- and race-specific rates of healthcare utilization (inpatient and outpatient) also were calculated. The rate of utilization, classified based on the primary diagnosis code as AF, other-CVD, and non-

CVD reasons, was calculated with the same approach as above for inpatient and outpatient utilization. A descriptive analysis, restricted to hospitalizations for other-CVD-related reasons and stratified by AF status and sex, was performed to identify the primary reasons for and rates of hospitalization.

Pre-specified 2-way multiplicative interactions of healthcare utilization (inpatient [MedPAR] and outpatient considered separately) with sex and race were examined. A subgroup analysis, restricted to matched AF and non-AF participants with similar propensity scores, was performed. All statistical analyses were performed with SAS, version 9.2 (SAS Institute, Cary, NC).

## **11.4 RESULTS**

Of the original 15,792 ARIC participants, our final analytic sample included 3,705 participants (944 with AF and 2,761 without AF) who were enrolled in FFS Medicare for at least 12 continuous months between January 1, 1991 and December 31, 2009. Characteristics of the study sample, stratified by AF status and updated to reflect closest ARIC study exam values preceding AF diagnosis or matching, are shown in Table 11.1. Overall, the mean age at AF diagnosis or matching was 73.3 years (standard deviation 4.7 years) and women comprised approximately 45 percent and blacks nearly 15 percent of the study sample; the distribution of these characteristics was similar among those with and without AF. Participants with AF were more likely to be current smokers, have higher body mass indices, hypertension, diabetes mellitus, left ventricular hypertrophy, HF and coronary heart disease.

During a mean follow-up of 4.1 years, there were 2,615 hospitalizations among the 944 participants with AF; the median LOS was 5 days (interquartile range [IQR]: 3 - 9). Among the 2,761 without AF, there were 3,005 hospitalizations during a mean follow-up of 4.2 years. The median LOS was 5 days (IQR: 3 - 8). The unadjusted days per year in the hospital were 13.1 (95% CI: 11.5 – 15.0) and 2.8 (95% CI: 2.5 – 3.1) for participants with and without AF, respectively (Table 11.2). After accounting for matching criteria, the number of days hospitalized per year was 4.80 (95% CI: 3.99 – 5.78) times higher among participants with AF compared to those who remained free of AF. After adjustment for potential confounders, the rate of days in the hospital was 3.85 (95% CI: 3.20 – 4.62) times greater, among those with AF. Healthcare utilization in the outpatient setting was higher among participants with AF compared to those without AF (Table 11.2); the median number of claims during follow-up was 122 ([IQR: 47 – 229.5) for those with AF and 50 (IQR: 17 – 114) for those without AF, based on unique claims per date of service. The unadjusted annual rate of outpatient utilization was 53.2 (95% CI: 50.4 – 56.1) and 23.0 (22.2 – 23.8) for those with and without AF, respectively. After accounting for matching criteria and other potential confounders, the rate ratio for outpatient utilization remained significantly greater among those with AF compared to those without AF (rate ratio: 2.13, 95% CI: 1.99 – 2.28).

The interaction of sex with AF in the assessment of inpatient (MedPAR) healthcare utilization was of borderline statistical significance ( $p = 0.07$ ), while the interaction was not significant for outpatient utilization ( $p = 0.33$ ). The unadjusted rate of inpatient (MedPAR) healthcare utilization was highest for women with AF (Table 11.3),

15.6 per year (95% CI: 12.8 – 19.0), and lowest for women without AF, 2.6 (95% CI: 2.2 – 3.0). Yet, after adjustment for matching criteria and additional potential confounders, the rate ratio for days hospitalized per year was similar among women and men without AF (Figure 11.2); among women, the rate ratio among those with AF compared to those without AF was 4.75 (95% CI: 3.56 – 6.34), while among men the corresponding rate ratio was 3.26 (95% CI: 2.56 – 4.15).

The healthcare utilization following AF diagnosis did not differ significantly between whites and blacks for inpatient (MedPAR) (p for interaction = 0.90) or outpatient utilization (p for interaction = 0.16). Blacks with AF had the highest unadjusted rate of inpatient (MedPAR) utilization (rate: 17.4; 95% CI: 11.9 – 25.6) and outpatient utilization (rate: 53.7; 95% CI: 45.6 – 63.4) (Table 11.4).

Among participants with AF, the unadjusted annual rate of days hospitalized with AF as the primary diagnosis code was 0.5 (95% CI: 0.3 – 0.7). The annual rate of days hospitalized for other-CVD-reasons was 4.3 (95% CI: 3.5 – 5.2) among those with AF and 0.8 (95% CI: 0.6 – 0.9) among those without AF (Table 11.5). After adjustment for matching criteria and other potential confounders, the adjusted rate ratio for days hospitalized per year for other-CVD-related reasons was 4.76 (95% CI: 3.51 – 6.44) for those with compared to those without AF. The magnitude of the difference was smaller for non-CVD-related hospitalized days. Outpatient utilization followed a similar pattern; the magnitude of the difference between those with AF and those without AF was greatest for other-CVD-related reasons (adjusted rate ratio: 2.46 [95% CI: 2.24 – 2.70]).

