The Atrial Fibrillation Paradox - Connecting Hypertension to Atrial Disease and Stroke

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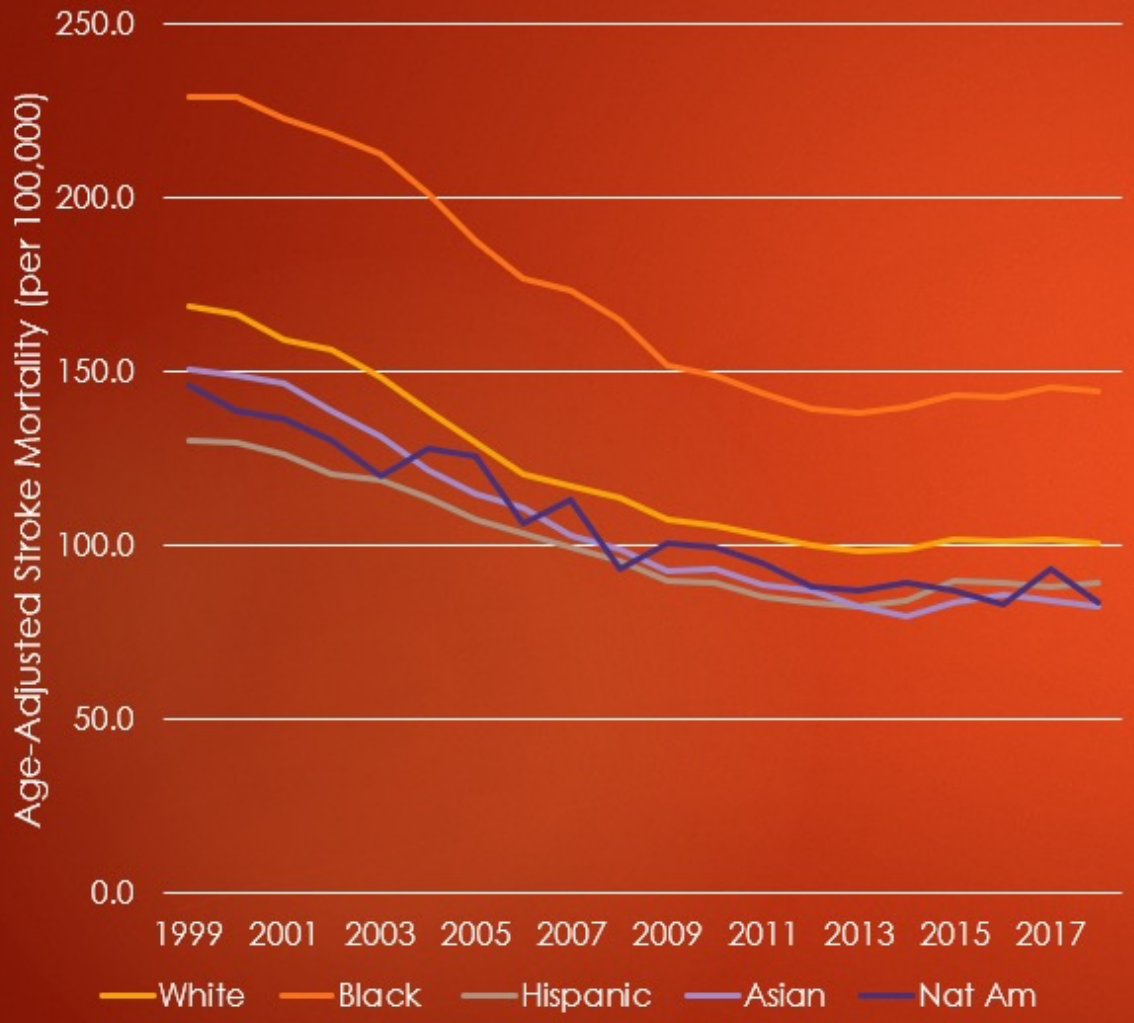
Preamble

