The Role of Race in the Development of Atrial Fibrillation and Risk of Embolic Stroke: A Systematic Review

Kimberly Anne Selzman, M.D.
April 13, 2009

Reviewed by:
Margaret L. Gourlay, M.D.
and
J. Paul Mounsey, M.D., PhD.

TITLE: The Role of Race in the Development of Atrial Fibrillation and Risk of Embolic Stroke: A Systematic Review.

INTRODUCTION

Atrial fibrillation [AF], the most common arrhythmia in the United States, affects an estimated 2.2 million people in this country alone. The prevalence of AF grows incrementally with increasing age, and the majority of people living with AF are over the age of 65 years. For people less than 55 years old the prevalence is 0.1%, compared to an approximate 10% prevalence in people over the age of 80 years. The incidence of AF is also on the rise resulting in predictions for AF to affect 10 million Americans by the year 2050.[1] This increase is likely due to the ongoing aging of the population and an increase in the prevalence of individuals in the community with one or more risk factors for developing AF.[2] Along these same lines, people are now living longer with medical conditions such as diabetes mellitus and hypertension, which predispose individuals to developing AF. The trend of increased AF prevalence in the U.S. in recent years and the projected continued increase over the next few decades will raise AF to unprecedented levels. In fact, current projections based on data from the Framingham Heart Study put the lifetime risk for developing AF in this country at approximately 16% for individuals around 40 years of age, and up to 25% if there is a prior history of congestive heart failure or myocardial infarction.[2]

Several clinical risk factors have been linked to the development of AF, particularly advancing age which is associated with structural changes such as fibrosis in the heart that predispose older individuals to AF.[3] In addition to age, other clinical risk factors for developing

AF include male sex, cardiovascular risk factors such as hypertension and diabetes mellitus, and other cardiac conditions such as valvular heart disease, prior myocardial infarction, and congestive heart failure.[4-6] Along with these traditional risk factors, more recently recognized risk factors such as obesity and sleep apnea have also been recognized. Echocardiography has also allowed detection of various validated cardiac structural risk factors such as left ventricular hypertrophy and increased left atrial size.[7, 8] Although race has never been considered a risk factor for developing AF, there is evidence to suggest that whites develop AF more than other racial groups out of proportion to the prevalence of the clinical risk factors mentioned here. As little is known about the interaction of race and AF, this paper seeks to review all relevant published data on race and AF.

Many experts have called AF in this country an emerging epidemic.[9, 10] The increasing prevalence of AF is important because AF is not a benign disease. Although once thought to be clinically unimportant and merely a nuisance to be tolerated by the individual, it is now recognized as a major risk factor for thromboembolic disease as well as a factor in overall long-term mortality. The single most feared sequela of AF is an ischemic stroke due to thromboembolic complications from a left atrial or left atrial appendage thrombus, or possibly an aortic atheroma. AF is felt to be responsible for about 15% of all ischemic strokes.[11, 12] Embolic strokes due to AF tend to be larger and are more likely to be fatal compared to small vessel strokes. Systemic embolization appears to be less common but can be equally devastating with resultant ischemic bowel or ischemia and necrosis of distal extremities. Embolization is one of the reasons why AF carries a 1.5-2-fold increase in mortality risk compared to individuals without AF. In fact, in large observational studies such as Framingham, AF carries long-term

significant morbidity and mortality even when controlling for other co-morbidities such as heart disease and diabetes.

Randomized placebo-controlled trials have estimated the overall risk of stroke in patients with AF who are not anticoagulated to be approximately 4.5-5% per year.[13] This is a general risk assessment when considering all AF patients in aggregate. However, extensive research has been conducted looking at individual risk factors for stroke in patients with non-valvular AF to determine which AF patients are low risk and which are high risk for thromboembolic complications. This has important clinical implications for patients with AF since these clinical risk factors help stratify the risk of stroke and tailor anticoagulation therapy for individual patients. Similar to the risk factors for developing AF in the first place, congestive heart failure, hypertension and advanced age (i.e. greater than 75 years old) are all known risk factors for ischemic stroke in AF patients. Additionally, known diabetes mellitus and a history of prior stroke are also known to elevate the risk for thromboembolic complications.[2] These are currently the main risk factors considered when determining the need for anticoagulation in a patient with AF.

It is not surprising that AF is a burden on the healthcare system as well as the individual given that it is a chronic disease which can be refractory to treatment. The management of AF often involves various diagnostic studies, pharmacologic treatments and long term management with anticoagulation therapy. AF can also have a synergistically negative effect on overall health when combined with other cardiovascular diseases. For example, in patients with well controlled heart failure due to systolic or diastolic dysfunction, AF can precipitate an exacerbation that may require admission to the hospital. Similarly, AF with rapid ventricular rate can contribute to active coronary ischemia in a patient whose ischemia burden is typically well controlled.

Although multiple prior studies have closely scrutinized the relationship between the development of AF and age, gender, and multiple medical conditions, only recently has race or ethnicity been mentioned as a possible "risk factor" worth investigating. Relatively little is known about varying susceptibility to AF, or differences in incidence and prevalence among different ethnic groups. It is unknown if race truly affects AF rates or whether there is a different pattern of AF expression. It is also unknown if the risk of stroke varies for AF patients of different ethnic populations. We therefore sought to perform a systematic review of all clinical studies looking at ethnicity as a risk factor for developing AF, and as a risk factor for ischemic stroke in patients with non-rheumatic valvular AF.

METHODS

Methods for Systematic Review of the Literature: MEDLINE and The Cochrane Database of Systematic Reviews were searched for abstracts, papers, clinical trials and reviews. Four primary PubMed searches were performed using the following search terms: (1) MeSH term atrial fibrillation with subheading ethnology yielded 31 articles written in English. (2) MeSH terms atrial fibrillation and continental population groups (i.e. race) yielded 69 studies, all of which were redundant from MeSH search (1) or irrelevant to our focused interest. This search yielded one additional publication of interest. (3) MeSH terms atrial fibrillation, ethnicity and epidemiology yielded 3 additional relevant studies out of 44 total publications. (4) MeSH terms atrial fibrillation and stroke with subheading ethnology yielded another two relevant studies out of ten total. Although no limits were used for publication date, all the Medline articles included were published between 1997 and 2008. The Cochrane Database search was done in three ways, using atrial fibrillation as a keyword, as a review topic, and as a MeSH term. This resulted in no relevant articles that analyzed racial or ethnic differences with respect to atrial fibrillation. We

also used references obtained from bibliographies in articles generated from the MEDLINE searches.

Due to the general paucity of data on the interaction between ethnicity and atrial fibrillation and between ethnicity and stroke, we considered all study types and any date of publication. Although there were no pre-specified criteria for selection of trials in terms of trial design, trials that tested a surgical procedure, a catheter ablation procedure, a pacemaker, or an antiarrhythmic drug were excluded. Trials and observational studies that included race/ethnicity as part of the demographic information studied were emphasized. Studies that did not analyze by race, either because few non-white patients were included, or because they did not choose to look at race, were excluded. For example, the Framingham cohort was not included since few non-white participants were included and no analysis by race was done. Since no intervention was assessed, data from only one randomized controlled trial were felt to be relevant. Although no limits for publication dates were pre-specified, all studies were conducted between 1990 to present with the exception of the Framingham database studies since Framingham data collection began in 1948. All studies included adult subjects only; no pediatric populations were included in this review. Searches were restricted to the English language. Studies based in racially homogenous countries that did not enroll non-Caucasian subjects or subjects of African descent were excluded. The references of the selected publications were also reviewed for additional studies and publications.

A total of 18 population-based longitudinal cohort studies, 5 of which were retrospective studies, 2 cross-sectional studies, and 1 post-hoc analysis of a prospective randomized controlled trial were included. In addition, 8 articles including reviews and editorials met the search term criteria. The two outcomes for analysis and review were (1) development of atrial fibrillation in

the general population including individuals with hypertension and other predisposing conditions, and (2) occurrence of ischemic thromboembolic stroke in patients with atrial fibrillation. One reviewer collected the data. Two additional readers reviewed the studies and their results.

Methodological quality assessment

The method for determining the quality of the trial or cohort study was a combined assessment of study quality, internal validity, and handling of confounding variables. The assessment rating was largely based on the 2001 Center for Reviews and Dissemination (CRD) Report 4 which focuses on the quality assessment of cohort studies.[14, 15] The level of evidence was not specifically rated in this review since none of the studies were randomized controlled trials, and almost all studies were either cross sectional or observational studies. The checklist of criteria used is provided in Table A.

Table A. Quality Assessment Checklist**

1. Are the groups being compared and the confounding variables adequately described?
a. Are the groups reasonably similar at baseline (comorbidities, age)?
b. Were the groups comparable on confounding variables?
c. Are the groups at a similar point in disease progression?
2. Was there adequate adjustment for the differences and confounding variables?
3. Are the inclusion/exclusion criteria reasonable?
4. Was bias (selection, performance, measurement, attrition) present?
5. Were the drop out rates similar between groups and at an acceptable level? Were all participants accounted for at the end of the study?
5. Does the study have internal validity?
a. Adequate sample size to detect difference?
b. Was a power calculation done?
c. Prevention of systematic errors or bias?
6. Was the follow up long enough and did the entire cohort have follow-up?
7. Was the determination of race done reliably, consistently, clearly described?
8. Are the enrolled subjects representative of the population at large? Is there sufficiently broad representation of the population who is at risk for developing atrial fibrillation?
9. Was the cohort followed prospectively?
10. Was the detection and diagnosis of Afib made reliably and equally between groups?

****** This is a modified checklist for observational cohort studies based on the Centre for Reviews and Dissemination (CRD) Quality Assessment Checklist.

RESULTS

Eighteen publications met the primary search term criteria. Of these, eleven looked at race and atrial fibrillation, and seven looked at race and stroke etiology. Studies that had multiple publications over time were only counted once. There were no randomized controlled studies that fit our search criteria; most studies included were prospective observational or retrospective cross sectional studies. The Framingham Heart study was not included since it consists of a predominantly white cohort and was never analyzed for ethnic differences in lifetime risk of AF.[2, 16] The landmark randomized controlled studies that compared different anticoagulation strategies in AF patients were not included in this review because either a breakdown of the cohort by race was not done, or there were too few African American patients enrolled.[17-21]

Quality Assessment: The source population in the studies reviewed here which looked at AF incidence and race often were adequate and appropriate in that they were large studies using a comprehensive database. The biggest problem with some of these observational studies was the low enrollment of non-white subjects which can make conclusions or even the formulation of hypotheses difficult. For example, the ATRIA study, whose source population was Kaiser HMO patients with non-transient AF, blacks made up only 3.6% of the total cohort. The VA study by Borzecki et al used the 1999 Large Health Survey of Veteran Enrollees post-hoc and had 12% black enrollment which is reasonably large. However, it was a survey study which makes it prone to non-respondent bias. Cohort studies that collected the data prospectively were considered to be of higher quality than studies which collected the data post-hoc. Regardless of data collection method, the studies in this review which were observational were certainly prone to bias. Since the groups were not determined by random allocation, selection bias is a concern.