A sex-specific analysis of type (inpatient or outpatient) and primary reason for healthcare utilization (AF-related, other-CVD-related or non-CVD-related) revealed that other-CVD-related hospitalization days was the driving difference for sex differences in utilization (Table 11.6); the unadjusted rate of days hospitalized per year for other-CVD-related reasons was 2.7 (95% CI: 2.1 – 3.4) and 1.1 (95% CI: 0.8 – 1.3) for men with and without AF, respectively. The corresponding values for women with and without AF were 6.6 (95% CI: 4.8 – 9.1) and 0.5 (0.3 – 0.6), respectively. The adjusted rate ratio for annual days hospitalized due to other-CVD-related causes was 11.94 (95% CI: 7.08 – 20.13) for women with AF compared to those without AF, while the corresponding rate ratio was 2.41 (95% CI: 1.67 – 3.47) for men. A descriptive analysis revealed that cerebrovascular disease was the leading cause of non-AF CVD-related hospitalizations for both men and women without AF, 20.4 and 13.9, per 1,000 person-years, respectively. Among those with AF, however, the rate of non-AF CVD-related hospitalization was greatest for HF, 45.1 and 59.2, per 1,000 person-years, for men and women, respectively (Table 11.7).

In a subgroup analysis, restricted to matched AF and non-AF participants with similar propensity scores, the primary results were corroborated. The unadjusted days per year in the hospital were 9.4 (95% CI: 7.7 – 11.6) and 2.1 (95% CI: 1.6 – 2.8) for participants with and without AF, respectively (Table 11.8). After adjustment for potential confounders, the number of days hospitalized per year was 4.90 (95% CI: 3.51 – 6.85) times higher among participants with AF compared to those who remained free of AF. In the outpatient setting, the unadjusted annual rate of utilization was 47.8 (95% CI:



43.9 – 52.0) and 21.9 (19.7 – 24.4) for those with and without AF, respectively. Based on the primary diagnosis code, in the fully adjusted model, the rate ratio for days hospitalized per year for other-CVD-related reasons was 6.30 (95% CI: 3.62 – 10.95) for those with AF compared to those without AF (Table 11.9). The adjusted rate ratio for other-CVD-related reasons in the outpatient setting was 2.70 (95% CI: 2.26 – 3.24) for those with compared to those without AF.

## **11.5 DISCUSSION**

In this sample of AF patients and matched controls from a community-based prospective study, rates of healthcare utilization, both inpatient (MedPAR) and outpatient, were substantially higher among participants with AF compared to those matched with cases and without AF. There was modest evidence of sex modifying the association between AF and inpatient (MedPAR) utilization; AF was associated with higher inpatient utilization in women than in men. In both the inpatient and outpatient setting, healthcare utilization was greatest for non-CVD-related reasons for those with as well as those without AF. However, the magnitude of the difference in utilization between those with and without AF was greatest for other-CVD-related reasons; this difference was especially pronounced for days hospitalized among women.

Overall, our findings underscore the high prevalence of cardiovascular comorbidities, particularly HF, triggering healthcare utilization among AF patients. At the time of AF diagnosis or matching, HF was almost three times more prevalent in AF patients compared to matched participants. The prevalence of other comorbidities,

including hypertension, diabetes, and coronary heart disease, were significantly higher among AF patients compared to the non-AF matched controls. Although AF has long been thought of as an electrical conduction problem, the high prevalence of cardiovascular comorbidities and the higher rate of healthcare utilization among those with AF, especially for other-CVD-related reasons, provide evidence that AF should not be considered just as an electrical problem, but as a marker of underlying vascular disease and overall cardiovascular risk. A Danish nationwide study reported that, within each age group, hospitalization rates for CVD and non-CVD admissions were higher among those with AF compared to those without AF.<sup>220</sup> Furthermore, a 30-year follow-up of Olmsted County, Minnesota, residents diagnosed with lone AF, considered to be purely an electrical conduction problem, revealed that those with AF had slightly elevated risk of developing HF or a cerebrovascular event compared to the age- and sex-matched Minnesota population.<sup>221</sup> Moreover, in a contemporary anticoagulated AF population, 90% of deaths were due to reasons other than stroke,<sup>222</sup> corroborating the impact of cardiovascular comorbidities on mortality reported from the AFFIRM<sup>223</sup> and the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trials.<sup>224</sup> In the present study, the associations between AF and inpatient (MedPAR) and outpatient healthcare utilization remained significant, but were attenuated, after adjusting for comorbidities. The overall adjusted rate ratio for days hospitalized due to other-CVD-reasons was 4.76 (95% CI: 3.51 – 6.44) among those with AF compared to those without AF; the corresponding adjusted rate ratio for outpatient utilization was 2.46 (95% CI: 2.24 – 2.70). This suggests that it is not just the presence of AF that causes healthcare

utilization, but the company it keeps— hypertension, diabetes mellitus, HF and coronary heart disease—that contributes, in part, to higher rates of healthcare utilization among AF patients. Our results underline the importance of adequate management and control of these comorbidities. However, despite the attenuation with adjustment for comorbidities, healthcare utilization remained substantially greater among those with AF, indicating considerable additional medical demand among this subset of the population.

In addition to the burden placed on the healthcare system, it is important to consider the burden of AF to the patient.<sup>225,226</sup> Based on this study, the median number of days hospitalized per year for those with AF was 10, compared with zero among those without AF. Furthermore, outpatient utilization was approximately two and one half times greater among those with AF. This considerably higher utilization impacts quality of life for the patient and his/her caregivers.<sup>227</sup>

There was suggestive evidence of sex modifying the association between AF and inpatient (MedPAR) healthcare utilization; the differential utilization was most pronounced for other-CVD-related hospitalizations. Prior studies found the relative risk for cardiovascular events, including stroke, were higher among women with AF compared to men.<sup>91,228,229</sup> Lower rates of anticoagulation in women compared to men, particularly among the elderly, have been implicated as an important factor.<sup>230-232</sup> However, a recent study suggests that elderly women, especially those aged  $\geq 75$ , are at increased risk of stroke compared to elderly men, irrespective of their risk profile or warfarin use.<sup>233</sup> The mechanisms underlying the increased relative risk of stroke among women compared to men with AF have not been fully elucidated; potential reasons for

this sex difference include hormonal factors, physiology, and psychosocial factors. Despite published disparities in AF treatment between whites and blacks,<sup>217,218,234</sup> our study did not identify a differential impact of AF by race on inpatient (MedPAR) or outpatient utilization. However, the number of blacks with AF was small (n = 131) and from just two geographic areas, so it is possible that our study was underpowered to detect a difference.