Stroke and African Americans

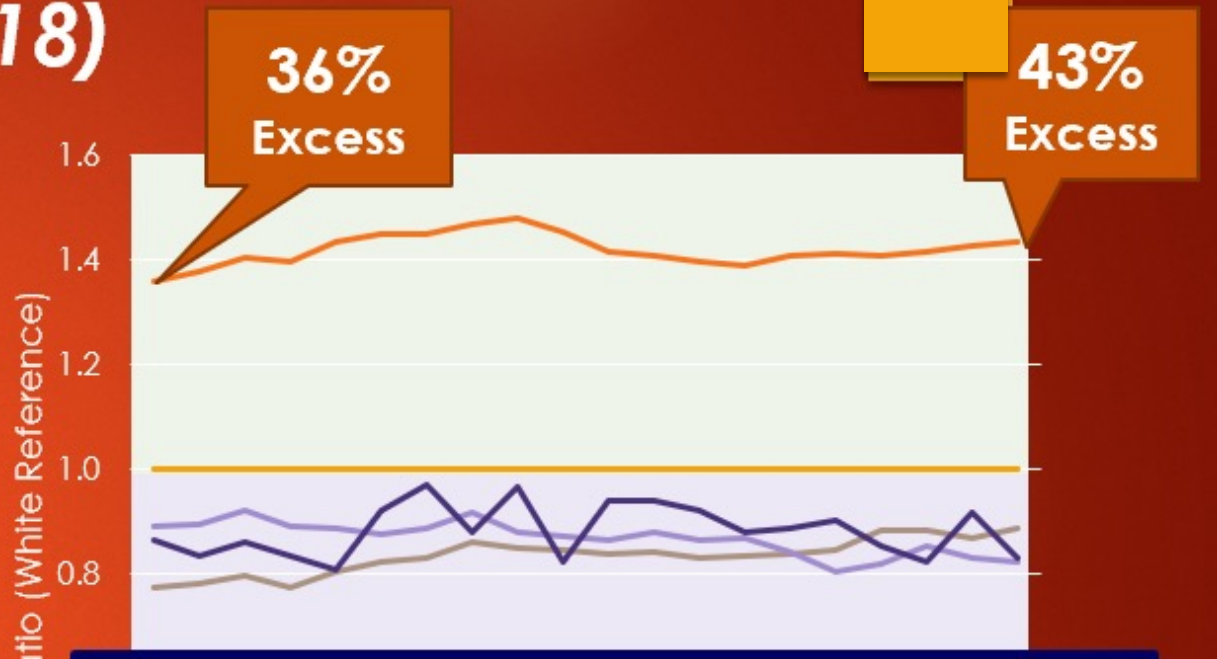
- African Americans are 50 percent more likely to have a stroke (cerebrovascular disease), as compared to their white adult counterparts.
- Black men are 60 percent more likely to die from a stroke as compared to non-Hispanic whites.
- African American women are twice as likely to have a stroke as compared to non-Hispanic white women.

https://minorityhealth.hhs.gov/omh/browse.aspx?lvl=4&lvlid=28

Recent Pattern of Racial/Ethnic Disparities in Stroke Mortality *(1999 – 2018)*



Races are shown for non-Hispanic population, and Hispanic population is shown for all races.



- **Between 1949 and 1951 the white-to-nonwhite (largely black) stroke mortality ratio was 1.63 for men and 1.92 for women**
- **We have made little progress to reduce the racial disparity in stroke mortality in the last 70 years!**

Stroke in young: Black /White differences

Stroke in the Young

- Accounts for 10% to 15% of all stroke
- Incidence rates: 2005 GCNKSS study, age 20-54 years
  - whites, 48 per 100,000; blacks, 128 per 100,000
  - ischemic (69%), ICH (17%), SAH (10%), unknown (5%)
- Case Fatality: FUTURE study, age 18-50 yrs
  30-day fatality 4.5%; one-year mortality for survivors 1.2% for TIA, 2.4% for ischemic stroke, and 2.9% for ICH.

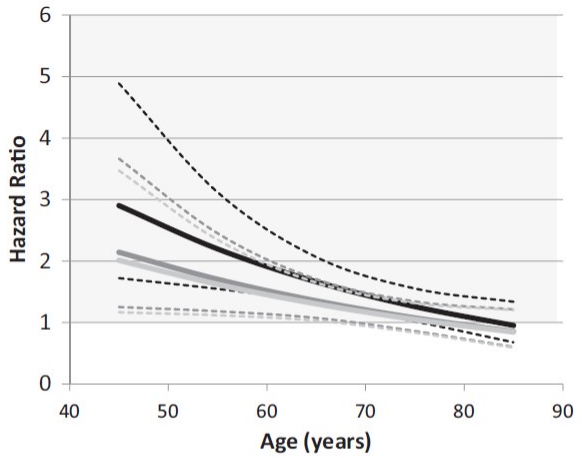


Figure. Estimated black/white hazard ratio as a function of age and covariate adjustment. Black lines show hazard ratio and 95%