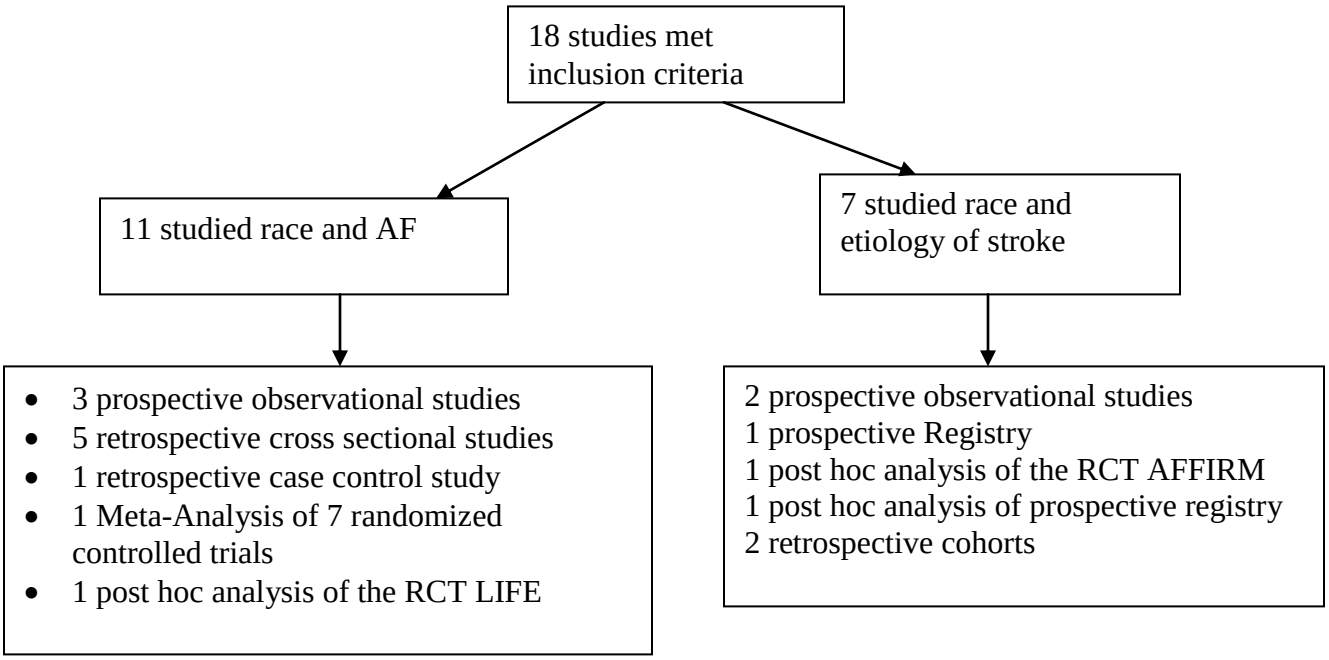
Furthermore, given that the groups were determined based on race, the groups may vary by socioeconomic status or access to healthcare. The studies using the Kaiser HMO dataset should not have some of the concerns with systematic differences between the white and black subjects in the sense that access to healthcare and detection of Afib should be relatively similar. However, generalizability of the source population may be of concern, Bias may also result due to misclassification of race. There was no unifying method for race determination. Some studies used patient self reporting where other studies relied on the demographic data from the electronic medical record. The data collection regarding race was also fairly simplified, where persons of mixed heritage were reported as a single race. This certainly oversimplifies the complicated issue of genetic heritage and may classify a person as black or white when in fact they may classify themselves as Indian or of mixed descent.

Description of Studies:

Studies on race and AF: There were 3 prospective observational studies, and one post-hoc analysis of a prospective randomized controlled trial. The Cardiovascular Health Study was the only multi-center prospective trial that looked at the incidence of AF. The other studies looking at the role of ethnicity in developing AF were 6 retrospective cross sectional studies and 1 Meta-Analysis of seven randomized controlled trials (Table I). The studies looking at race and AF were conducted in the U.S. and therefore the patients designated as being Black or African American in these studies resemble the African American demographics of this country. The mean age of participants in ten of the eleven studies from Table I (excluding the EKG database study which ranged from 20 years to 99 years old) ranged from 55 to 80 years old. Women made up 43% to 58 % of the participants in these trials except for the VA study which was 100% male. Enrollment dates for these studies ranged from 1996-2000 except for the Cardiovascular Health

Study which used data from 1990-1993 to determine incidence of AF in that cohort, and the EKG study which looked at EKGs from 1996-1998 at a single institution.

Studies on race and stroke: Of the 7 studies looking at stroke and race, two were prospective observational studies, one was a prospective registry, and two were post hoc analyses of prospectively collected data. (Table III). These studies looked at racial differences in risk factors for AF, prevalence of AF at time of stroke, and stroke subtype. Some of these studies were conducted in England and the non-white patients were typically of African, Caribbean, or South Asian descent. The mean age of participants in these 6 studies ranged from 67-80 years old. Women made up 39-54% of the enrollees in these studies. Enrollment dates ranged from 1990-2005. Only two studies examined the risk of ischemic stroke or intracranial hemorrhage in AF patients over time (The AFFIRM outcomes analysis by Bush et al and the Kaiser Permanente retrospective analysis by Shen et al, both listed in Table III).[22, 23] The other studies looking at the role of ethnicity were stroke studies that calculated the prevalence of AF in patients who presented with stroke.



African American Race and Risk Factors for developing AF

Since the early 1990's, many large clinical studies like ARIC (Atherosclerosis Risk in Communities) sponsored by NHLBI and NHANES (National Health and Nutrition Examination Survey) have repeatedly demonstrated that African Americans have a greater prevalence than whites of the comorbidities associated with the development of AF. These include hypertension, ventricular hypertrophy, and diabetes. The greater prevalence of these risk factors for AF in black subjects has been shown in various types of studies with various disease states being investigated from hypertension to heart failure, to stroke. For example, it has been shown that left ventricular hypertrophy is more prevalent in blacks than whites whether assessed by MRI, echocardiography or by EKG[24] and is quite common in both black men and women. Many studies have shown that the prevalence of type II Diabetes Mellitus is greater in blacks compared to whites, but the ARIC Study also showed that the incidence of diabetes is greater as well.[25] And a recent systematic review of cardiovascular risk factors reviewing 16 studies found that blacks had higher rates of hypertension and diabetes.[26]

In the AFFIRM trial which enrolled patients with known AF and moderate risk factors for stroke, although African Americans only comprised 6.6% of the cohort, a retrospective analysis did look for racial differences in risk factors. The AFFIRM data showed that African Americans with AF were significantly younger (65.7 vs. 70.3) and that they were more likely to have hypertension (68.3 vs. 49.3%) and heart failure (36.2 vs. 21.9%) compared to the white subjects with AF.[22]

Population studies have also shown that medical conditions which elevate risk of AF such as hypertension and diabetes are in fact more prevalent in the African American community

than the Caucasian community. A comprehensive review of secular trends of hypertension over the past four decades shows that African Americans consistently have had a greater prevalence of high blood pressure compared to whites. Although the gap seems to be narrowing significantly in the recent past, overall, hypertension is still more prevalent in African Americans.[27] Recent data from NHANES and NHLBI estimate that hypertension affects approximately 32% of non-Hispanic white adults and 44% of non-Hispanic black adults.[28]

Estimates of diabetes prevalence broken down by ethnic group are provided by the CDC sponsored National Health Interview Survey (NHIS) which surveyed individuals from 2004 to 2006. This survey of people which included adults over 20 years old revealed that 6.6% of whites, 7.5% of Asians, 10.4% of Hispanics, and 11.8% of blacks have known diabetes.[29] A study looking at a sample of Medicare beneficiaries aged 67 or older also showed that although the prevalence of diabetes is increasing across the board, it is most prevalent in blacks and Hispanics.[30] And probably for a multitude of social, economic and individual factors, the number of deaths attributed to diabetes per 100,000 population for blacks is twice that compared to whites (47.0 versus 22.5).[31]

Smoking, a risk factor for overall cardiovascular health, also has varying prevalence among the different racial groups. Studies have demonstrated that the rate of new smokers is greater for blacks than whites, and conversely the rate of smoking cessation is less for blacks. In the 10 year longitudinal CARDIA study which began in 1985, African American men and women had higher smoking prevalence rates, higher smoking initiation rates and lower cessation rates than whites. The cause for this was felt to be largely socioeconomic. The smoking rates for Blacks and Whites as of 2007 are 21.5% and 19.7% according to the national BRFSS telephone survey.

In summary, the well known risk factors for developing AF such as hypertension and diabetes mellitus are more common in blacks than whites in this country. The reasons for this are likely multifactorial, including socioeconomic factors, access to healthcare, as well as genetics. It seems logical to infer that AF would be more prevalent in blacks than whites, but this is not what is demonstrated in the studies looking at this.

The Racial Paradox with AF

Given the well reported racial discrepancy in disease states such as diabetes and hypertension, when researchers at the Kaiser Permanente Health Maintenance Organization (HMO) recognized that the prevalence of AF among different racial groups was quite variable, and in particular whites had a much higher prevalence compared to blacks, this seemed paradoxical. Why would a group of patients with a greater prevalence for many of the AF risk factors have a lower incidence or prevalence of AF? They used their Kaiser Permanente database of northern California to look at the prevalence of AF in roughly 1.9 million people. They specifically looked at AF incidence in patients over 50 years old and compared black patients to white patients within the HMO. AF appeared to be more common in whites than blacks (2.2% vs. 1.5% $p<0.001$).[32] They also broke down the cohort by 10-year increments and showed that the difference between blacks and whites persisted into the 7^{th} and 8^{th} decade of life. For patients between 80-89 years old, the AF prevalence was 9.9% vs. 7.7% respectively ($p=0.001$). Although these are crude rates that are unadjusted for co-morbidities, this helps to dispel the possibility that the smaller prevalence of AF for African Americans in many trials and observational studies is in large part due to the younger age of the black cohort compared to the white subjects.

In terms of correlating risk factors for AF to actually developing AF, The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study is another large dataset of patients with essential hypertension and LVH that was analyzed post hoc for AF incidence in 8831 black and white patients.[33] They hypothesized that a reduction in LVH would translate into a reduction in AF incidence. Interestingly, a marker of LVH (the Cornell voltage-duration product) during treatment was found to be a strong predictor of AF only in the non-black patients. Black patients also had a lower incidence of new-onset AF compared to whites (4.8% vs. 8.1% p=0.007). The fact that LVH was not a predictor of AF in blacks may have been due to the much lower prevalence of AF in blacks or less likely due to a higher prevalence of other risk factors for developing AF in this group.[8]

It has been shown in large observational studies that patients with AF do have an increased overall mortality risk when compared to similar patients without AF.[16] It has also been shown in congestive heart failure (CHF) studies that CHF and AF in combination synergistically confer a high mortality. Studies have shown that blacks with CHF tend to have higher mortality rates than whites with a similar degree of heart failure.[34, 35] Again, the researchers at Kaiser Permanente asked an important question: Is it possible that the AF paradox reverses in the CHF population and an increased prevalence of AF is a contributor to the increased mortality seen in blacks with CHF compared to whites? They looked at all Kaiser patients admitted to any of sixteen Kaiser hospitals in northern California with a diagnosis of CHF between July 1, 1999 and June 30, 2000 (the EPOCH study). Among 1,373 patients with CHF, 37% had AF. However, when broken down by race, the prevalence of AF in the African American cohort was 20% compared to 38% in the white cohort ($p<0.001$).[36] This is despite a significantly greater prevalence of hypertension and an equal prevalence of diabetes. The Black cohort was younger

than the white cohort (mean of 67 vs. 74 years respectively) however this was adjusted for in their multivariate model where race persisted as a significant factor.

These results were corroborated by the Yale CHF study which looked at roughly 400 consecutive CHF admissions to Yale hospital. African Americans comprised 21% of the cohort. Similar to the EPOCH study, African Americans tended to be younger with a greater prevalence of hypertension, and a significantly lower prevalence of AF at the time of admission (28% vs. 14% p=0.01).[37] In addition, whites were more likely to develop AF prior to discharge from the hospital (16.6% versus 7.3%, p=0.04). Another smaller prospective observational CHF study with 163 patients also found that the African American patients were younger (64 vs. 71 years p=0.003), and more likely to have hypertension and less likely to have AF (42% vs. 21% p=0.006).[38]

A Veterans Affairs study retrospectively merged two large databases and picked a random sample of 1.4 million veteran enrollees who were included in the study by returning a mailed questionnaire.[39] They had over 650,000 respondents and roughly 5% were Black. The prevalence of AF was 6.1% in Caucasians, 2.6% in African Americans, 2.6% in Hispanics, and 3.4% in Asians. The Odds Ratio for having AF in whites was greater than all other ethnic groups and the biggest difference was in comparison to the black cohort (OR 1.84).