There are several limitations of this study. The CMS Medicare files for ARIC analysis did not contain line items and therefore multiple claims for the same date of service with identical diagnosis(es) code(s) could not be included in this study. Without the line items, it is impossible to know if the claims are for multiple services (lab, x-ray, physician) related to the same condition or for the same claim submitted multiple times. By excluding all claims with identical diagnostic codes for the same date of service, our estimates are conservative and, if anything, underestimate healthcare utilization. Additionally, our study had to be restricted to FFS Medicare enrollment windows because Medicare Advantage plans are not required to submit claims on their beneficiaries. Although exclusion of Medicare Advantage enrollment windows limits the generalizability of study findings, the results are applicable to the FFS Medicare population. A weakness of the ARIC study is that it includes whites and blacks from only three and two communities, respectively, and might not be generalizable to all whites and blacks in the US. Lastly, due to small numbers, the power to detect significant effect modification by sex or race was low. Consequently, we described healthcare utilization

by subgroups but cannot make conclusive statements about similarities or differences by sex or race.

This study also has several strengths. Claims data contain little information on clinical characteristics, as their primary purpose is for reimbursement. In this study, data collected as part of the ARIC study exams were linked to CMS data and, consequently, information unavailable in claims data, such as detailed and validated demographic, behavioral and comorbid conditions measured using standardized methodology, were present and included in analyses. Second, prior research on AF did not study outpatient healthcare utilization.<sup>30,213</sup> Furthermore, previous studies were conducted in a predominately white population<sup>213</sup> or did not consider differences by sex or race.<sup>30,213</sup> In response to the above gaps in the literature, we described overall healthcare utilization among participants with and without AF as well as sex- and race-specific utilization for both inpatient (MedPAR) and outpatient services.

In conclusion, this study provides evidence of the burden of AF healthcare utilization. The results highlight that AF is not just an electrical problem and treatment guidelines should incorporate assessment of overall cardiovascular risk and provide recommendations on comprehensive management of the patient. Participants with AF had greater underlying vascular disease and spent significantly more days hospitalized and seeking outpatient care than similar individuals without AF. The magnitude of the difference in utilization between those with and without AF was greatest for other-CVD-related reasons and emphasizes the need to treat the underlying vascular disease in addition to rhythm or rate management among those with AF.

## 11.6 TABLES

**Table 11.1: Characteristics of participants by atrial fibrillation status based on closest Atherosclerosis Risk in Communities Study exam preceding atrial fibrillation diagnosis or matching**

	<b>AF (n = 944)</b>	<b>No AF (n = 2,761)</b>	<b>p-value</b>
Age at matching, years	73.5 ± 4.8	73.3 ± 4.6	0.23
Women, %	43.9	45.2	0.46
Black, %	13.9	14.3	0.74
High school graduate, %	74.8	76.9	0.18
Current smoker, %	19.2	13.5	<0.0001
Current drinker, %	49.7	51.7	0.29
BMI (kg/m <sup>2</sup> )	29.4 ± 5.7	28.3 ± 5.2	<0.0001
Hypertension, %	59.9	48.8	<0.0001
Antihypertensive medication, %	47.5	35.7	<0.0001
Diabetes mellitus, %	21.3	16.4	0.001
Total cholesterol, mg/dL	199.8 ± 37.4	203.9 ± 37.5	0.004
LDL-c, mg/dL	124.0 ± 34.6	126.7 ± 34.3	0.04
HDL-c, mg/dL	44.6 ± 18.1	46.0 ± 18.5	0.04
Triglycerides, mg/dL	147.3 ± 83.4	144.9 ± 84.3	0.46
Left ventricular hypertrophy, %	3.9	2.1	0.002
Heart failure, %	10.4	3.8	<0.0001
Coronary heart disease, %	18.9	9.4	<0.0001

AF = atrial fibrillation

BMI = body mass index

Continuous variables presented as mean ± standard deviation (SD)

**Table 11.2: Association of atrial fibrillation with inpatient (MedPAR) and outpatient healthcare utilization among Atherosclerosis Risk in Communities Study participants**

	<b>AF (n = 944)</b>	<b>No AF (n = 2,761)</b>
<b>Follow up, years (mean ± SD)</b>	4.1 ± 3.6	4.2 ± 3.6
<b>Inpatient (MedPAR) Utilization, days</b>		
Per person, median (IQR) <sup>*</sup>	10 (0 - 29)	0 (0 - 7)
Unadjusted rate <sup>†</sup>	13.1 (11.5 - 15.0)	2.8 (2.5 - 3.1)
Unadjusted rate ratio	4.81 (4.00 - 5.78)	Reference
Rate ratio adjusted for matching criteria <sup>‡</sup>	4.80 (3.99 - 5.78)	Reference
Fully adjusted rate ratio <sup>**</sup>	3.85 (3.20 - 4.62)	Reference
<b>Outpatient Utilization<sup>§</sup></b>		
Per person, median (IQR) <sup>*</sup>	122 (47 - 229.5)	50 (17 - 114)
Unadjusted rate <sup>†</sup>	53.2 (50.4 - 56.1)	23.0 (22.2 - 23.8)
Unadjusted rate ratio	2.33 (2.17 - 2.49)	Reference
Rate ratio adjusted for matching criteria <sup>‡</sup>	2.32 (2.16 - 2.48)	Reference
Fully adjusted rate ratio <sup>**</sup>	2.13 (1.99 - 2.28)	Reference