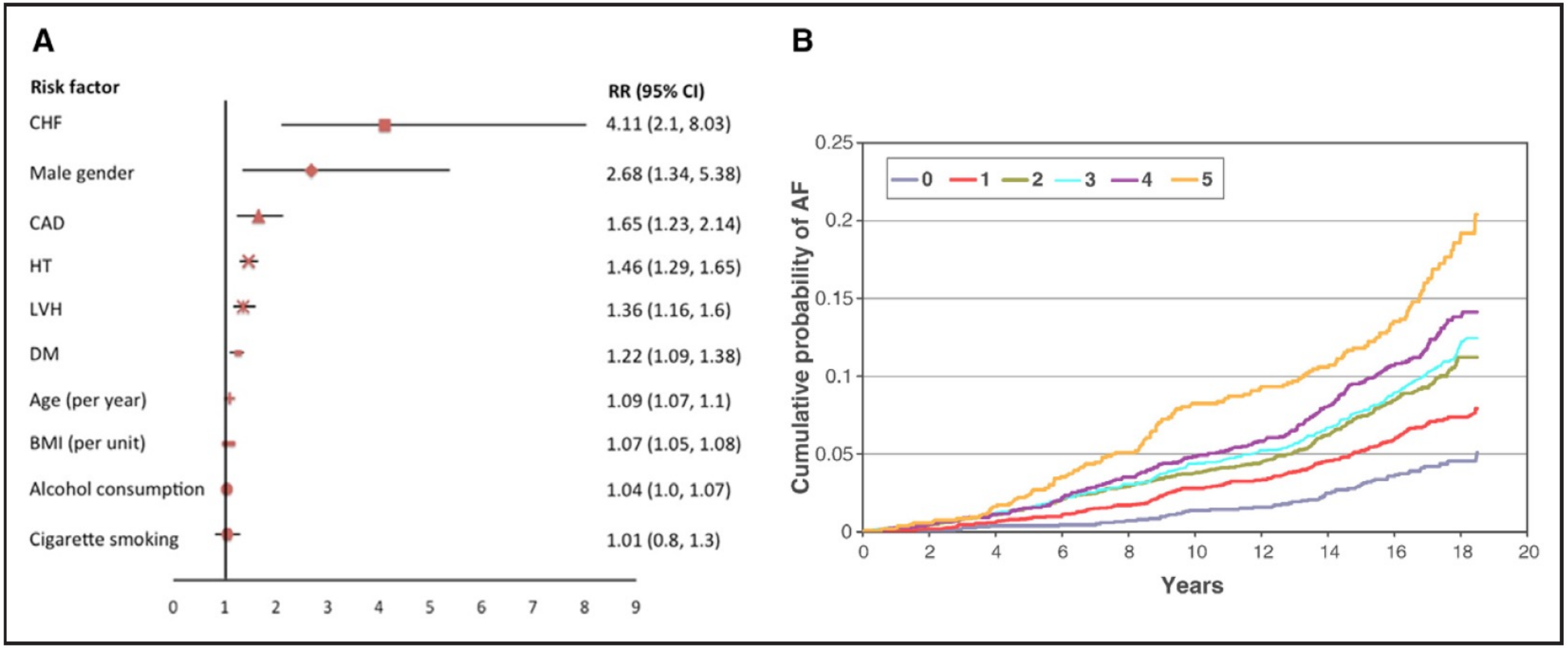
	Men			Women		
Age, y	Black Death Rate	White Death Rate	Black/White Mortality Ratio	Black Death Rate	White Death Rate	Black/White Mortality Ratio
45–54	45.5	12.2	3.7	34.8	9.9	3.5
55–64	106.9	32.3	3.3	66.7	24.7	2.7
65–74	240.4	110.1	2.2	166.0	88.9	1.9
75–84	544.0	394.5	1.4	471.3	370.9	1.3
≥85	1103.5	1142.3	1.0	1268.6	1325.4	1.0

Rates provided for non-Hispanic whites and non-Hispanic blacks.

Data taken from Centers for Disease Control and Prevention, National Center for Health Statistics. CDC WONDER Online Database, compiled from Compressed Mortality File 1999–2009 Series 20 No. 20, 2012. Accessed October 28, 2012 at http://wonder.cdc.gov/cmf-icd10.html.