The paradox between prevalence of AF risk factors and prevalence of AF in the African American community has also been shown in an electrocardiography (EKG) study where everyone who had an EKG as part of their evaluation was included. Only gender and age were known, not medical conditions or duration of the arrhythmia. Still, the cohort was approximately 40% black lending itself to a reasonable comparison. Looking at all ages combined, the prevalence of AF on the EKG was 2.5% for blacks and 7.8% for whites ($p<0.001$).[40]

Lending even more evidence that Blacks may truly develop AF less often than Whites do, a study compared Black and White patients with Alzheimer's disease. Similar to the stroke studies that show racial differences in AF prevalence in a group that shares a medical condition in common i.e. stroke, this study shows the racial differences in medical co-morbidities in an Alzheimer's cohort. Again, Blacks had a greater prevalence of hypertension and a significantly lower prevalence of AF.[41]

The various studies have looked at a general medicine cohort, a CHF cohort, stroke patients, and even Alzheimer's disease and regardless of the underlying medical conditions, African Americans consistently have a lower burden of AF than their Caucasian counterparts even after adjustment for potential confounding factors such as age. It does not appear to be simply a discrepancy in the detection of AF or an increased incidence of mortality in black subjects with AF. The underlying reason is still unknown.

Asian Race and Risk for developing AF

The risk of developing AF in the Asian community in this country has not been well studied. There are only a few studies that actually separated the Asian patients from the other non-white patients for analysis purposes. The large VA outpatient database study mentioned previously was mostly white, but Asians did comprise 3.6% of the study cohort.[39] Asians had a similarly low incidence of AF as Blacks did (3.6% vs. 3.4% respectively compared to 5.7% for whites). The odds ratio for AF by race was 1.4 for whites compared to Asians.

One EKG database study out of a public hospital in San Diego looked at over 80,000 EKGs and approximately 4,000 had a diagnosis of AF, 737 of which correlated to a first time hospitalization.[42] Asian patients comprised 11% of these 737 EKGs. When looking at these AF

patients, the Asian patients were similar in age to the white patients and had similar rates of diabetes. However, there was a significantly greater prevalence of left ventricular hypertrophy by EKG criteria in Asians corresponding to an odds ratio of 2.76 for hypertrophy. One possible explanation is that Asians share the well known risk factors for AF, but in addition, ventricular hypertrophy plays a more prominent role in terms of risk stratification. A recent meta-analysis of seven large acute coronary syndrome trials looked at the frequency of AF in patients with acute coronary syndromes over time also found a lower frequency of AF in Asians compared to Whites (4.7% vs. 7.6%, $p<0.001$). This analysis included over 94,000 patients total with 1,735 being of Asian descent.[43] Asian patients tended to be younger but with a greater prevalence of diabetes. Unfortunately, ventricular hypertrophy was not investigated in this analysis. Another limitation of this analysis is that under the designation "Asian" are pooled together Chinese, Japanese, Korean and various other Asian nationalities making the Asian group probably quite heterogeneous and certainly limits the use of ethnicity as a surrogate for possible genetic differences.

A population based study in China examined the prevalence of AF in their community.[44] This was a population screening of almost 2,000 Chinese people and the overall AF incidence was quite low at 1.5%. Again this was just an observational study, and conducted outside the U.S. Another observational study out of mainland China demonstrated a prevalence of AF of 0.65%, which is lower than the U.S. prevalence despite a much greater prevalence of rheumatic heart disease.[45] This limited data does suggest that Asians too have a diminished incidence and prevalence of AF compared to whites.

These data highlight the importance of enrolling various minorities in these observational studies, not just black and white, who may have a different prevalence and incidence of AF.

Only then can it be further delineated if there is in fact a true difference in susceptibility to AF among the various racial groups. Although difficult to do in this country due to small sample size, keeping the many ethnic groups separate rather than lumping them together under "Asian" would provide further data of potential differences in risk factors for AF and prevalence.

Hispanic Race and Risk for developing AF

The data on AF in the Hispanic community as compared to whites or blacks is also very limited. Again, the only large cohort to look at the prevalence of AF in Hispanics was the 1999 Large Health Survey of Veteran Enrollees. As in other studies, whites were significantly older than the other racial groups. The mean age for whites and Hispanics were 65 and 61 years respectively. When adjusted for age, AF prevalence was only 3.0% in Hispanics, which was significantly lower than the 5.7% in whites.[39] This corresponds to an OR for AF of 1.77 for white versus Hispanic subjects. While whites had a greater prevalence of conditions considered risk factors for AF such as coronary disease and valvular disease, Hispanics had the highest prevalence of diabetes mellitus (27.5%). The authors maintain that there is a racial variation and that there may be a genetic basis for this difference.

When looking at the AFFIRM Trial which only enrolled subjects with AF, only 3.3% (132 subjects) were Hispanic making comparisons limited. In terms of baseline characteristics, Hispanics were younger than whites (65 vs. 70 years, $p<0.001$). Despite their younger age, Hispanics were sicker in that they were more likely to have a history of cardiomyopathy with a depressed ejection fraction or heart failure. It isn't described whether Hispanics and whites had comparable rates of hypertension and diabetes. Therefore, it is unclear if any differences exist based on this dataset, however it suggests that ventricular dysfunction may play a greater role in Hispanics for development of AF. Given the small enrollment of Hispanics in this trial, it is

difficult to draw definitive conclusions and in fact seems to raise more questions regarding racial differences of AF since rhythm control reduced mortality in the Hispanic cohort only and not the other groups.

The Northern Manhattan Stroke Study was the first to look at stroke patients from a multiracial community and determine racial differences in stroke risk factors.[46] This study was based on an ongoing prospective registry of all acute stroke patients who present to the urban Presbyterian Hospital of New York City which has a large black and Hispanic patient population. Hispanics had a significantly lower prevalence of AF compared to whites (4% vs. 8%) despite having a greater prevalence of hypertension and diabetes. The authors also calculated the population attributable risk for individual risk factors including AF. The attributable risk of AF as a cause of stroke was very high in whites and essentially zero in blacks or Hispanics. The majority of strokes in the Hispanic group were attributed mostly to hypertension, diabetes and physical inactivity. Although whites were older, the comparison groups were matched by age, so this should not be a factor in the differences.

Both the AF cohort and the stroke cohort studies showed that similar to blacks, Hispanics tended to be younger than whites, with a greater prevalence of hypertension and diabetes yet a lower prevalence of AF. Although this is complicated by the heterogeneity of the Hispanic race in the U.S., the numbers tend to be too small to separate out the differing ancestries among the subjects grouped as Hispanic. Similarly, although whites comprised the majority, they were not separated by ancestry either, and there is most likely some heterogeneity among the whites as well. Nonetheless, the trend seems consistent when looking at patients with AF or at patients with stroke and their risk factors.

Risk of Stroke in patients with AF

There are over 750,000 new strokes in this country every year.[47] The prevalence of stroke in the Original Cohort from the Framingham Study was 18% over a 51 year follow up period, and the overwhelming majority of these strokes were ischemic in nature (86%).[48] In the ARIC population study sponsored by NHLBI, the biggest risk factors for having a stroke were hypertension, smoking and diabetes mellitus.[12, 49] AF is also a well known risk factor for stroke and felt to approximately increase the risk of stroke for an individual by five-fold.[50] Although the pathophysiology of stroke in the setting of AF is still somewhat unclear and likely multifactorial, it is believed that the majority of strokes are due to cardiac embolism, either from the left atrium or more likely the left atrial appendage. In the landmark SPAF trial conducted in the late 1980's, patients with AF were randomized to either warfarin, aspirin or placebo.[18] The combined rate of stroke and systemic embolism was 7.4% in the placebo arm. When looking at the SPAF III trial results for patients with AF with no prior stroke and only on aspirin therapy, there were 48 strokes in 1073 patients over 1.8 years, or a rate of 2.5 strokes per 100 person-years.[51] The more recent AFFIRM trial where patients were anticoagulated with warfarin had an overall stroke rate of 6.3%, of which approximately half were believed to be embolic in nature.[52] Although the medical community tends to extrapolate the stroke risk in these studies to all patients, the overwhelming majority of enrolled subjects in SPAF I, III and AFFIRM were white and male, with blacks comprising only 6% and the combined group of Hispanics, Asians and "other" comprising 10% of the total cohort.

It is worth noting that in aggregate, for patients with AF, approximately one third of strokes are not cardioembolic. There is more recent data that perhaps some of these are due to aortic atheroma embolization. And the SPAF trials showed that warfarin is ineffective for

preventing non-cardioembolic strokes. It therefore stands to reason that for patients who have AF but are at greater risk for a non-embolic stroke, the risk benefit ratio of warfarin therapy may vary from what is quoted in the AF Guidelines.

Pathophysiology of hypertension and diabetes in ischemic stroke

Looking beyond the risk of stroke in all-comers with AF, the risk of stroke in a given individual patient with AF is very dependent on their co-morbidities. There are different risk stratification schemes to assess whether a given individual with AF is at high, intermediate, or low risk for thromboembolic complications. One of the most widely used scoring systems is the $CHADS_2$ score which assesses risk of stroke based on the presence of; cardiac failure, hypertension, age >75 years, diabetes, and history of prior stroke.[53] Just as advanced age and any co-morbidity listed above tend to increase the risk of developing AF, they also increase the risk for stroke in patients who are living with AF. Although the potentiation of stroke risk by these individual co-morbidities in AF patients is well documented in the literature, the pathophysiology behind the increased stroke risk in patients with AF is not as well described.

Hypertension, the most common risk factor for stroke in patients with and without AF, probably causes an ischemic stroke by aggravating cerebral atherosclerosis and increasing vascular resistance in arteries and arterioles over time. These structural changes protect the cerebral circulation in the short term but impair its ability to vasodilate predisposing to ischemia in the long term. The small caliber vessels seem particularly prone to hypertension-induced morphological changes such as microaneurysms, which then can rupture or become occluded.[54]

Diabetes mellitus is also a common comorbidity in patients with stroke. Nearly twenty percent of stroke patients have diabetes mellitus. One probable cause for the association between

diabetes and stroke is the known effects of diabetes on vascular endothelial function and the accelerated development of atherosclerosis.[55] Diabetes has also been shown to increase blood viscosity, platelet aggregation and elevated levels of clotting factors which can predispose to vessel thrombosis or embolization as well as possibly accelerate the atherosclerotic process.[56] One pertinent example of diabetes induced vasculopathy is nephrotic proteinuria. Diabetic patients with proteinuria have a higher risk of ischemic stroke than diabetic patients without proteinuria, alluding to the fact that proteinuria is a marker for a systemic derangement of the vascular system. In addition, albuminuria in of itself has been shown to lead to increased coagulation factors.[57]

Risk of Stroke in African Americans

Blacks have a higher stroke rate in this country compared to whites and Hispanics.[27] The Behavioral Risk Factor Surveillance System (BRFSS) is a state-based system of telephone health surveys that was established in 1984 and sponsored by the Centers for Disease Control (CDC). The 2005 BRFSS Survey found that whites and Hispanics have a similar overall prevalence of stroke at 2.3% and 2.6% respectively, while Asians/Pacific Islanders have a lower prevalence at 1.6% and blacks have a higher prevalence at 4.0%.[12, 58] Although other studies have shown Hispanics to have a greater prevalence of strokes compared to whites, the data have consistently shown blacks to have a significantly greater prevalence of stroke compared to whites.

According to data from ARIC and NHLBI, the risk of a first stroke is almost twice as great for African Americans than whites. As African Americans tend to have less AF but more strokes than whites, it is not surprising that the etiology of the stroke was also shown to be different between ethnic groups with blacks having a three-fold higher risk for lacunar, non-

embolic ischemic strokes. The South London Community Stroke Registry included 1254 first strokes between 1995 and 1998. Approximately 80% were white and 16% of participants were black. Similar to data in the U.S., the black stroke patients had significantly less AF but greater hypertension and diabetes mellitus. The black patients were also quite younger than their white counterparts (63 years vs. 74 years p=0.001).[59] A subsequent study from London (the South London Ethnicity and Stroke Study) again demonstrated higher prevalence of hypertension, diabetes, and obesity but lower prevalence of MI and AF in the African and Caribbean community (all with p< 0.01).[60] Accordingly, the number one etiology of ischemic stroke in black patients was small vessel disease and in whites it was a cardioembolic source. The pathophysiology of small vessel disease is not fully understood, but the biggest risk factor for developing small vessel disease is hypertension.