\* During follow-up

† Rate per year

‡ Adjusted for matching criteria: age (within 2 years), sex, race and field center

\*\* Adjusted for matching criteria and high school graduate, current smoking, current drinking, body mass index, hypertension, antihypertensive medication, diabetes mellitus, and prior heart failure and coronary heart disease

§ Outpatient utilization defined as unique claims per date of service

IQR = interquartile range

**Table 11.3: Association of atrial fibrillation with inpatient (MedPAR) and outpatient healthcare utilization among Atherosclerosis Risk in Communities Study participants stratified by sex**

	Men		Women	
	AF (n = 530)	No AF (n = 1,512)	AF (n = 414)	No AF (n = 1,249)
<b>Follow up, years (mean ± SD)</b>	4.1 ± 3.6	4.0 ± 3.5	4.0 ± 3.5	4.4 ± 3.7
<b>Inpatient (MedPAR) Utilization, days</b>				
Per person, median (IQR) <sup>*</sup>	9 (0 - 27)	0 (0 - 7)	10 (0 - 32)	0 (0 - 7)
Unadjusted rate <sup>†</sup>	11.2 (9.5 - 13.4)	3.0 (2.6 - 3.5)	15.6 (12.8 - 19.0)	2.6 (2.2 - 3.0)
Unadjusted rate ratio	3.82 (2.99 - 4.87)	Reference	6.30 (4.77 - 8.32)	Reference
Rate ratio adjusted for matching criteria <sup>‡</sup>	3.57 (2.80 - 4.55)	Reference	6.53 (4.92 - 8.67)	Reference
Fully adjusted rate ratio <sup>**</sup>	3.26 (2.56 - 4.15)	Reference	4.75 (3.56 - 6.34)	Reference
<b>Outpatient Utilization<sup>§</sup></b>				
Per person, median (IQR) <sup>*</sup>	124 (48 - 241)	48 (17 - 113)	113 (40 - 223)	52 (15 - 116)
Unadjusted rate <sup>†</sup>	52.8 (49.5 - 56.4)	23.9 (22.7 - 25.1)	54.6 (48.9 - 58.6)	21.9 (20.7 - 23.1)
Unadjusted rate ratio	2.25 (2.04 - 2.44)	Reference	2.45 (2.20 - 2.72)	Reference
Rate ratio adjusted for matching criteria <sup>‡</sup>	2.20 (2.01 - 2.40)	Reference	2.45 (2.20 - 2.72)	Reference
Fully adjusted rate ratio <sup>**</sup>	2.04 (1.87 - 2.23)	Reference	2.25 (2.02 - 2.51)	Reference

\* During follow-up

† Rate per year

‡ Adjusted for matching criteria: age (within 2 years), sex, race and field center

\*\* Adjusted for matching criteria and high school graduate, current smoking, current drinking, body mass index, hypertension, antihypertensive medication, diabetes mellitus, and prior heart failure and coronary heart disease

§ Outpatient utilization defined as unique claims per date of service

IQR = interquartile range



**Table 11.4: Association of atrial fibrillation with inpatient (MedPAR) and outpatient healthcare utilization among Atherosclerosis Risk in Communities Study participants stratified by race**

	White		Black	
	AF (n = 813)	No AF (n = 2,366)	AF (n = 131)	No AF (n = 395)
<b>Follow up, years (mean ± SD)</b>	4.2 ± 3.6	4.2 ± 3.6	3.5 ± 3.1	4.0 ± 3.6
<b>Inpatient (MedPAR) Utilization, days</b>				
Per person, median (IQR) <sup>*</sup>	10 (0 - 29)	0 (0 - 7)	7 (0 - 34)	0 (0 - 5)
Unadjusted rate <sup>†</sup>	12.4 (10.8 - 14.3)	2.8 (2.5 - 3.1)	17.4 (11.9 - 25.6)	3.2 (2.3 - 4.4)
Unadjusted rate ratio	4.66 (3.84 - 5.65)	Reference	5.61 (3.18 - 9.88)	Reference
Rate ratio adjusted for matching criteria <sup>‡</sup>	4.65 (3.83 - 5.64)	Reference	5.65 (3.20 - 9.97)	Reference
Fully adjusted rate ratio <sup>**</sup>	3.89 (3.21 - 4.72)	Reference	3.74 (2.08 - 6.75)	Reference
<b>Outpatient Utilization<sup>§</sup></b>				
Per person, median (IQR) <sup>*</sup>	127 (49 - 236)	53 (18 - 118)	93 (32 - 175)	36 (8 - 97)
Unadjusted rate <sup>†</sup>	53.1 (50.2 - 56.1)	23.3 (22.4 - 24.2)	53.7 (45.6 - 63.4)	21.0 (18.6 - 23.7)
Unadjusted rate ratio	2.29 (2.13 - 2.46)	Reference	2.57 (2.05 - 3.23)	Reference
Rate ratio adjusted for matching criteria <sup>‡</sup>	2.27 (2.12 - 2.44)	Reference	2.59 (2.07 - 3.26)	Reference
Fully adjusted rate ratio <sup>**</sup>	2.10 (1.95 - 2.25)	Reference	2.34 (1.87 - 2.93)	Reference