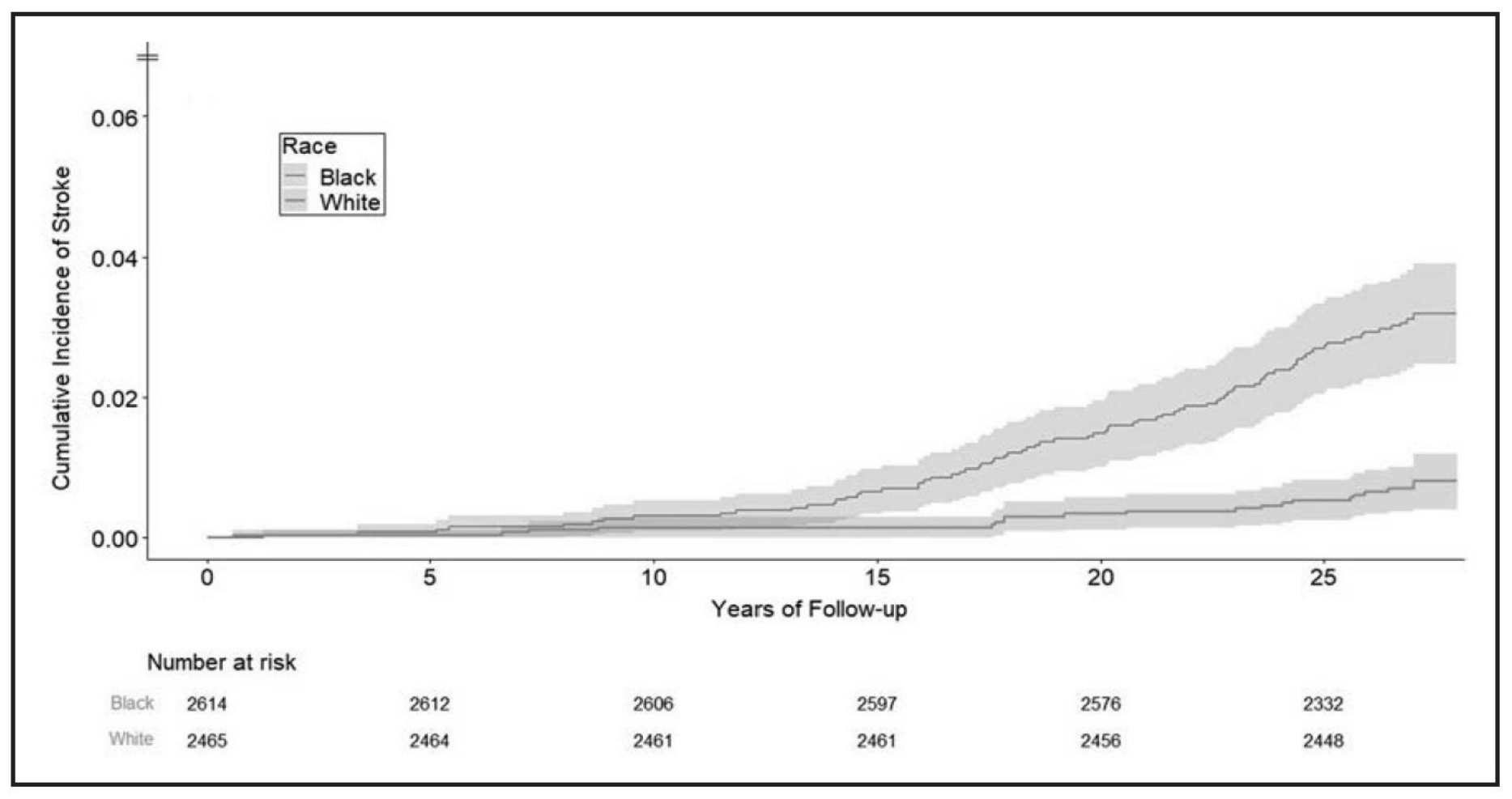
Stroke. 2013;44[suppl 1]:S126-S128

Impact of RF over time in the development of AF



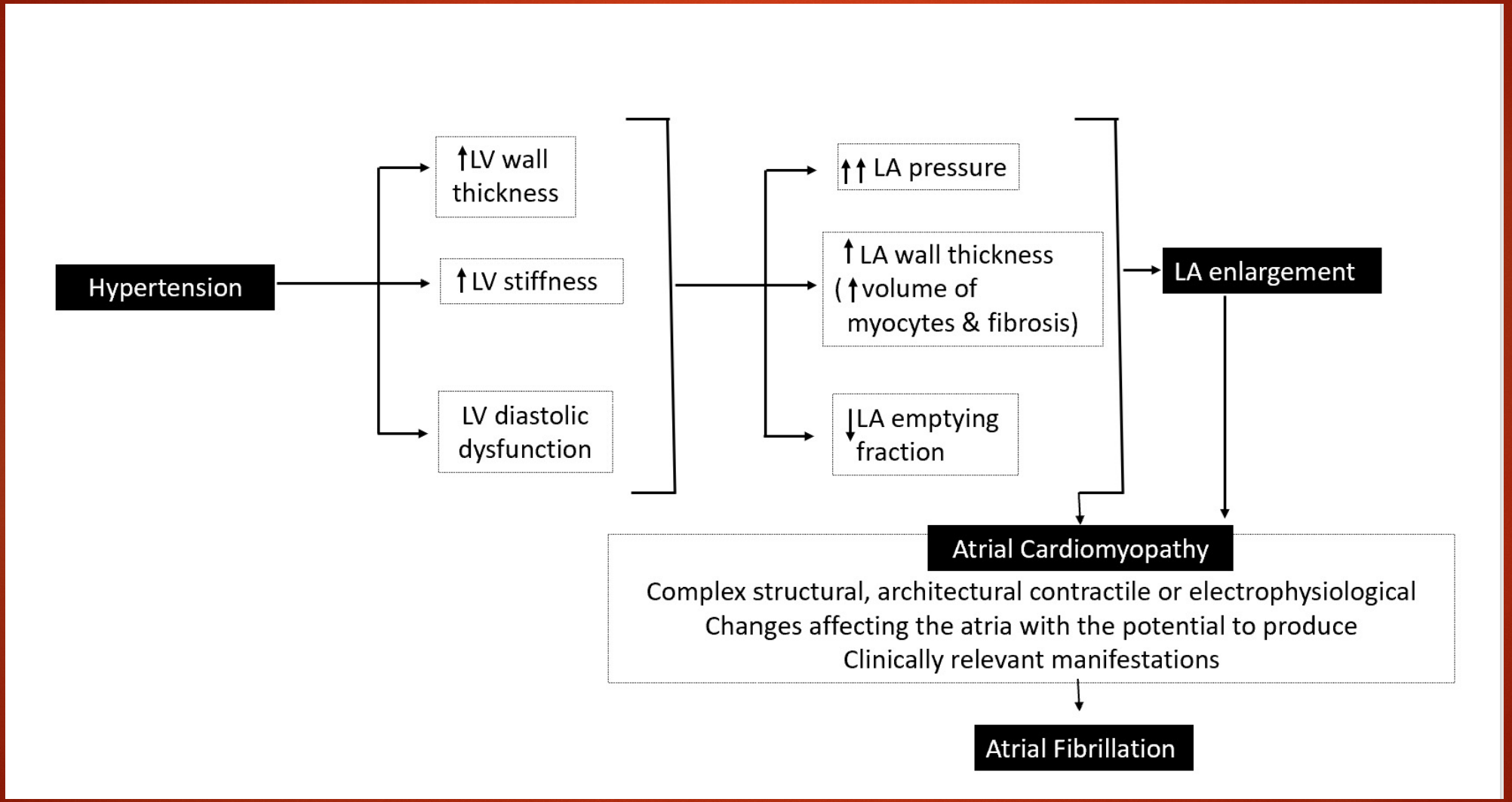
Circulation. 2017;136:583–596. DOI: 10.1161/CIRCULATIONAHA.116.023163