Although the black patients in this cohort were mostly first generation immigrants from the Caribbean which may be different than the African Americans in the U.S., similar data has come from the Northern Manhattan Stroke Study already mentioned. Blacks had a significantly greater prevalence of hypertension and LVH compared to whites and a significantly lower prevalence of AF (11% vs. 29% p<0.01). The subsequent case control study showed that AF correlated to a 2.5 times greater risk of stroke overall (OR 2.5, p=0.0001) when controlled for age, sex, and ethnicity. Again there were similar discrepancies in AF prevalence with Blacks at 5% and whites at 8%. When broken down by race, ethnic-specific odds ratios for AF as a risk factor for stroke were seen (OR for whites=4.4 and OR for blacks =1.7). Blacks were younger than Whites similar to other stroke registries such as the London Registry (70 years vs. 80 years p<0.01)[61] but it is important to note that the lower prevalence of AF in the black cohort cannot be explained by their younger age since the ORs were calculated while matching for age.[46] When

the investigators looked at the etiology and subtype of ischemic stroke among the different ethnic groups, whites had a significantly greater proportion of cardioembolic stroke than blacks ($p=0.03$) although the absolute incidence rate of all ischemic stroke subtypes was higher in blacks compared to whites.[62] This is consistent with prior reports that blacks overall have a greater stroke incidence than whites but AF as a contributing cause of the stroke is more problematic for whites than blacks.

Risk of Stroke in Hispanic Americans

The Northern Manhattan Study mentioned previously, which is one of the first stroke studies to include a large Hispanic cohort, showed that the annual age adjusted incidence of first ischemic stroke of any type was almost twice as great for Hispanics as for whites. And although whites had a greater prevalence of AF and greater proportion of cardioembolic strokes than Hispanics, Hispanics had higher relative rates of all ischemic stroke subtypes, including cardioembolic (relative rate =1.42).[62] This contrasts with the BRFSS findings from the CDC and a small prospective study looking at racial differences in stroke type, which both found that the stroke type rates were not different between whites and Hispanics.[63]

Looking at a Hispanic-only cohort, one study conducted in Chile found that hypertension was the most common risk factor for stroke, and that the most common stroke type was small-vessel disease. Although AF was the most common reason for cardioembolic stroke type, cardioembolic strokes were one third less common than small vessel strokes in this cohort.[64]

A large Medicare cohort study looked at the risk/benefit ratio of warfarin therapy in patients with AF. The unadjusted analysis showed that for AF patients taking warfarin, the stroke rate for Hispanics was more than twice that for whites. Although warfarin appeared to reduce the

incidence of ischemic stroke by 35% compared to no antithrombotic therapy for the total cohort, this stroke reduction benefit was not apparent for Hispanics and blacks.[65] In fact, warfarin did not appear more protective than either aspirin or no antithrombotic therapy for the black and Hispanic Medicare recipients. Unfortunately, these data are somewhat difficult to interpret since no data was provided on INR levels, or percent time that an individual had a therapeutic INR. Although the authors did control for frequency of INR monitoring, they did not have the actual INR values. Additionally, only the incidence of ischemic stroke was reported, and this was not broken down into embolic and non-embolic etiologies. Therefore, it remains unclear if the higher stroke rate seen in Hispanics was due to inadequate monitoring, or due to an increased incidence of non-embolic strokes which are less preventable with therapeutic anticoagulation.

A smaller study from Houston, Texas of approximately 400 subjects (the BASIC Project) compared ischemic stroke subtypes between Mexican Americans to non-Hispanic whites. The Mexican subjects were younger and with a significantly greater prevalence of diabetes. Although they found no difference in the distribution of ischemic stroke subtype between the two groups, cardioembolic stroke was 16% for Mexican Americans versus 26% for Caucasians.[66] Although the authors concluded that this does not represent a difference in stroke subtype between the two groups, it is worth noting that Mexican Americans had far fewer embolic strokes despite an equal prevalence of atrial fibrillation (11% versus 16% p=0.14). The difference in AF prevalence and cardioembolic stroke may have been statistically significant if the study was better powered and if the nonlacunar strokes of unknown etiology were better able to be classified as embolic or not.

Risk of Stroke in Asian Americans

The first large scale observational study on AF conducted in mainland China on 29,000 participants showed an incidence of 0.65% prevalence of AF in the community. This is surprisingly low considering that hypertension and diabetes are not rare, and this cohort included a small number of patients with rheumatic heart disease. Since only 2.7% received warfarin, they were able to determine the prevalence of stroke in un-anticoagulated AF patients which was 13% versus 2.3% risk in patients without AF. This 13% incidence includes a one-time visit with a single EKG, or perhaps going through prior medical records in patients who reported a history of AF..[45] Therefore, although this shows that AF carries a high risk of stroke in Chinese patients, the incidence may be higher than what is reported in this study.

Conversely, an American study by Kaiser Permanente in California looking at almost 19,000 patients hospitalized for AF, where 3.9% were of Asian descent, found that Asians had lower rates of ischemic stroke compared to the other ethnicities in both the coumadin group and the no-coumadin group.[67] It is unknown if this difference between stroke risk in Chinese patients in China and in the U.S. is due to external factors, and need to be further studied with prospective studies that include Chinese Americans.

.It does appear that Asians are more prone to intracranial hemorrhage or hemorrhagic stroke than whites, blacks or Hispanics. Hemorrhagic stroke comprises 30% of all strokes in Asians which is much greater than other ethnic groups.[68] When looking at AF patients on warfarin therapy in the Kaiser database, the Asian sub-group had a 15-fold increase in intracranial hemorrhage compared to Asians with AF who did not take coumadin.[23, 69]

While blacks and Hispanics with AF on coumadin had roughly twice the rate of hemorrhagic stroke compared to white AF patients taking coumadin, Asian patients had 6 times

the rate of hemorrhagic stroke compared to whites. Although there are studies showing that Asians tend to have genetic polymorphisms that make them more sensitive to warfarin therapy and require smaller doses, this study did not show that the increased risk of intracranial hemorrhage in the Asian subgroup was due to a greater incidence of supratherapeutic INR levels. The level of anticoagulation was similar between the groups so overanticoagulation in the non-white subjects is not a likely explanation. These data along with the ethnic variation in AF as a risk factor for stroke suggest that there may be different risk/benefit ratios for different ethnicities when it comes to using warfarin.

Race vs Ethnicity

What are the implications of studying race or ethnicity with respect to a medical condition? What is the difference between race and ethnicity and is there an important distinction between the two when discussing a specific disease process? Ethnicity and race are often used interchangeably; however, generally speaking they are not the same thing. Ethnicity represents a social group with a shared history, geography and culture. People with different skin colors can belong to the same ethnic group. Race is a grouping of people based on physical characteristics such as skin color. Race is a social construct and not based on genetics or country of origin. There is, in fact, a lot of genetic diversity within racial groups. Nonetheless, race is typically what is reported in medical journal articles. It has also been used by investigators as a proxy for socioeconomic status or access to medical care. It is typically easier to acquire a person's race which is now commonly self-reported and widely available in databases as compared to other demographics such as education level and zip code.

Although it is a valid argument that race is not a good proxy for social and environmental factors which are more difficult to measure, race is an important means to measure health disparities. Race can serve as a first step when determining whether the relationship between outcomes and populations is truly related to race or other factors.[80]

For the medical community, one of the potential great promises of studying race is to help predict an individual's medical history and assess risk factors for various disease processes. As race is now frequently reported, it is often considered a factor in an individual's health. However, the notion that different racial groups share health-related genetic traits amongst themselves that differ from other groups is only theoretical at this point and has not been determined. In fact, all human beings share 99.9% of their genetic material. Whereas race is not based on genetics, ancestry does involve genetics more directly. Ancestry and race are only moderately correlated. However, ancestry can be very complicated with lineages form multiple regions of the globe and not as easy to report as race. Studies have shown that there is genetic variation between populations from Asia, Europe and Asia. Therefore, people from one region may have fewer differences than people form different regions. Although genetic ancestry and geographic ancestry do correlate, they are not synonymous and genetic similarities are found in people from neighboring regions.

If genetic differences do exist between populations, it is likely due to either (1) the presence of genetic variants of susceptibility in one group but not another, (2) genetic variants of susceptibility vary in frequency between groups, or (3) some genetic variants have different effects on different populations. To really know whether different racial groups have differing risk factors based on genetic differences, a variant gene that is known to influence health should be studied in terms of frequency and effect among the different races.[81] The future promise of

personalized risk assessment based on genetic testing will replace race as the tests become widely available and understood, and this will provide individual rather than group-based assessments.

There are well documented disparities in the prevalence and incidence of multiple medical conditions in the U.S. such as obesity, HIV infection and hypertension. These conditions disproportionately affect minority groups. It is unknown what degree of influence is accounted for by genetic differences shared by individual racial groups. Many health disparities in fact are more strongly influenced by environment than genetics. Racial differences in access to health care, dietary choices and exposure to health hazards are well documented. In the U.S., minority groups tend to have less access to healthcare and services than Caucasian residents with disparities in treatment and outcomes demonstrated in a wide array of medical conditions including acute coronary syndrome and heart failure. It is very difficult to determine if there is any genetic causality and to what degree. However, when looking at the incidence and prevalence of AF, Caucasians are disproportionately affected. Therefore, environmental factors such as health care disparities seem irrelevant or counter intuitive when talking about AF. This makes the possibility of an underlying genetic difference more plausible. Only further large population studies can determine if there are any confounders not yet known such as younger age of African American subjects in the studies done so far.

AF and Genetics

Traditionally, AF has been thought of as a disease that is caused by environmental factors such as co-morbidities and underlying cardiac substrate, or caused by "bad luck" in the case of lone AF where the person has a structurally normal heart and no readily identifiable risk factors

for AF. Only in the recent past have studies revealed a probable link between genetics and AF. The offspring cohort of the Framingham Heart Study, which consisted of over 5000 individuals whose parents were enrolled in the Framingham Heart Study, was analyzed to assess whether parental AF had an effect on the risk of developing AF in their children. They found that a history of AF in at least one parent did increase the risk of AF in the next generation with an OR of 1.85 ($p=0.02$).[70] A genetic predisposition to AF was also shown in a population based genetic study done in Iceland by Dr. Arnar and colleagues. They used a national genealogical database and found that first degree relatives of those with AF had a 1.8 higher relative risk for AF compared to the general population. This relative risk increased to 4.7 when only looking at individuals younger than 60 years.[71]

In terms of identifying specific genes, Brugada and colleagues were the first to identify a genetic locus for AF.[72] They reported 3 families with autosomal dominant AF which linked to the genetic locus 10q22-24. Although they did not determine its exact genetic function, they hypothesized that it was possibly an ion channel or pore protein gene. Another genetic study looking at a single family of Chinese descent found a mutation on KCNQ1, which is the potassium channel $I_{KS.}$ They were able to map a serine to glycine missense mutation on chromosome 11 in affected family members.[73] There have been other reports by other investigators of autosomal dominant familial AF which localized to other loci, but these genetic mutations identified interestingly all correspond to an increase in potassium channel function which in turn shortens the atrial action potential duration and the atrial effective refractory period creating a favorable milieu for reentry and AF.[74, 75] While autosomal dominant AF is rare, non-autosomal dominant AF is probably more common.