\* During follow-up

† Rate per year

‡ Adjusted for matching criteria: age (within 2 years), sex, race and field center

\*\* Adjusted for matching criteria and high school graduate, current smoking, current drinking, body mass index, hypertension, antihypertensive medication, diabetes mellitus, and prior heart failure and coronary heart disease

§ Outpatient utilization defined as unique claims per date of service

IQR = interquartile range

**Table 11.5: Primary reason for inpatient (MedPAR) and outpatient healthcare utilization stratified by atrial fibrillation status**

	AF (n = 944)	No AF (n = 2,761)	Adjusted Rate Ratio <sup>t</sup>
<b>Inpatient (MedPAR) Utilization, days</b>			
Unadjusted rates <sup>*</sup>			
AF related	0.5 (0.3 - 0.7)	--	--
Other CVD related	4.3 (3.5 - 5.2)	0.8 (0.6 - 0.9)	4.76 (3.51 - 6.44)
Non-CVD related	8.1 (7.0 - 9.4)	2.0 (1.8 - 2.3)	3.38 (2.76 - 4.15)
<b>Outpatient Utilization<sup>§</sup></b>			
Unadjusted rates <sup>*</sup>			
AF related	4.8 (4.3 - 5.4)	0.01 (0.01 - 0.02)	--
Other CVD related	9.1 (8.4 - 9.7)	3.3 (3.1 - 3.5)	2.46 (2.24 - 2.70)
Non-CVD related	38.7 (36.5 - 40.9)	19.5 (18.8 - 20.2)	1.85 (1.72 - 1.98)

\* Rates are days per year for inpatient (MedPAR) data and number of unique claims per date of service per year for outpatient claims  
<sup>t</sup> Adjusted for matching criteria and high school graduate, current smoking, current drinking, body mass index, hypertension, antihypertensive medication, diabetes mellitus, and prior heart failure and coronary heart disease

<sup>§</sup> Outpatient utilization defined as unique claims per date of service

**Table 11.6: Primary reason for inpatient (MedPAR) and outpatient healthcare utilization stratified by atrial fibrillation status and sex**

	Men			Women		
	AF (n = 530)	No AF (n = 1,512)	Adjusted Rate Ratio <sup>t</sup>	AF (n = 414)	No AF (n = 1,249)	Adjusted Rate Ratio <sup>t</sup>
<b>Inpatient (MedPAR) Utilization, days</b>						
Unadjusted rates <sup>*</sup>						
AF related	0.6 (0.4 - 1.1)	--	--	0.3 (0.2 - 0.5)	--	--
Other CVD related	2.7 (2.1 - 3.4)	1.1 (0.8 - 1.3)	2.41 (1.67 - 3.47)	6.6 (4.8 - 9.1)	0.5 (0.3 - 0.6)	11.94 (7.08 - 20.13)
Non-CVD related	7.7 (6.3 - 9.4)	2.0 (1.7 - 2.3)	3.37 (2.57 - 4.43)	8.6 (6.9 - 10.7)	2.1 (1.8 - 2.5)	3.24 (2.37 - 4.43)
<b>Outpatient Utilization<sup>§</sup></b>						
Unadjusted rates <sup>*</sup>						
AF related	4.7 (4.1 - 5.4)	--	--	5.0 (4.2 - 5.9)	--	--
Other CVD related	8.9 (8.2 - 9.7)	3.7 (3.4 - 4.0)	2.18 (1.93 - 2.46)	9.2 (8.1 - 10.4)	2.9 (2.7 - 3.1)	2.88 (2.49 - 3.33)
Non-CVD related	38.6 (35.9 - 41.5)	19.9 (18.9 - 20.9)	1.82 (1.66 - 1.99)	38.7 (35.3 - 42.5)	18.9 (17.9 - 20.0)	1.88 (1.69 - 2.10)

\* Rates are days per year for inpatient (MedPAR) data and number of unique claims per date of service per year for outpatient claims

<sup>t</sup> Adjusted for matching criteria and high school graduate, current smoking, current drinking, body mass index, hypertension, antihypertensive medication, diabetes mellitus, and prior heart failure and coronary heart disease

<sup>§</sup> Outpatient utilization defined as unique claims per date of service

**Table 11.7: Descriptive analysis of the primary diagnosis codes for non-atrial fibrillation cardiovascular disease related hospitalizations stratified by atrial fibrillation status and sex**

	Men				Women			
	AF (n=530)		No AF (n=1,512)		AF (n=414)		No AF (n=1,249)	
	Number <sup>*</sup>	Rate <sup>†</sup>	Number	Rate	Number	Rate	Number	Rate
<b>Total non-AF CVD-related hospitalizations</b>	<b>446</b>	<b>203.1</b>	<b>478</b>	<b>78.5</b>	<b>364</b>	<b>219.8</b>	<b>256</b>	<b>46.2</b>
Hypertensive disease (401 - 405)	14	6.4	15	2.5	26	15.7	12	2.2
Myocardial infarction (410)	44	20.0	58	9.5	31	18.7	28	5.0
Coronary atherosclerosis, native vessel (414.01)	62	28.2	90	14.8	35	21.1	30	5.4
Heart failure (428)	99	45.1	51	8.4	98	59.2	31	5.6
Cerebrovascular disease (430 - 438)	79	36.0	124	20.4	63	38.0	77	13.9