Stroke incidence comparing black and white patients from the CARDIA study[11]



Gerber, Y, et. al., Hypertension. 2021;77:1683–1693

Relationship between Hypertension, LV changes, and Atrial Fibrillation



Circ Res.2018;122:352-368. DOI: 10.1161/CIRCRESAHA.117.311402

Effect of Intensive vs Standard BP Lowering on Incident AF in SPRINT

Treatment arm	Participants (n)	Events (n)	Event Rate (1000 person-years)	HR (95% CI)*	*P* Value
Intensive BP lowering	4003	88	6.21	0.74 (0.56–0.98)	0.037
Standard BP lowering	4019	118	8.33		

*Clinical site at randomization was used as a stratification factor. AF indicates atrial fibrillation; BP, blood pressure; HR, hazard ratio; and SPRINT, Systolic Blood Pressure Intervention Trial.

Solimon, E Z; et. al. Effect of Intensive Blood Pressure Lowering on the Risk ofAtrial Fibrillation; Hypertension. 2020;75:1491-1496.

Stroke and Cardiovascular Risk summary points

- We know that the accumulation of cardiovascular risk factors predispose individuals to stroke as well as atrial fibrillation
- Exposure to risk factors over time increase the burden of disease
- Risk factors, and particularly hypertension, may play a unique and important role for the risk of stroke in Black individuals

The AF Paradox…

A double paradox exists between traditional cardiovascular risk factors and the development of atrial fibrillation (AF) in black individuals. This contrast as observed between Black and White individuals is further complicated by the significant difference in stroke.

Simply stated, "Why do Black individuals have more traditional cardiovascular risk factors, more stroke, yet lower rates of atrial fibrillation?"

THE AF PARADOX: Background and History

Atrial Fibrillation in Ethnicity; the known, the unknown and the paradox;
Future Cardiology (2009) 5(6) 547-556