When looking at non-autosomal dominant AF, the genetic basis for AF is due to a genetic variant or polymorphism rather than a mutation. The majority of AF patients with a genetic predisposition fall into this category. Several investigators have looked at potassium channels in these patients with conflicting results which likely speaks to the multiple factors influencing the underlying mechanisms of AF. Dr. Arnar and his research team out of Iceland performed a genome-wide association scan in subjects of European descent and Chinese subjects living in Hong Kong. They found a strong association between two sequence variants on chromosome 4q25 and AF in both ethnic groups. The risk of having AF was greater in the subjects with this variant approximately 1.5 times per copy of the genetic sequence.[76] Another Chinese study found that when studying the slow delayed rectifier potassium channel (Iks), a single nucleotide polymorphism in the K channel accessory subunit, KCNE4 had differences between the AF group and the control group.[77]

Aside from potassium channel subunits, researchers have also started looking at sodium channel subunits, sarcoplasmic reticulum calcium ATPase regulatory protein, the renin-angiotensin system, and connexin 40. Although the studies are small in size, they are an intriguing groundwork for future studies. Clearly, future studies not only need to be larger, but need to be inclusive of different ethnic groups. A comprehensive review by Tsai and colleagues on the genetic studies of AF shows that all studies to date have been done in either Caucasians or Asians (predominantly Chinese).[74] A study of patients with diverse ethnic backgrounds with and without AF who are matched for AF risk factors could potentially shed light on important genetic markers and their interaction with risk factors for developing AF. A study like this may also elucidate which genetic changes are induced by environmental factors, and which genetic changes are due to a remodeling effect of the AF itself. Even if further genetic research shows

that ion channel mutations are uncommon causes of AF, genetic studies with a broad ethnic population would detect possible genetic differences that correlate to prevalence and incidence differences among different populations.

Inflammation and AF

Inflammation, as detected as C-reactive protein (CRP), has also been implicated as a risk factor for developing AF.[78] It was also shown that CRP levels rise as AF burden increases, suggesting that persistent AF occurs in the setting of atrial inflammation.[79] Unfortunately, there are no studies looking at whether differences in CRP exist among different races. (*For more details on inflammation and AF, please see Addendum.*)

Clinical Implications of Studying Race and AF

The studies to date consistently show that whites have a higher prevalence of AF compared to other racial groups regardless of whether it is a heart failure cohort, stroke cohort, or a large out-patient database such as an HMO or the VA healthcare system. However, whites are consistently older than blacks and Hispanics in these same studies. One important question that needs to be addressed is," Are non-whites truly less prone to develop AF or do Black patients die at a younger age than whites making the prevalence appear to be less? Or, are Blacks more likely to have heart failure and strokes than whites at a young age distorting the AF prevalence when looking at these groups? In other words, what seems to be an advantage might simply be a distorted narrow glimpse of a broader picture. These are difficult questions and would require a large prospective population study that is multi-racial. Large ethnically diverse cohorts such as the VA or Medicare could be studied prospectively as well.

If there truly are differences in the prevalence of AF among the different racial groups, this would have tremendous implications for ongoing research on multiple levels. First, risk factor management has become an important part of cardiology clinical practice. If risk factor prevention could be tailored to specific groups of patients, this could greatly enhance prevention efforts. In addition, patients who are high risk for AF could have more aggressive screening for AF. For example, white patients over 65 years could need arrhythmia surveillance at more aggressive intervals than others, whereas black patients may need more aggressive hypertension screening and treatment algorithms than white patients. Second, the realm of genetics is still in its early stages. Although the medical community has to use this technology cautiously, it could potentially lead to medicine tailored not to certain groups, but to individuals. Another benefit of understanding the genetics behind AF is that it can be an area of promising treatment development down the road. Third, when different people respond to physiologic stress differently, this can be an opportunity to better understand the underlying pathophysiology. In other words, if one group of patients with a high prevalence of diabetes and hypertension has a low prevalence of AF, whereas another group with less diabetes and hypertension has a higher prevalence of AF, what is the underlying difference between the groups? Fourth, if we understood better how the different risk factors for AF actually cause AF, this would lead to a better understanding of the pathophysiology. While white patients with AF often have coronary disease, many black patients with AF have hypertension. Is the pathophysiology of atherosclerosis different from the pathophysiology of hypertension as a cause or predisposing factor for AF? Or perhaps there are unexplored environmental factors that differentiate the racial groups? There may also be racial differences for newer identified AF risk factors such as neurohormonal influences and inflammation. Lastly, if there is a difference in the development

of AF between races, it raises the question of whether there are differences in stroke risk for patients with AF. Identifying a group at less risk than can be treated with a less aggressive treatment than systemic warfarin would be valuable information saving patients from the risks and inconvenience of warfarin.

Since insufficient data are currently available on non-white patients, the most recent guidelines for AF, based on mostly white cohorts, should continue to be applied to other ethnic groups. The ACC/AHA/ESC 2006 Guidelines for the management of patients with AF does state that based on limited data, "the age-adjusted risk of developing AF in blacks seems less than half that in whites". There is no discussion, however, that much of the data presented is based on largely white cohorts. Although the Guidelines do not explicitly state that the recommendations apply to all patients, this is appropriate given the paucity of available of data.

Implications for future research

National research establishments such as the NIH and NHLBI have recognized the importance of enrolling female and minority patients in clinical research studies. The current focus on disparities in healthcare and outcomes only further underscores the insight that is gained by enrolling a diverse cohort and the limitations of extrapolating findings in one group to all patients. Although there have been large hypertension and heart failure clinical studies, they have yet to be leveraged to look for racial differences for other comorbidities such as AF. Future prospective population studies need to have a better representation of racial minorities to further explore differences that may exist in prevalence, treatment and outcome of many diseases such as AF. Lastly, future genetic studies should look at the genetics of not only whites, but also Blacks, Asians and Hispanics with the same clinical disease to assess for similarities and

differences. Genetics holds the promise for moving beyond skin color to an individual's genetic basis for disease susceptibility and prevalence.

A prospective cohort study designed to detect racial differences in the risk of developing AF and the risk of having a stroke due to AF would be costly and lengthy. It is also difficult for a single study to capture all age groups, all races and a fair representation of women. However, there are already large, robust data sets available such as Medicare and the VA that are being used to prospectively collect data on other medical conditions. In addition, smaller case control retrospective studies can be done comparing a specific ethnic group to non-Hispanic white controls. Although a retrospective case control study is more susceptible to bias, it could provide an additional perspective by controlling for the confounding variables in the observational cohort studies presented in this review such as age, diabetes and hypertension. Lastly, more post hoc studies using a hypertension or diabetes randomized controlled trial data set would help confirm the findings of the few studies presented here.

DISCUSSION

We included 11 studies in this review that examine the interaction of ethnicity and AF (Table 1). They are for the most part a mixture of prospective and retrospective cohort studies. Although they do vary in size and scope, they consistently show the incidence of AF to be lower in blacks compared to whites. In fact, we did not find any study that showed the incidence of AF to be equal to or greater than in whites. This difference in AF incidence appears to be irrespective of the prevalence of co-morbidities that increase the risk of developing AF. For example, most studies did show a greater prevalence of diabetes mellitus and hypertension in African Americans. Although many of the studies had a significant age differential with blacks

being younger than whites, the difference in AF prevalence was maintained when age was controlled for in statistical regression models.

We then included seven studies that examine the interaction of ethnicity and embolic stroke in patients with atrial fibrillation. Again, they were mostly prospective and retrospective cohort studies looking at the risk factors of patients who present with a documented stroke. The studies consistently showed that in patients with an acute ischemic stroke, the concomitant finding of AF was greater in whites compared to blacks. Similar to the AF studies, blacks tended to be younger with greater rates of hypertension. Some of the stroke cohort studies controlled for age to assess whether the difference in AF prevalence was simply a matter of the age differential between white and black, but the increased risk of having AF in whites persisted.

Prior historical population studies which first looked at the prevalence and incidence of AF in this country typically enrolled mostly white patients. Accordingly, the traditional statistics that are commonly used as a reference for prevalence and incidence as well as risk factors for developing AF are based on a white cohort. For example, the initial cohort in the Framingham Study which began in 1948 consisted of 5209 patients between the ages of 30 and 62, and was overwhelmingly white.[82] The Cardiovascular Health Study looked at a sample of over 5000 patients over 65 years old who were Medicare recipients, however, only 4.7% were Black.[83] And although statistics were done comparing men to women, no a priori analysis was done looking at race or ethnicity.

Due to the limitations of the studies in terms of a homogeneous population, the 2006 ACC AHA ESC Guidelines on AF are only able to state that, “Based on limited data, the age-adjusted risk of developing AF in blacks seems less than half than in whites.” This is based on just 3 studies.[5, 32, 36] The EPOCH study is a retrospective look at the prevalence of AF in a heart

failure population with Kaiser Permanente Health Insurance; the ATRIA study is also a retrospective look at AF patients in the same HMO; and the Cardiovascular Health Study is a prospective study looking at the incidence of AF in Medicare patients. The percent of blacks enrolled in these three studies were 16.2%, 3.6%, and 4.8% respectively. While ATRIA and EPOCH showed a significant difference in AF prevalence between black and white, the only prospective study looking at the incidence of AF, the Cardiovascular Health Study, did not find the difference to reach statistical significance. Since a large difference was found (Relative Risk for blacks developing AF was 0.47), the lack of statistical significance is very possibly due to the small percent of black patients in the study and lack of power.

Heart failure studies that looked at AF similarly enrolled a predominantly Caucasian cohort. A post-hoc retrospective analysis of the SOLVD study which looked at the benefits of ACE-inhibitor in heart failure patients with left ventricular dysfunction was 98.4% Caucasian.[84] The Consensus Trial, which also looked at the effect of ACE-inhibitor therapy in heart failure patients, was conducted in Scandinavia.[85] Another example is the MERIT HF Trial which enrolled approximately 4,000 patients and had a prevalence of AF of 16-17%.[86] Only 5% were black and the prevalence of AF was not broken down by race. These studies collectively are used to demonstrate the prevalence of AF in heart failure patients in the 2006 ACC/AHA/ESC 2006 Guidelines for the Management of AF.[53]

Although AF has been studied for decades, only recently has it become recognized as one of the most important cardiac conditions. This is due in part to its escalating prevalence and in part to the emerging ability to treat AF with catheter-based technology rather than anti-arrhythmic or rate controlling medications. As we are learning more about the treatment for AF, understanding the pathophysiology and genetics of the disease also become more important.

Understanding why someone with more traditional risk factors for AF is less likely to develop AF will likely lead us to some of these answers. Are there other risk factors that have yet to be explored? Is there an underlying factor that confers protection that needs to be explored? This paradoxical difference between whites and blacks as well as other minorities may mean that landmark population studies such as Framingham are not relevant for everyone and additional population studies need to be done with this in mind.

To further our understanding of the differences in prevalence and incidence of AF among the different ethnic groups, further large population research is needed. For one, the Medicare database was already used in the Cardiovascular Health Study but blacks were underrepresented. Using a larger dataset of patients with a better representation of blacks as well as Hispanics and Asians will provide a clearer picture of true prevalence differences in patients 65 years and older. Looking at a relatively narrow range of ages (for example 65 to 80 years) will help ensure that the differences seen in prior studies is not due to a difference in mean age between groups. Secondly, leveraging other prospective ongoing database studies which have a large percentage of African Americans such as the ARIC study will provide insight into the incidence of AF specifically in the African American community. Third, genetic studies are becoming more and more an important aspect of understanding a disease process. All the genetic studies focusing on AF have been in either white or Chinese patients. Not only are more genetic studies needed, but genetic studies that include non-white patients. Genetic studies in black patients with and without AF may reveal significant differences in terms of which genes seem to be associated and which mutations are occurring. Lastly, differences between ethnic groups can only be discovered and researched further if the medical community makes a concerted effort in general to look at racial

and ethnic differences. It has become fairly commonplace for studies to automatically do analyses based on sex, and the same should happen for ethnicity.