<sup>†</sup> Unadjusted rates per 1,000 person-years

Total person-years of follow up: Men with AF: 2,196, men without AF: 6,090, women with AF: 1,656 and women without AF: 5,54

**Table 11.8: Association of atrial fibrillation with inpatient (MedPAR) and outpatient healthcare utilization among propensity score matched Atherosclerosis**

**Risk in Communities Study participants**

	<b>AF (n = 360)</b>	<b>No AF (n = 360)</b>
<b>Follow up, years (mean ± SD)</b>	4.4 ± 3.7	4.1 ± 3.6
<b>Inpatient (MedPAR) Utilization, days</b>		
Per person, median (IQR) <sup>*</sup>	8 (0 - 26)	0 (0 - 6)
Unadjusted rate <sup>†</sup>	9.4 (7.7 - 11.6)	2.1 (1.6 - 2.8)
Unadjusted rate ratio	4.58 (3.30 - 6.36)	Reference
Rate ratio adjusted for matching criteria <sup>‡</sup>	4.57 (3.28 - 6.36)	Reference
Fully adjusted rate ratio <sup>**</sup>	4.90 (3.51 - 6.85)	Reference
<b>Outpatient Utilization<sup>§</sup></b>		
Per person, median (IQR) <sup>*</sup>	128 (48 - 220)	43 (13 - 113)
Unadjusted rate <sup>†</sup>	47.8 (43.9 - 52.0)	21.9 (19.7 - 24.4)
Unadjusted rate ratio	2.19 (1.92 - 2.51)	Reference
Rate ratio adjusted for matching criteria <sup>‡</sup>	2.18 (1.90 - 2.48)	Reference
Fully adjusted rate ratio <sup>**</sup>	2.19 (1.92 - 2.50)	Reference

\* During follow-up

† Rate per year

‡ Adjusted for matching criteria: age (within 2 years), sex, race, field center and propensity score

\*\* Adjusted for matching criteria and high school graduate, current smoking, current drinking, body mass index, hypertension, antihypertensive medication, diabetes mellitus, and prior heart failure and coronary heart disease

§ Outpatient utilization defined as unique claims per date of service

IQR = interquartile range

**Table 11.9: Primary reason for inpatient (MedPAR) and outpatient healthcare utilization among propensity score matched Atherosclerosis Risk in Communities Study participants stratified by atrial fibrillation status**

	<b>AF (n = 360)</b>	<b>No AF (n = 360)</b>	<b>Adjusted Rate Ratio<sup>t</sup></b>
<b>Inpatient (MedPAR) Utilization, days</b>			
Unadjusted rates <sup>*</sup>			
AF related	0.2 (0.1 - 0.4)	--	--
Other CVD related	2.7 (2.0 - 3.7)	0.5 (0.3 - 0.8)	6.30 (3.62 - 10.95)
Non-CVD related	6.4 (5.1 - 8.2)	1.6 (1.2 - 2.2)	4.02 (2.76 - 5.85)
<b>Outpatient Utilization<sup>§</sup></b>			
Unadjusted rates <sup>*</sup>			
AF related	4.2 (3.5 - 5.0)	--	--
Other CVD related	7.5 (6.7 - 8.4)	2.9 (2.5 - 3.4)	2.70 (2.26 - 3.24)
Non-CVD related	35.7 (32.7 - 39.1)	19.0 (17.1 - 21.2)	1.87 (1.63 - 2.14)

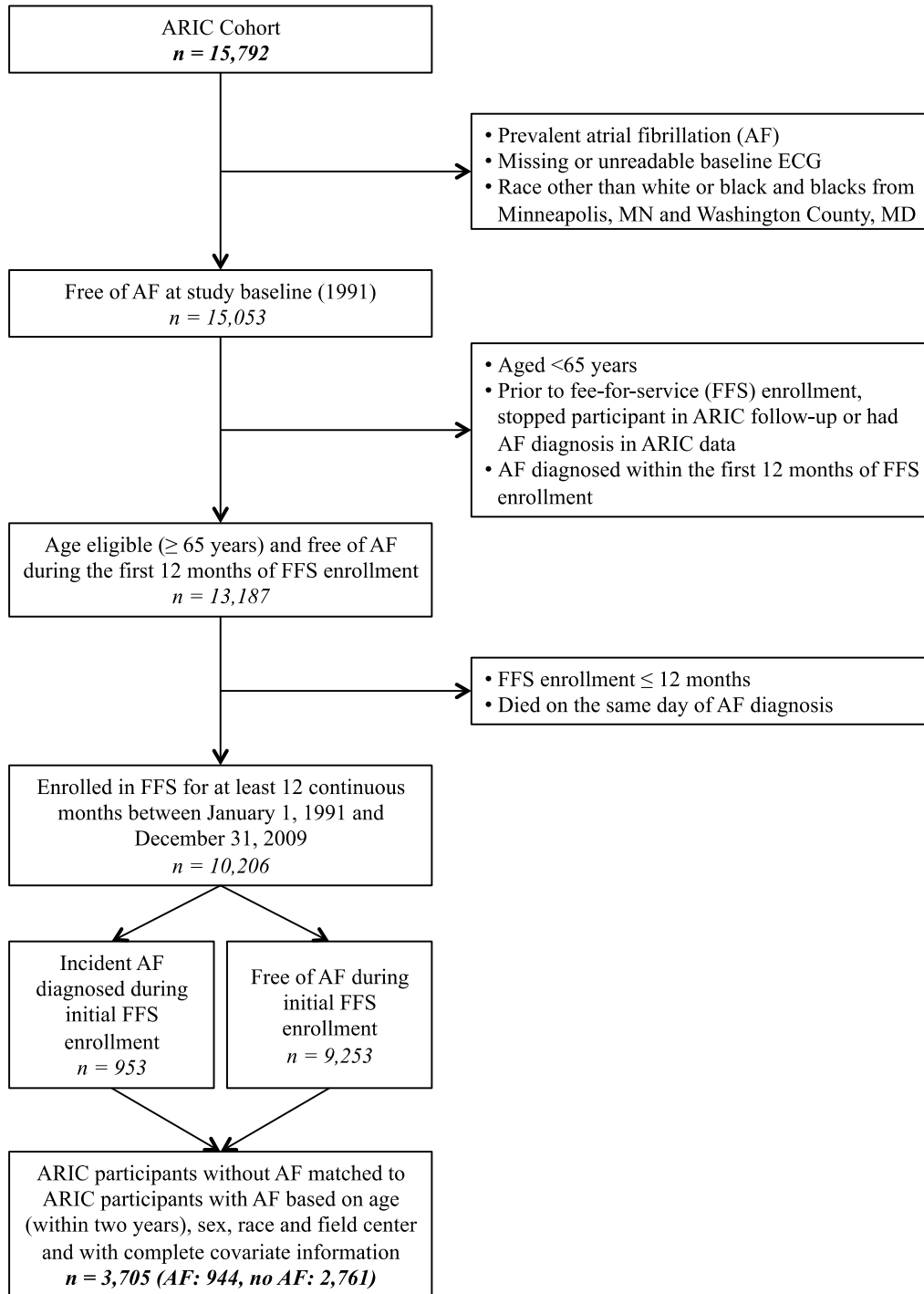
\* Rates are days per year for inpatient (MedPAR) data and number of unique claims per date of service per year for outpatient claims