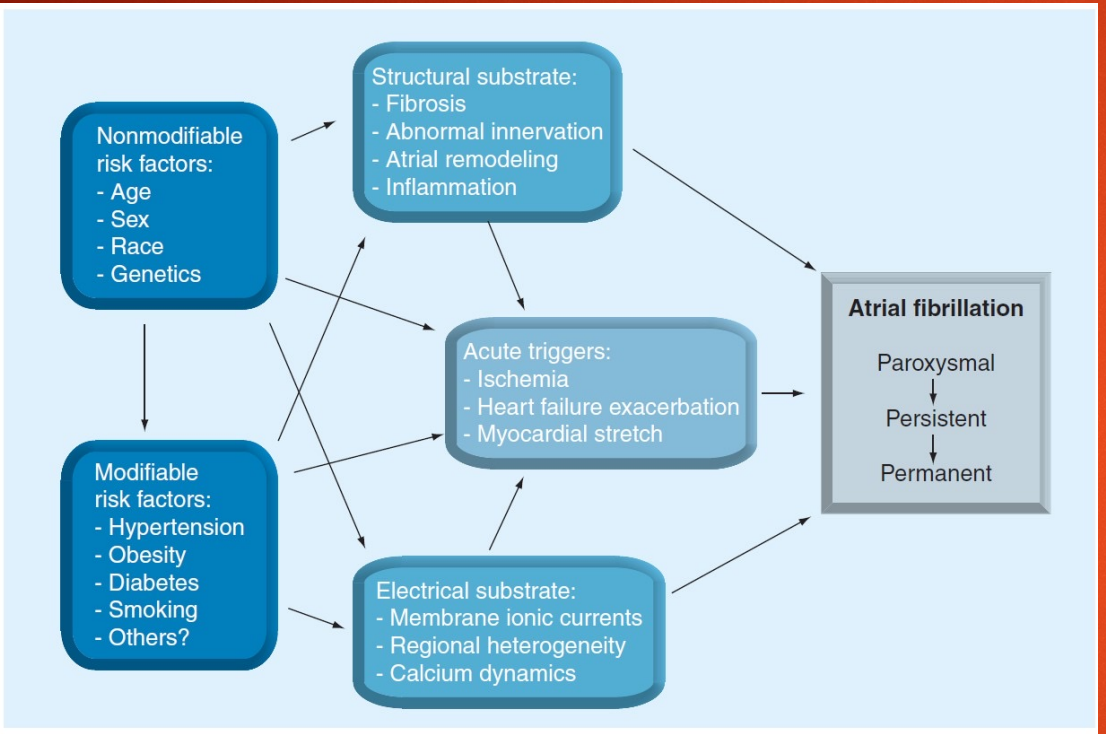


Figure 1. A conceptual model of the pathogenesis and progression to atrial fibrillation over the lifetime of individuals who are at risk.
Adapted from [7].

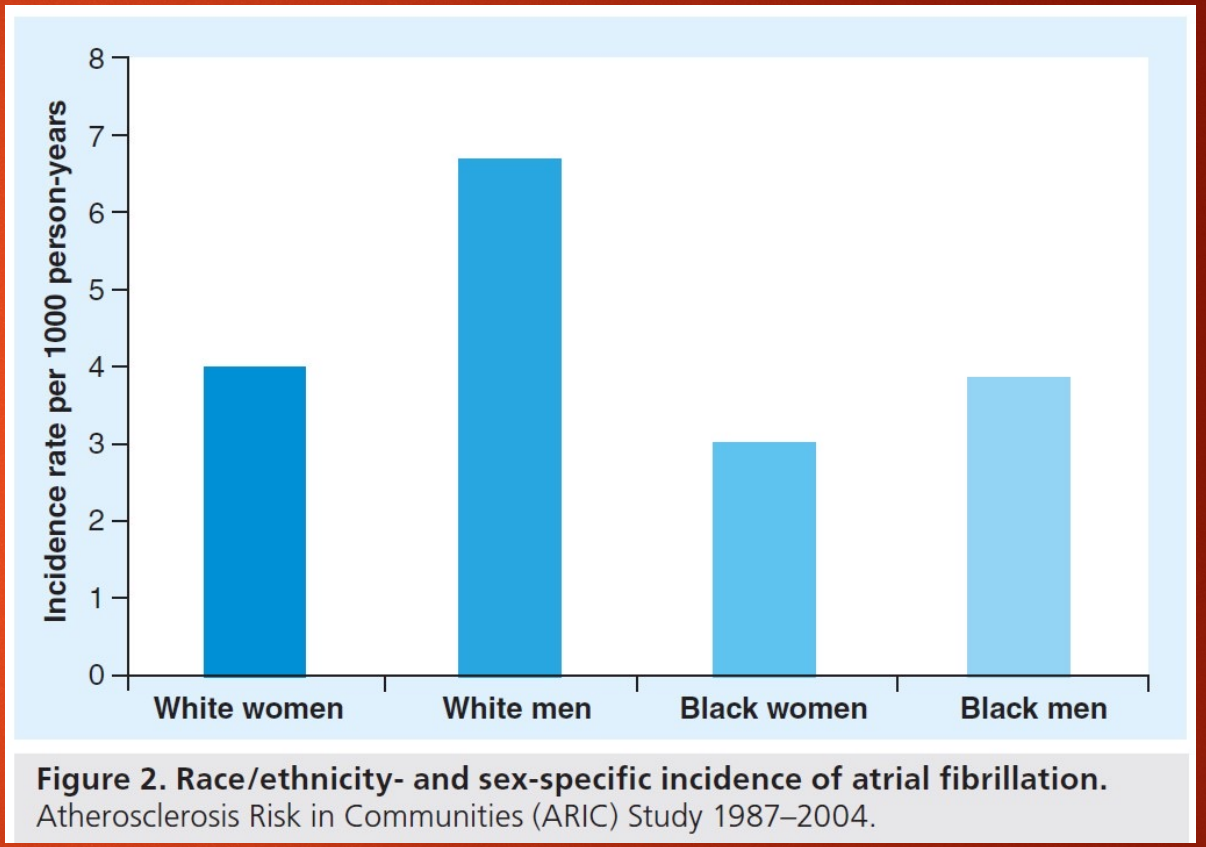


Figure 2. Race/ethnicity- and sex-specific incidence of atrial fibrillation.
Atherosclerosis Risk in Communities (ARIC) Study 1987–2004.