In summary, in order to possibly some day risk stratify patients differently or prescribe medical therapy differently for whites versus the various minority groups, future clinical trials need to determine the morbidity and mortality of AF in these groups rather than assuming the Framingham data accurately reflects all groups. Specifically, future studies should address the following unanswered questions;

1. What is the ischemic stroke risk for Black, Hispanic, and Asian patients with AF on aspirin and on coumadin?
2. What is the relative risk of mortality for Black, Hispanic, and Asian patients with AF compared to Black, Hispanic, and Asian patients without AF?
3. Is the paradox of AF incidence in Blacks and Whites real or is it due to confounding, particularly the older age and greater prevalence of coronary disease in whites?

Our review of the literature has several limitations. There were only 11 studies included with respect to the interaction of AF and ethnicity. Very few studies looking at AF have analyzed racial or ethnic differences and so there is a paucity of data in the literature. Only English language literature was used. Although our main focus was ethnic differences regarding AF in the U.S., it is possible that a non-English speaking European study looking at ethnic differences was overlooked. The selected studies are a mix of prospective and retrospective cohort studies lacking uniform data reporting. The studies also had a wide range of ages which impacts the incidence and prevalence of AF in all groups. The results are also subject to error since the

determination of race was variable. In some studies race was self-reported, in others it was obtained from the insurance records or medical chart and may be incorrect.

Despite these limitations, the fact that various studies show a consistent difference despite differences in geographical location, age of enrolled subjects, and ethnic diversity of the population studied is valuable information. In aggregate, these studies do support the notion that there is a true difference rather than a sampling error or issues of under-reporting. This is especially true given the consistent findings and that many studies compare patients with the same insurance or living within similar geographic region which has been validated as a surrogate for socio-economic status.[87]

AF is the most common arrhythmia. The risk of developing AF increases with advancing age and the presence of other medical conditions including hypertension and diabetes mellitus. There are also additional risk factors more recently identified such as obesity and sleep apnea. When analyzing the data along ethnic lines, African Americans tend to have greater rates of hypertension, LVH and diabetes compared to white cohorts with lower rates of AF. When looking at the issue of AF from the angle of ischemic stroke, the etiology of the stroke is often hypertension in blacks and AF in whites. This ethnic difference has only recently been elucidated with the focus in the medical scientific community to look at issues of race and ethnicity as well as to improve the enrollment of minority populations. Genetics is a new area and has potential problematic uses for discrimination or racial profiling but also has merit and real promise in terms of helping medicine be tailored to individuals. Learning more about the differential risk of AF between ethnic groups has the potential to improve upon our understanding of the pathophysiology of AF in general.

Table 1 Selected Studies Looking at the Interaction of Ethnicity and Atrial Fibrillation

Author(Year)Ref	**Study Design**	**n**	**Analysis**	**Source Population**	**Study Population**	**Results**
Afzal (1999)[38]	Prospective observational study	163 [113 black (69%), 50 white (31%)]	t-test	CHF patients	Consecutive patients admitted to city hospital with acute CHF	Blacks were younger, had greater prevalence of HTN, 21% of blacks & 42% of whites were in AF (p=<.001)
Borzecki (2008)[39]	Retrospective cross sectional study	35,470, 86.7% white, 6% black	Logistic regression with OR	Male veterans in the U.S. V.A. Health System	2 V.A. administrative DB and 1999 Health Survey	AF more prevalent in Whites than Blacks and Hispanics. OR for AF in Whites is 1.8
Dang (2004)[42]	Retrospective cross sectional study	737, 16.4% white, 59.2% Hispanic, 10.3% black	Logistic regression with OR	Inpatients and outpatients at 2 hospitals	Any EKG obtained during 1999 with AF that matched to 1st hospitalization for AF	Blacks with AF had younger mean age than Whites with AF (59.4% versus 64.2% p<0.05)
Go (2001)[32]	Retrospective cross sectional study	17,974, 84.7% white, 3.6% black, 2.5% Hispanic	X^2 test	Patients in California HMO	The ATRIA Study Patients in California HMO with AF. Missing ethnicity status on 11%.	AF more prevalent in Whites (2.2%) than Blacks (1.5%) p<0.001.
Psaty (1997)[5]	Prospective observational study	4844, 234 blacks (4.8%), no other races identified	Logistic regression with OR	Medicare recipients in 4 geographic locales	The Cardiovascular Health Study Blacks are 4.8% of cohort	AF incidence was lower in Blacks than Whites (12 vs. 19.5 per 1000 person- years with RR for Blacks=0.47) but p=NS
Ruo (2004)[36]	Retrospective cross-sectional study	1,373, 223 blacks (16%), 1150 whites	Multi-variable logistic regression	Patients in California HMO admitted with CHF	The EPOCH Study Random sample of patients admitted between 7/1/99-6/30/00	Blacks had adjusted OR for AF of 0.51 compared to whites

Author(Year)Ref	**Study Design**	**n**	**Analysis**	**Source Population**	**Study Population**	**Results**
Upshaw (2002)[40]	Retrospective EKG DB review	2123, 922 B (43%), 1201 W (57%)	X^2 test	Patients admitted to Piedmont Hospital, Atlanta, Ga.	All EKGs between 10/28/96-6/30/98	94 whites (7.8%) had AF & 23 blacks had AF (2.5%) p<0.01
Zamrini (2004)[41]	Retrospective case control	167 B, 167 W	ANOVA and X^2	Database from the Univ. of Alabama Alzheimer's Disease Center	Black and White patients with Alzheimer's disease	<1% B and 8% W had AF (p-0.001). 30% B and 19% W had HTN (p=0.025)
Novaro (2008)[43]	Meta-Analysis of 7 RCT	94,785, 98.2%W, 1.8% A	Chi square for OR, Breslow-Day for homogen-eity across studies	7 RCTs enrolling patients with an ACS, enrolled Asian subjects	GUSTO I, IIb, III, V, PURSUIT, IMPACT II, PARAGON A	6/7 studies showed Asians have less AF than whites. W develop AF more than A (4.7% vs. 7.6% p<0.001)
Okin (2006)[8]	Post-hoc analysis of the prospective double blinded RCT the LIFE Trial	8831, B=518 (4.8%) W=94%	Cox proportion al hazard model to assess relation-ship between LVH by EKG and AF	Subjects enrolled in LIFE Trial	Hypertensive patients with LVH on EKG (cornell or Sokolow-Lyon) with no history of AF	AF was diagnosed in 4.8% of B, 8.1% W (p<0.01)
Vaccarino (2002)[37]	Prospective cohort (consecutive enrollment)	398, W=79%, B=21%	Baseline demo-graphics X^2 and Student t tests	patients admitted with CHF to Yale New Haven Hospital	Black and White CHF patients with varying socioeconomic backgrounds	AF present on EKG at time of admission in W=28%, B=14.6% (p=0.01)

A= Asian ACS= Acute Coronary Syndrome AF=atrial fibrillation B=black African American, DB=database CHF=congestive heart failure DM=Diabetes Mellitus, H=Hispanic, JACC=journal of the American College of Cardiology HMO=health maintenance organization JAMA=Journal of the American Medical Association JMNA=Journal of the National Medical Association NS=not significant OR=odds ratio RR=relative risk, W=white, Caucasian.

Table 2 Quality Ratings for Studies Looking at the Interaction of Ethnicity and Atrial Fibrillation

Each Study is rated on a scale from 0 to 3. [0=poor, 1=fair, 2=good 3=excellent. Refer to Legend at end of Table 4 for further description]

Author (Year)Ref	**Source Population Adequately Described? Inclusion criteria reasonable?**	**Study Population Represents Source Population? Are the groups comparable?**	**Adequate Data Collection? Detection of AF adequate? Determination of race made by subject?**	**Internal Validity: Appropriate Analysis? Adequate sample size? Cohort followed prospectively?**	**Results Reported Adequately? Follow-up adequate? Drop out similar between groups?**	**Was bias present? If so, what type? Was it addressed?**
Afzal (1999) [38]	consecutive admissions 2	Blacks in study higher proportion than hospital , Blacks had more LV dysfunction 1	Race determined by chart, confirmed by interview, AF determined by admit EKG 3	Sample size small, only looked at AF prevalence at admission 1	No follow up 2	BP possibly; it was addressed 2
Borzecki (2008)[39]	Merged retrospective data sets with cross sectional data 2	women excluded, <50% responded to survey Blacks only comprise 6% 1	race self-reported 3, used ICD-9 codes for AF	No prospective data collection 2	Adjustment made for age, other confounders 2	BS present; W more likely to respond than B to survey, but not fully addressed 0
Dang (2004)[42]	EKG database queried and then matched to admission 1	Hispanics 60% of cohort so not truly representative of U.S. No exclusion criteria 1	Race determined by EKG/hospital DB, only admit EKG collected 1	Large sample with adequate minority representation 2	No follow up 2	BP is unknown, not addressed, however presumably care is similar between groups 1
Go (2001)[32]	Strict inclusion criteria 3	very low percentage of Hispanic and Black subjects 1	11% missing race data, race determined by administrative files, used ICD-9 codes for AF 1	3	No follow up 2	All patients in same HMO, all subjects identified and followed by same method 3
Psaty (1997)[5]	Large prospective cohort based on random sampling of Medicare 3	only enrolled patients >65 years, B only 5% of study, didn't look at A or H 3	unclear how race was determined AF could be self reported without EKG data 1	3	Follow up=3.3 years 3	BP is unknown, patients received medical care at various centers, BD present and discussed but not fully addressed (AF self reporting allowed, not reliable) 0
Ruo (2004)[36]	Random sample of CHF admissions Included Aflutter 2	All subjects from same HMO, H and A not in cohort 2	Race determined by database or admission records. AF determined by ICD-9 codes and EKGs 2	Reasonable sample size, B=16% of cohort 3	Adjustment made for age, other confounders No follow up 2	All patients in same HMO, all subjects identified by same method 3

Author (Year)Ref	**Source Population Adequately Described? Inclusion criteria reasonable?**	**Study Population Represents Source Population? Are the groups comparable?**	**Adequate Data Collection? Detection of AF adequate? Determination of race made by subject?**	**Internal Validity: Appropriate Analysis? Adequate sample size? Cohort followed prospectively?**	**Results Reported Adequately? Follow-up adequate? Drop out similar between groups?**	**Was bias present? If so, what type? Was it addressed?**
Upshaw (2002)[40]	Paroxysmal AF and Aflutter included 1	Unknown confounders or if groups comparable 0	unclear how race was determined Co-morbidities not collected 1	not adjusted for confounders 2	Adjustment not made for age, other confounders No follow up 1	BP present possibly although all patients received medical care at single institution 2
Zamrini (2004)[41]	2	Groups are well matched, unclear if all subjects have true Alzheimer's 2	Unclear how race determined AF determined by baseline EKG 1	Adjusted for confounders 2	No follow up 2	BP possibly present, all patients received care at same Memory Disorder Clinic but previous care unknown 2
Novaro (2008)[43]	3	Very few Asians enrolled. Post-ACS does not represent patients at large 1	Race self reported Unclear how AF diagnosis made 1	Large sample size 2	Drop out unknown 1	BP likely present since prior care unknown, however RCTs used many sites, many locations 2
Okin (2006)[8]	Double blinded RCT 3	Used EKG criteria rather than echo criteria which may be less specific in Blacks 1	Race self reported AF determined by annual EKG 1	2	Drop-out not well described 5 year follow up 2	Double blinded RCT 3
Vaccarino (2002)[37]	3	H and A not enrolled, single urban center 1	Race self reported 2	Likely socioeconomic confounding present 2	No follow up Small number of Blacks enrolled 2	BA due to high (20%) mortality rate doesn't affect baseline comparisons. Consecutive prospective enrollment minimizes BA. 2

A= Asian ACS= Acute Coronary Syndrome AF=atrial fibrillation B=black African American, BA= attrition bias, BM= measurement bias, PB=performance bias, BS= selection bias, DB=database CHF=congestive heart failure DM=Diabetes Mellitus, H=Hispanic, JACC=journal of the American College of Cardiology HMO=health maintenance organization JAMA=Journal of the American Medical Association JMNA=Journal of the National Medical Association NS=not significant OR=odds ratio RR=relative risk, W=white, Caucasian.