<sup>t</sup> Adjusted for matching criteria and high school graduate, current smoking, current drinking, body mass index, hypertension, antihypertensive medication, diabetes mellitus, and prior heart failure and coronary heart disease

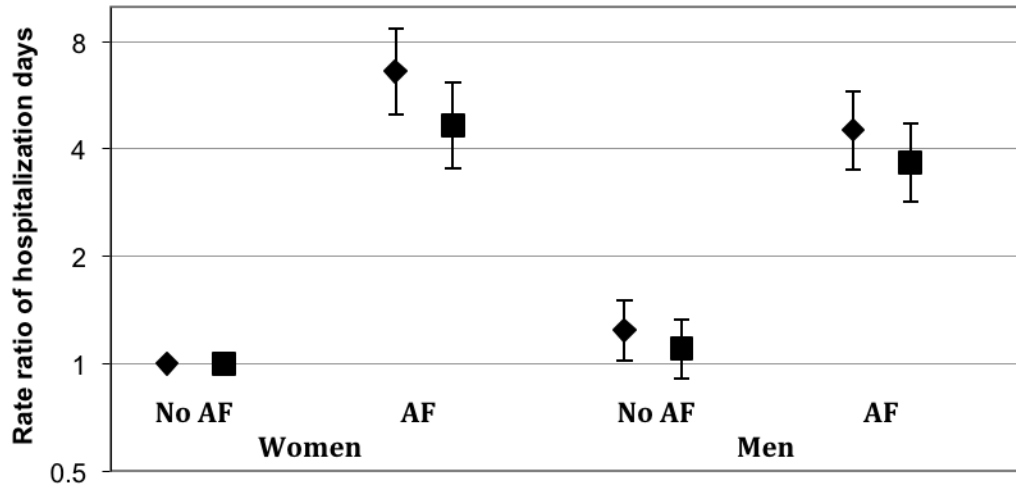
<sup>§</sup> Outpatient utilization defined as unique claims per date of service

## 11.7 FIGURES

**Figure 11.1: Derivation of study sample**



**Figure 11.2: Rate ratio of days hospitalized per year stratified by sex and atrial fibrillation status**



Reference: Women without AF

Diamonds represent rate ratios adjusted for matching criteria: age (within 2 years), sex, race and field center

Squares represent rate ratios adjusted for matching criteria and high school graduate, current smoking, current drinking, body mass index, hypertension, antihypertensive medication, diabetes mellitus, and prior heart failure and coronary heart disease



## 12.0 SUMMARY

The primary aims of this dissertation were to assess temporal trends in the occurrence and prognosis of AF among acute MI patients, to determine the usefulness of administrative data to identify incident AF and to describe the impact of AF on healthcare utilization.

The aims of the first manuscript were to address the lack of precision in trend analyses and the scarce data in nonwhite populations.<sup>22,168</sup> In this large population-based sample, the prevalence of AF accompanying MI increased slightly over the 23-year study period, from 11% to 15%. Overall, co-occurrence of AF in the setting of MI was associated with an increased risk of death; the multivariable adjusted odds of 1-year mortality were 1.47 times greater (95% CI: 1.07 – 2.01) among MI patients with AF compared to those without AF. However, there was no evidence that the impact of AF on MI survival changed over time or differed over time by sex, race or MI classification.