- Traditional risk factors AF - differential effect
- High stroke rates – inconsistent burden of AF

- Blacks and AF detection methodology
- Racial variations in context of genes and environmental factors/P wave indices

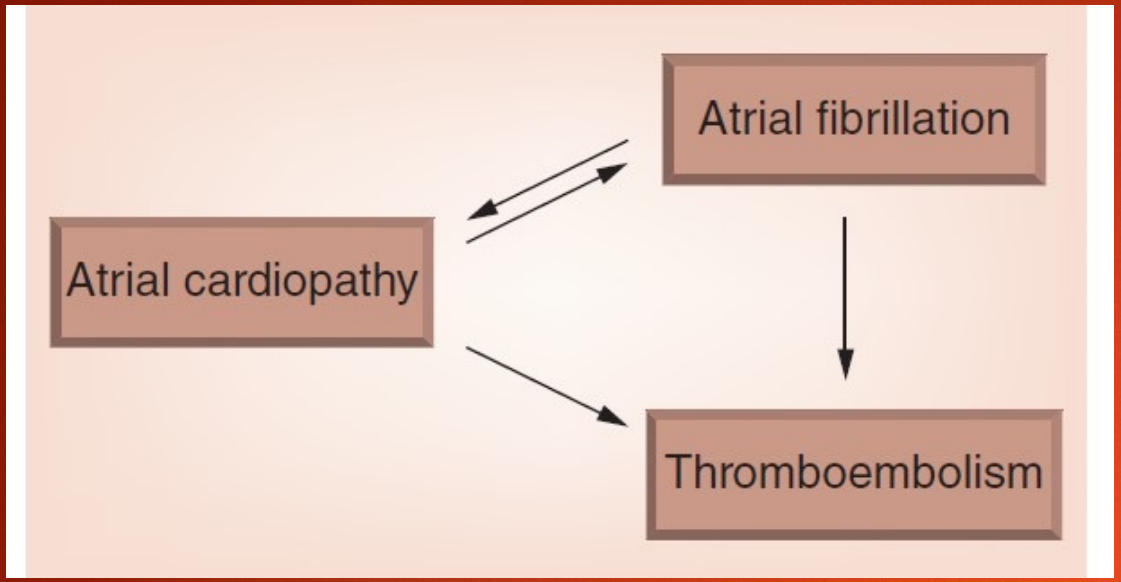
Background and History

Racial Differences in Atrial Fibrillation Prevalence and Left Atrial Size; *The American Journal of Medicine (2010) 123, 375*

- *ECG confirmed atrial fibrillation is more common in Caucasians than in African Americans, which might be related to the larger left atrial diameter observed in Caucasians*
  - *prevalence confirmed in ARIC, SCCS studies in 2012*

Differential impact of race and risk factors on incidence of atrial fibrillation; Am Heart J 2011;162:31-7

- *Despite some common risk factors for atrial fibrillation (AF) being more prevalent among blacks, African Americans are increasingly being reported with lower prevalence and incidence of AF compared with whites*



Atrial cardiopathy as a stroke risk factor. In this formulation, the driving force of thromboembolism is not simply atrial fibrillation but rather underlying atrial tissue changes, with the dysrhythmia feeding back to both worsen the tissue changes and worsen left atrial contractile function, thereby increasing the risk of thromboembolism even further.

Box 1. Summary of key arguments.

Arguments against atrial fibrillation as the root cause of left atrial thromboembolism

- AF is not always temporally related to stroke
- AF does not show a dose-response relationship with stroke
- AF imparts differing degrees of stroke risk depending on risk factors

Arguments for atrial cardiopathy as the root cause of left atrial thromboembolism

- Vast majority of AF occurs in setting of abnormal atrial substrate
- Left atrial abnormality is associated with stroke independently of AF diagnosis