Table 3 Selected Studies Looking at the Interaction of Ethnicity and Stroke

Author (Year)Ref	Study Design	n	Source Population	Study Population	Analysis	Results
Bush (2006)[22]	Post-hoc analysis of the prospective RCT The AFFRIM Trial	3996, 90.1% W, 6.6% B, 3.3% H	Patients with AF	AFFIRM trial enrollees	t-test, Chi-square or Fisher's exact tests; KM for time to endpoint	B and H younger than whites. B had more HTN and less CAD than whites. Ischemic strokes were 5.7% H, 9.5% B, 6.1% W (p values not done) Overall survival did not differ among W, B, H.
Conway (2003)[93]	Post-hoc analysis of prospective registry cohort	832, 70% W, 14% A, 16% B	Patients admitted with acute non-hemorrhagic stroke	Patients between 4/1/98-3/31/2000 in Birmingham, UK (West Birmingham Stroke Project)	t-test, Logistic regression, Cox hazard ratios	Afro-Caribbeans had an OR for AF=0.27 compared to W despite ORs for DM =4 and HTN=2
Gunarathne (2008)[94]	Retrospective registry cohort	2,405 non – hemorr-hagic stroke, 17%A, 12% B, 71% W	regional computerized database from 1997-2005 in Birmingham, UK	Patients hospitalized with first-time non-hemorrhagic stroke	t-test, ANOVA, Chi-square, KM, Cox regression	9% of Afro-Caribbeans and 34.8% of European Caucasians had AF p<0.001. B had more HTN and DM p<0.001.
Markus (2007)[60]	Prospective observational registry (South London Stroke Study) with matched white cohort	1,200 (600 B 600 W)	Stroke patients admitted to 3 hospitals in south London from 1999-2005(The South London Ethnicity and Stroke Study)	Black and white patients hospitalized with stroke (first and recurrent)	Logistic regression with OR	11.2% of B and 32.4% of W had AF p<0.001, OR 0.28 when adjusted for age and other risk factors. B had more strokes due to SVD (p<0.01), and W had more strokes due to CE (p<0.01).
Sacco (1995)[61]	Prospective Observational Registry (Northern Manhattan Stroke Study)	430, 19% W, 35% B, 46% H	Patients admitted to Presbyterian Hospital with stroke from 1990-1993	Black, White and Hispanic stroke patients >39 years old who reside in Manhattan	Chi-square, Fisher's exact, unpaired t-test, logistic regression	11% of B and H had AF, 29% of W (p<0.01 for W vs. B and vs. H). W patients were older with less HTN and heart disease.
Shen (2007)[23]	Retrospective cohort	18,867 hospital-izations for AF, 78.5 W, 8.1% B, 9.5% H, 3.9% A	Kaiser HMO patients in California	First-time hospitalization for AF between 1/1/95-12/31/00	Kruskal-Wallis, Chi-square, Poisson regression, Cox proportional hazard	B were younger with more HTN, DM, HF than W. OR for ICH in B=2, H=2, A=4 compared to W.
Hajat (2001)[62]	Prospective observational registry (South London Community Stroke Register	1254, 79%W, 16%B	Community registry, some overlap with the South London Study	Hospitalization for first ever stroke	Univariate analysis with X^2 test	AF present in 25% W and 6.8% B (p<0.01). HTN and DM were more prevalent in B (p<0.001)

A=Asian, AFFIRM=Atrial Fibrillation Follow-Up Investigation of Rhythm Management trial, B= Black, African American, CAD=coronary artery disease, CE=cardioembolic source, H= Hispanic, HTN=hypertension, ICH= intracranial hemorrhage, JHH=Journal of Human Hypertension KM=Kaplan-Meier, OR=odds ratio, RCT=randomized controlled trial, SVD=small vessel disease, UK=United Kingdom, W=white, Caucasian.

Table 4 Quality Ratings for Studies Looking at the Interaction of Ethnicity and Stroke

Each Study is rated on a scale from 0 to 3. [0=poor, 1=fair, 2=good 3=excellent. Refer to Legend at end of Table 4 for further description]

Author (Year)Ref	**Source Population Adequately Described? Inclusion criteria reasonable?**	**Study Population Represents Source Population? Are the groups comparable?**	**Adequate Data Collection? Detection of AF adequate? Determination of race made by subject?**	**Appropriate Analysis? Adequate sample size? Cohort followed prospectively?**	**Results Reported Adequately? Follow-up adequate? Drop out similar between groups?**	**Was bias present? If so, what type? Was it addressed?**
Bush (2006)[22]	Used RCT data 3	Very low enrollment for A, B, H Greater LV dysfunction for B and H 0	Event free survival was compared for W, B, H, but not stroke, AF well documented at baseline 2	Power limited by low enrollment of non-whites 1	Baseline differences documented 2	Used RCT DB 3
Conway (2003)[93]	Hemorrhagic stroke excluded 2	British study, not U.S. 2	Too few non-whites with AF 1	Adjusted for age, sex 2	2	Used Registry DB, all patients with national British health insurance, not RCT 2
Gunarathne (2008)[94]	cross referenced ICD-10 codes with hospital's stroke DB and chart review 2	British study, not U.S., inner city hospital 2	Diagnosis of AF based on single admission EKG 0	Large sample 3	Only looked at baseline variables 3	Used verified DB, all patients with national British health insurance, not RCT 2
Markus (2007)[60]	Case control design matching B and W subjects 2	British study, unclear if any exclusion criteria	AF diagnosis made by history, clinic chart 1	2	Only looked at baseline variables 3	Time delay between B and W cohort enrollment not specified 1
Sacco (1995)[61]	well defined geographic location,	3 hospitals	race was self-identified 3	3	3	Hospital receives 80% of stroke patients in region, BP possible 2
Shen (2007)[23]	Kaiser HMO 3	Aflutter included, paroxysmal AF included 2	Unclear how race determined 1	Very large cohort 3	3	HMO DB used, patient treatment should not differ within single HMO 2
Hajat (2001)[62]	3	3	AF by EKG or history Race determined by physician 1	2	3	Used Registry DB, all patients with national British health insurance, not RCT 2

AF=atrial fibrillation B=Black, DB=database H=Hispanic, HMO=Health Maintenance Organization ICH=intracranial hemorrhage RCT=randomized controlled trial W=white.

Legend for Score Rating (0-3):

- *Source population adequately described?*
  - Were data on hypertension, age, diabetes, heart failure, provided?
  - Were subjects with atrial flutter included (less rigorous)?
  - Was it described if the AF was paroxysmal or persistent?
- *Study Population representative?*
  - Do the study subjects represent AF patients in the U.S.?
  - Are their confounding variables that make comparing the groups problematic?
- *Detection of AF and race determination adequate?*
  - Was AF detected by routine EKG only or was more aggressive surveillance done?
  - Was race determined by the individual subjects (most reliable) or by the investigator, or the medical record (least reliable)?
- *Internal Validity adequate?*
  - Did authors identify and adjust for confounders?
  - Was the study sufficiently powered?
  - Was cohort followed prospectively (more valid) or was data collected post hoc?
- *Follow-up and drop-out reported and reasonable?*
  - Were all subjects followed (more robust) or only a percentage?
  - Were the drop-out rates reasonable and fairly equitable between the two groups?
- *Bias present?*
  - Selection Bias: Was there a systematic difference between groups?
  - Performance Bias: Did the groups receive different medical care such as treatment for hypertension?
  - Detection Bias: Were the methods used to detect AF equal between groups?
  - Attrition bias: Were the losses of subjects different between groups?

Master's Paper Addendum:

Inflammation and AF

Using the large cohort from the Cardiovascular Health Study, Aviles et al determined that an elevated CRP level at baseline is predictive of an increased risk of developing new onset AF in the future although this is not necessarily a causal relationship.[88] This remained true even after controlling for other risk factors for AF such as diabetes, hypertension, and advanced age. Although this cohort included an additional 687 black participants in addition to the original Health Study cohort which was 94% white, there was no breakdown of CRP by race. In addition, the analysis of race appeared to be divided into white and non-white, although presumably a large percentage of the non-white group was black. Another large prospective study looking at CRP levels in patients with and without AF also concluded that high CRP levels were predictive of an increased risk of AF later on. This study, the Intermountain Heart Collaborative Study, was done in a homogenous white population from the Salt Lake City, Utah region and so race was not factored into the analyses.[89] Some European centers have also looked at the relationship between CRP and AF but had predominantly white cohorts, and race was therefore not described in the baseline patient characteristics[90-92] Therefore, whether there are racial differences in CRP levels, and whether this is a possible explanation for the difference in AF prevalence is not known.

References

1. Chen LY, Shen WK. Epidemiology of atrial fibrillation: a current perspective. *Heart Rhythm.* Mar 2007;4(3 Suppl):S1-6.
2. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation.* Aug 31 2004;110(9):1042-1046.
3. Kannel WB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. *Med Clin North Am.* Jan 2008;92(1):17-40, ix.
4. Benjamin EJ, Levy D, Vaziri SM, et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *Jama.* Mar 16 1994;271(11):840-844.
5. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation.* Oct 7 1997;96(7):2455-2461.
6. Ryder KM, Benjamin EJ. Epidemiology and significance of atrial fibrillation. *Am J Cardiol.* Nov 4 1999;84(9A):131R-138R.
7. Manolio TA, Gottdiener JS, Tsang TS, et al. Left atrial dimensions determined by M-mode echocardiography in black and white older (> or =65 years) adults (The Cardiovascular Health Study). *Am J Cardiol.* Nov 1 2002;90(9):983-987.
8. Okin PM, Wachtell K, Devereux RB, et al. Regression of electrocardiographic left ventricular hypertrophy and decreased incidence of new-onset atrial fibrillation in patients with hypertension. *Jama.* Sep 13 2006;296(10):1242-1248.
9. Camm J. 'Atrial fibrillation--an end to the epidemic?' *Circulation.* Aug 23 2005;112(8):iii.
10. Steinberg JS. Atrial fibrillation: an emerging epidemic? *Heart.* Mar 2004;90(3):239-240.

11. Lin HJ, Wolf PA, Benjamin EJ, et al. Newly diagnosed atrial fibrillation and acute stroke. The Framingham Study. *Stroke.* Sep 1995;26(9):1527-1530.

12. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart Disease and Stroke Statistics--2009 Update. A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* Dec 15 2008.

13. Feinberg WM. Anticoagulation for prevention of stroke. *Neurology.* Sep 1998;51(3 Suppl 3):S20-22.

14. Understanding systematic reviews of research on effectiveness. Center for review and dissemination report #4. Second Edition. 2001. Available at: http://www.york.ac.uk/inst/crd/CRD_Reports/crdreport4_content.pdf.

15. Khan KS, ter Riet G, Glanville J, et al. Undertaking Systematic Reviews of Research on Effectiveness CRD's Guidance for those Carrying Out or Commissioning Reviews. CRD Report Number 4 (2nd edition) March 2001.

16. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation.* Sep 8 1998;98(10):946-952.

17. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. *N Engl J Med.* Nov 29 1990;323(22):1505-1511.

18. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation.* Aug 1991;84(2):527-539.

19. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet.* Mar 19 1994;343(8899):687-691.

20. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet.* Sep 7 1996;348(9028):633-638.

21. Connolly SJ, Laupacis A, Gent M, et al. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol.* Aug 1991;18(2):349-355.

22. Bush D, Martin LW, Leman R, et al. Atrial fibrillation among African Americans, Hispanics and Caucasians: clinical features and outcomes from the AFFIRM trial. *J Natl Med Assoc.* Mar 2006;98(3):330-339.

23. Shen AY, Yao JF, Brar SS, et al. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. *J Am Coll Cardiol.* Jul 24 2007;50(4):309-315.

24. Drazner MH, Dries DL, Peshock RM, et al. Left ventricular hypertrophy is more prevalent in blacks than whites in the general population: the Dallas Heart Study. *Hypertension.* Jul 2005;46(1):124-129.

25. Brancati FL, Kao WH, Folsom AR, et al. Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study. *Jama.* May 3 2000;283(17):2253-2259.