In the second manuscript the objectives were to address the limited knowledge regarding the usefulness of administrative data to determine AF incidence, the lack of inpatient and outpatient claims comparison, and the paucity of data in nonwhite populations.<sup>180</sup> In this community-based prospective study, incidence rates of AF were slightly lower based on active ARIC follow-up compared to CMS surveillance; incidence rates per 1,000 person-years were 10.8 (95% CI: 10.1-11.6) and 13.6 (95% CI: 12.8-14.4) in ARIC and CMS, respectively. However, the rates by either method followed a similar pattern; they increased with age and were consistently higher among whites and men

compared to blacks and women, respectively. Concordance of incident AF between active ARIC follow-up and CMS surveillance was very good,<sup>208</sup> with a K statistic of 0.77 (95% CI: 0.75 – 0.80), although 19% more AF cases were identified from CMS largely due to outpatient AF ascertainment. Despite having to exclude 18,194 person-years of follow-up available to ARIC, out of 97,740 total person-years, because those participants were in Medicare Advantage plans and therefore had incomplete CMS claims, there was little bias in associations based exclusively on active ARIC follow-up versus surveillance including CMS.

Due to the substantial and increasing burden of AF on healthcare utilization, the limited knowledge about inpatient and non-inpatient utilization, and the lack of sex- and race-specific data,<sup>36,212,235</sup> the aims of the third manuscript were to heighten understanding of how AF patients utilize healthcare and to provide data that can be used to allocate adequate resources for the care of AF patients. In this sample of AF patients and matched controls from a community-based prospective study, rates of healthcare utilization, both inpatient and outpatient, were substantially higher among participants with AF compared to those matched with cases and without AF. The average numbers of days hospitalized per year were 13.1 (95% CI: 11.5-15.0) and 2.8 (95% CI: 2.5-3.1) for those with and without AF, respectively. The corresponding numbers of outpatient claims per year were 53.2 (95% CI: 50.4-56.1) and 23.0 (95% CI: 22.2-23.8) for those with and without AF, respectively. There was modest evidence of sex modifying the association between AF and inpatient utilization; AF was associated with higher inpatient utilization in women than in men. In both the inpatient and outpatient setting, healthcare utilization

was greatest for non-cardiovascular disease (CVD)-related reasons for those with as well as those without AF. However, the magnitude of the difference in utilization between those with and without AF was greatest for other-CVD-related reasons; for those with, compared to those without AF, the adjusted rate ratio for days hospitalized per year for other-CVD-related reasons was 4.76 (95% CI: 3.51 – 6.44) and for outpatient utilization the corresponding adjusted rate ratio was 2.46 (95% CI: 2.24 – 2.70).

Each of these manuscripts contributed to the AF literature by addressing an important knowledge gap of public health significance. In the first study, the negative impact of AF on survival in the setting of MI persisted throughout the study, from 1987 through 2009. Co-occurrence of AF in MI should be recognized as a critical clinical event. Currently, prognostic risk scores for MI do not consider AF in determining the risk of death and therapeutic decisions.<sup>195,196</sup> Inclusion of AF in prognostic scores should be explored, especially because prevalence of AF in the community is estimated to increase as the population ages,<sup>2,3</sup> and because AF often complicates MI.<sup>23,166</sup> Furthermore, the optimal treatment strategy is unresolved when the risks of thromboembolism and bleeding are considered<sup>197,198</sup> and new oral anticoagulant agents raise additional questions about the optimal treatment strategy.<sup>199,200</sup> In the second study, two very different methods to identifying incident AF produced similar results with comparable incidence rates, high concordance, and little evidence of bias of associations between AF and risk factors. The ability to identify incident AF events is particularly important for studies of healthcare utilization over the entire disease course of AF, comparative effectiveness research, and drug safety surveillance. This study provides support for the potential value

of utilizing multiple data sources to identify incident AF and suggests the need for caution about completeness of each data source. Each approach has unique strengths and limitations and, collectively, could provide a more complete picture of newly-diagnosed AF. Moving forward, ARIC and similar studies should evaluate how to incorporate Medicare and other administrative data in the ascertainment of outcomes, factoring in the data limitations regarding coverage and quality. In the third study, the substantially greater healthcare utilization (inpatient and outpatient) among those with AF, especially the differential utilization due to other-CVD-related reasons, highlighted the need for AF treatment to address the accompanying cardiovascular comorbidities in addition to rate or rhythm treatment. Treatment guidelines should incorporate assessment of overall cardiovascular risk and provide recommendations on comprehensive management of the patient.

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## 14.0 APPENDIX: DICTIONARY OF ABBREVIATIONS

ACME	Automated Classification of Medical Entities
AF	atrial fibrillation
AFL	atrial flutter
ARIC	Atherosclerosis Risk in Communities
AV	atrioventricular
BMI	body mass index
BPM	beats per minute
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CK	creatinine phosphokinase
CMS	Centers for Medicare and Medicaid Services
CPAP	continuous positive airway pressure
CRP	C-reactive protein
CVD	cardiovascular disease
ECG	electrocardiogram
FEV <sub>1</sub>	forced expiratory volume in one second
FFS	fee-for-service
FHS	Framingham Heart Study
HF	heart failure



HMO	health maintenance organization
HR	hazard ratio
ICD	implantable cardiac defibrillator
ICD-9	<i>International Classification of Diseases, 9<sup>th</sup> revision</i>
ICD-10	<i>International Classification of Diseases, 10<sup>th</sup> revision</i>
IQR	interquartile range
K	Kappa statistic
LOS	length of stay
MedPAR	Medicare Provider Analysis and Review
MI	acute myocardial infarction
NSTEMI	non-ST-Elevation myocardial infarction
OR	odds ratio
OSA	obstructive sleep apnea
PDE	Prescription Drug Event
PPV	positive predictive value
PREDICT	Predicting Risk of Death in Cardiac Disease Tool
PUFA	polyunsaturated fatty acid
SNPs	single-nucleotide polymorphisms
STEMI	ST-Elevation myocardial infarction
US	United States
WHS	Women's Health Study