26. Kurian AK, Cardarelli KM. Racial and ethnic differences in cardiovascular disease risk factors: a systematic review. *Ethn Dis.* Winter 2007;17(1):143-152.

27. Gorey KM, Trevisan M. Secular trends in the United States black/white hypertension prevalence ratio: potential impact of diminishing response rates. *Am J Epidemiol.* Jan 15 1998;147(2):95-99; discussion 100-102.

28. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* Jan 29 2008;117(4):e25-146.

29. *http://www.niddk.nih.gov/dm/pubs/statistics*. NDSAa.

30. McBean AM, Li S, Gilbertson DT, et al. Differences in diabetes prevalence, incidence, and mortality among the elderly of four racial/ethnic groups: whites, blacks, hispanics, and asians. *Diabetes Care.* Oct 2004;27(10):2317-2324.

31. *http:www.statehealthfacts.kff.org* Aa.

32. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *Jama.* May 9 2001;285(18):2370-2375.

33. Kjeldsen SE, Dahlof B, Devereux RB, et al. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (LIFE) substudy. *Jama.* Sep 25 2002;288(12):1491-1498.

34. Exner DV, Dries DL, Domanski MJ, et al. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. *N Engl J Med.* May 3 2001;344(18):1351-1357.

35. Carson P, Ziesche S, Johnson G, et al. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. *J Card Fail.* Sep 1999;5(3):178-187.

36. Ruo B, Capra AM, Jensvold NG, et al. Racial variation in the prevalence of atrial fibrillation among patients with heart failure: the Epidemiology, Practice, Outcomes, and Costs of Heart Failure (EPOCH) study. *J Am Coll Cardiol.* Feb 4 2004;43(3):429-435.

37. Vaccarino V, Gahbauer E, Kasl SV, et al. Differences between African Americans and whites in the outcome of heart failure: Evidence for a greater functional decline in African Americans. *Am Heart J.* Jun 2002;143(6):1058-1067.

38. Afzal A, Ananthasubramaniam K, Sharma N, et al. Racial differences in patients with heart failure. *Clin Cardiol.* Dec 1999;22(12):791-794.

39. Borzecki AM, Bridgers DK, Liebschutz JM, et al. Racial differences in the prevalence of atrial fibrillation among males. *J Natl Med Assoc.* Feb 2008;100(2):237-245.

40. Upshaw CB, Jr. Reduced prevalence of atrial fibrillation in black patients compared with white patients attending an urban hospital: an electrocardiographic study. *J Natl Med Assoc.* Apr 2002;94(4):204-208.

41. Zamrini E, Parrish JA, Parsons D, et al. Medical comorbidity in black and white patients with Alzheimer's disease. *South Med J.* Jan 2004;97(1):2-6.

42. Dang D, Patel R, Haywood LJ. Atrial fibrillation in a multiethnic inpatient population of a large public hospital. *J Natl Med Assoc.* Nov 2004;96(11):1438-1444.

43. Novaro GM, Asher CR, Bhatt DL, et al. Meta-analysis comparing reported frequency of atrial fibrillation after acute coronary syndromes in Asians versus whites. *Am J Cardiol.* Feb 15 2008;101(4):506-509.

44. Yap KB, Ng TP, Ong HY. Low prevalence of atrial fibrillation in community-dwelling Chinese aged 55 years or older in Singapore: a population-based study. *J Electrocardiol.* Mar-Apr 2008;41(2):94-98.

45. Zhou Z, Hu D. An epidemiological study on the prevalence of atrial fibrillation in the Chinese population of mainland China. *J Epidemiol.* 2008;18(5):209-216.

46. Sacco RL, Boden-Albala B, Abel G, et al. Race-ethnic disparities in the impact of stroke risk factors: the northern Manhattan stroke study. *Stroke.* Aug 2001;32(8):1725-1731.

47. Carandang R, Seshadri S, Beiser A, et al. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. *Jama.* Dec 27 2006;296(24):2939-2946.

48. Seshadri S, Beiser A, Kelly-Hayes M, et al. The lifetime risk of stroke: estimates from the Framingham Study. *Stroke.* Feb 2006;37(2):345-350.

49. Ohira T, Shahar E, Chambless LE, et al. Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities study. *Stroke.* Oct 2006;37(10):2493-2498.

50. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* Aug 1991;22(8):983-988.

51. Pearce LA, Hart RG, Halperin JL. Assessment of three schemes for stratifying stroke risk in patients with nonvalvular atrial fibrillation. *Am J Med.* Jul 2000;109(1):45-51.

52. Sherman DG, Kim SG, Boop BS, et al. Occurrence and characteristics of stroke events in the Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (AFFIRM) study. *Arch Intern Med.* May 23 2005;165(10):1185-1191.

53. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation):

developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation.* Aug 15 2006;114(7):e257-354.

54. Phillips SJ. Pathophysiology and management of hypertension in acute ischemic stroke. *Hypertension.* Jan 1994;23(1):131-136.

55. Jorgensen H, Nakayama H, Raaschou HO, et al. Stroke in patients with diabetes. The Copenhagen Stroke Study. *Stroke.* Oct 1994;25(10):1977-1984.

56. Moreno PR, Fuster V. New aspects in the pathogenesis of diabetic atherothrombosis. *J Am Coll Cardiol.* Dec 21 2004;44(12):2293-2300.

57. Guerrero-Romero F, Rodriguez-Moran M. Proteinuria is an independent risk factor for ischemic stroke in non-insulin-dependent diabetes mellitus. *Stroke.* Sep 1999;30(9):1787-1791.

58. Prevalence of stroke--United States, 2005. *MMWR Morb Mortal Wkly Rep.* May 18 2007;56(19):469-474.

59. Hajat C, Dundas R, Stewart JA, et al. Cerebrovascular risk factors and stroke subtypes: differences between ethnic groups. *Stroke.* Jan 2001;32(1):37-42.

60. Markus HS, Khan U, Birns J, et al. Differences in stroke subtypes between black and white patients with stroke: the South London Ethnicity and Stroke Study. *Circulation.* Nov 6 2007;116(19):2157-2164.

61. Sacco RL, Kargman DE, Zamanillo MC. Race-ethnic differences in stroke risk factors among hospitalized patients with cerebral infarction: the Northern Manhattan Stroke Study. *Neurology.* Apr 1995;45(4):659-663.

62. White H, Boden-Albala B, Wang C, et al. Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. *Circulation.* Mar 15 2005;111(10):1327-1331.

63. Singh R, Cohen SN, Krupp R, et al. Racial differences in ischemic cerebrovascular disease. *J Stroke Cerebrovasc Dis.* Sep-Oct 1998;7(5):352-357.

64. Lavados PM, Sacks C, Prina L, et al. Incidence, case-fatality rate, and prognosis of ischaemic stroke subtypes in a predominantly Hispanic-Mestizo population in Iquique, Chile (PISCIS project): a community-based incidence study. *Lancet Neurol.* Feb 2007;6(2):140-148.

65. Birman-Deych E, Radford MJ, Nilasena DS, et al. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. *Stroke.* Apr 2006;37(4):1070-1074.

66. Uchino K, Risser JM, Smith MA, et al. Ischemic stroke subtypes among Mexican Americans and non-Hispanic whites: the BASIC Project. *Neurology.* Aug 10 2004;63(3):574-576.

67. Shen AY, Yao JF, Brar SS, et al. Racial/Ethnic differences in ischemic stroke rates and the efficacy of warfarin among patients with atrial fibrillation. *Stroke.* Oct 2008;39(10):2736-2743.

68. Zhang LF, Yang J, Hong Z, et al. Proportion of different subtypes of stroke in China. *Stroke.* Sep 2003;34(9):2091-2096.

69. Shen AY, Chen W, Yao JF, et al. Effect of race/ethnicity on the efficacy of warfarin: potential implications for prevention of stroke in patients with atrial fibrillation. *CNS Drugs.* 2008;22(10):815-825.

70. Fox CS, Parise H, D'Agostino RB, Sr., et al. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *Jama.* Jun 16 2004;291(23):2851-2855.

71. Arnar DO, Thorvaldsson S, Manolio TA, et al. Familial aggregation of atrial fibrillation in Iceland. *Eur Heart J.* Mar 2006;27(6):708-712.

72. Brugada R, Tapscott T, Czernuszewicz GZ, et al. Identification of a genetic locus for familial atrial fibrillation. *N Engl J Med.* Mar 27 1997;336(13):905-911.

73. Chen YH, Xu SJ, Bendahhou S, et al. KCNQ1 gain-of-function mutation in familial atrial fibrillation. *Science.* Jan 10 2003;299(5604):251-254.

74. Tsai CT, Lai LP, Hwang JJ, et al. Molecular genetics of atrial fibrillation. *J Am Coll Cardiol.* Jul 22 2008;52(4):241-250.

75. Ellinor PT, Yi BA, MacRae CA. Genetics of atrial fibrillation. *Med Clin North Am.* Jan 2008;92(1):41-51, x.

76. Gudbjartsson DF, Arnar DO, Helgadottir A, et al. Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature.* Jul 19 2007;448(7151):353-357.

77. Zeng Z, Tan C, Teng S, et al. The single nucleotide polymorphisms of I(Ks) potassium channel genes and their association with atrial fibrillation in a Chinese population. *Cardiology.* 2007;108(2):97-103.

78. Issac TT, Dokainish H, Lakkis NM. Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data. *J Am Coll Cardiol.* Nov 20 2007;50(21):2021-2028.

79. Chung MK, Martin DO, Sprecher D, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation.* Dec 11 2001;104(24):2886-2891.

80. Winker MA. Measuring race and ethnicity: why and how? *Jama.* Oct 6 2004;292(13):1612-1614.

81. Bamshad M. Genetic influences on health: does race matter? *Jama.* Aug 24 2005;294(8):937-946.

82. Dawber TR, Kannel WB. The Framingham study. An epidemiological approach to coronary heart disease. *Circulation.* Oct 1966;34(4):553-555.

83. Furberg CD, Psaty BM, Manolio TA, et al. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol.* Aug 1 1994;74(3):236-241.

84. Vermes E, Tardif JC, Bourassa MG, et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: insight from the Studies Of Left Ventricular Dysfunction (SOLVD) trials. *Circulation.* Jun 17 2003;107(23):2926-2931.

85. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med.* Jun 4 1987;316(23):1429-1435.

86. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *Jama.* Mar 8 2000;283(10):1295-1302.

87. Thomas AJ, Eberly LE, Davey Smith G, et al. ZIP-code-based versus tract-based income measures as long-term risk-adjusted mortality predictors. *Am J Epidemiol.* Sep 15 2006;164(6):586-590.

88. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. *Circulation.* Dec 16 2003;108(24):3006-3010.

89. Anderson JL, Allen Maycock CA, Lappe DL, et al. Frequency of elevation of C-reactive protein in atrial fibrillation. *Am J Cardiol.* Nov 15 2004;94(10):1255-1259.

90. Dernellis J, Panaretou M. C-reactive protein and paroxysmal atrial fibrillation: evidence of the implication of an inflammatory process in paroxysmal atrial fibrillation. *Acta Cardiol.* Dec 2001;56(6):375-380.

91. Dernellis J, Panaretou M. Relationship between C-reactive protein concentrations during glucocorticoid therapy and recurrent atrial fibrillation. *Eur Heart J.* Jul 2004;25(13):1100-1107.

92. Conway DS, Buggins P, Hughes E, et al. Prognostic significance of raised plasma levels of interleukin-6 and C-reactive protein in atrial fibrillation. *Am Heart J.* Sep 2004;148(3):462-466.

93. Conway DS, Lip GY. Ethnicity in relation to atrial fibrillation and stroke (the West Birmingham Stroke Project). *Am J Cardiol.* Dec 15 2003;92(12):1476-1479.

94. Gunarathne A, Patel JV, Potluri R, et al. Secular trends in the cardiovascular risk profile and mortality of stroke admissions in an inner city, multiethnic population in the United Kingdom (1997-2005). *J Hum Hypertens.* Jan 2008;22(1):18-23.