Future Cardiol. (2015) 11(3), 323–331

Racial Differences in Atrial Cardiopathy Phenotypes in Ischemic Stroke Patients

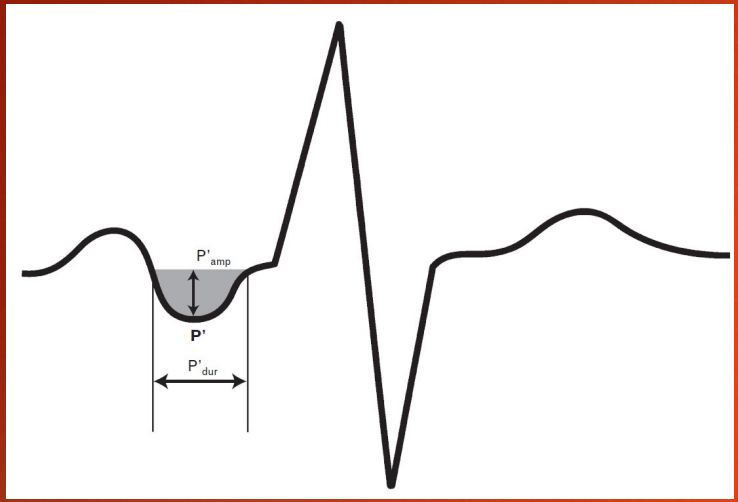
Thrombogenic atrial cardiopathy relevance to stroke-related racial disparities, we compared atrial cardiopathy phenotypes between Black versus White ischemic stroke patients

- Among 3246 ischemic stroke cases in Black/White patients without AF/AFL, 2,391 had a left atrial diameter measurement
- Black race was associated with smaller left atrial diameter in unadjusted.
- PTFV1 measurements were available in 3,209 patients Black race was associated with greater PTFV1 in unadjusted and adjusted models.

- ***We found systematic Black-White racial differences in left atrial structure and pathophysiology in a population-based sample of ischemic stroke patients, providing class II evidence that the rate of atrial cardiopathy is greater among Black people with acute stroke compared to White people.***

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000011197

Electrocardiographic left atrial abnormalities and risk of incident stroke in hypertensive patients with electrocardiographic left ventricular hypertrophy



P wave terminal force in electrocardiogram lead V1 was defined as the absolute value of the amplitude (P0 amp) multiplied by the duration (P0 dur) of the terminal portion of the P wave (P0 ; shaded area) in lead V1 of a standard 12-lead ECG.

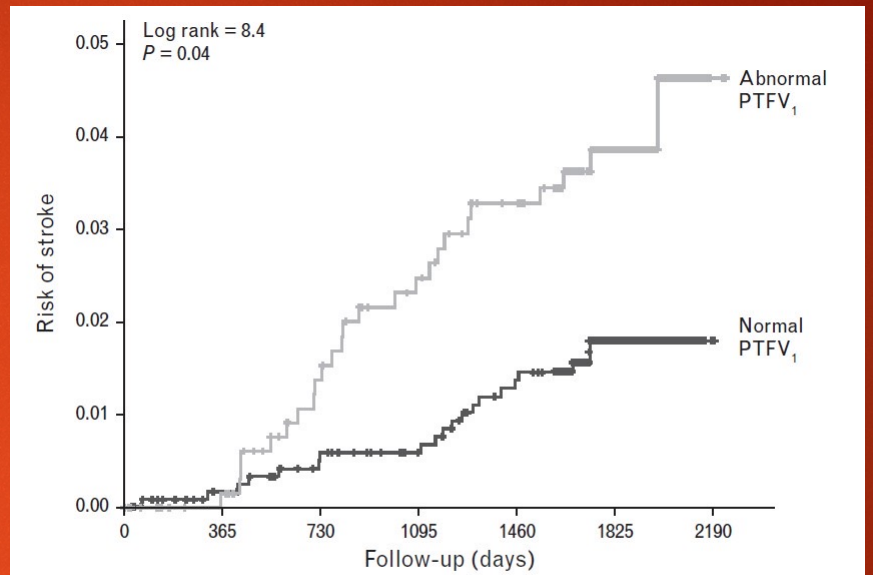


FIGURE 2 Univariate Kaplan–Meier survival curves illustrating the hazard of incident stroke according to the presence or absence of an abnormal P wave terminal force in electrocardiogram lead V_1 at study baseline.

Abnormal PTFV1, a marker of left atrial abnormality, was strongly associated with incident stroke in hypertensive patients, independent of in-treatment SBP and other predictors of incident stroke. This association, in the absence of detectable atrial fibrillation, suggests that an underlying atrial cardiopathy may cause left atrial thrombus formation and a subsequent stroke without intervening clinically recognized atrial fibrillation

J Hypertension Volume 34 Number 9 September 2016

Racial Differences in Atrial Cardiopathy Phenotypes in Ischemic Stroke Patients-top line summary of key points

- Thrombogenic atrial cardiomyopathy in racial disparities and stroke
- P-wave terminal force V1 as marker for LA fibrosis and impaired atrial conduction
- Blacks with smaller LA diameter and greater PTFV1
- Blacks - twice the risk of ischemic stroke vs whites – RF don't fully explain
- Causes of cryotogenic stroke – unexplained strokes in the absence of AF/AFL – may account for racial variance.
- Lacks social determinant of health, complete ancestry
- Diagnostic standards for AF may need to evolve to understand the variety and complexity of acquired atrial CM and racial impact

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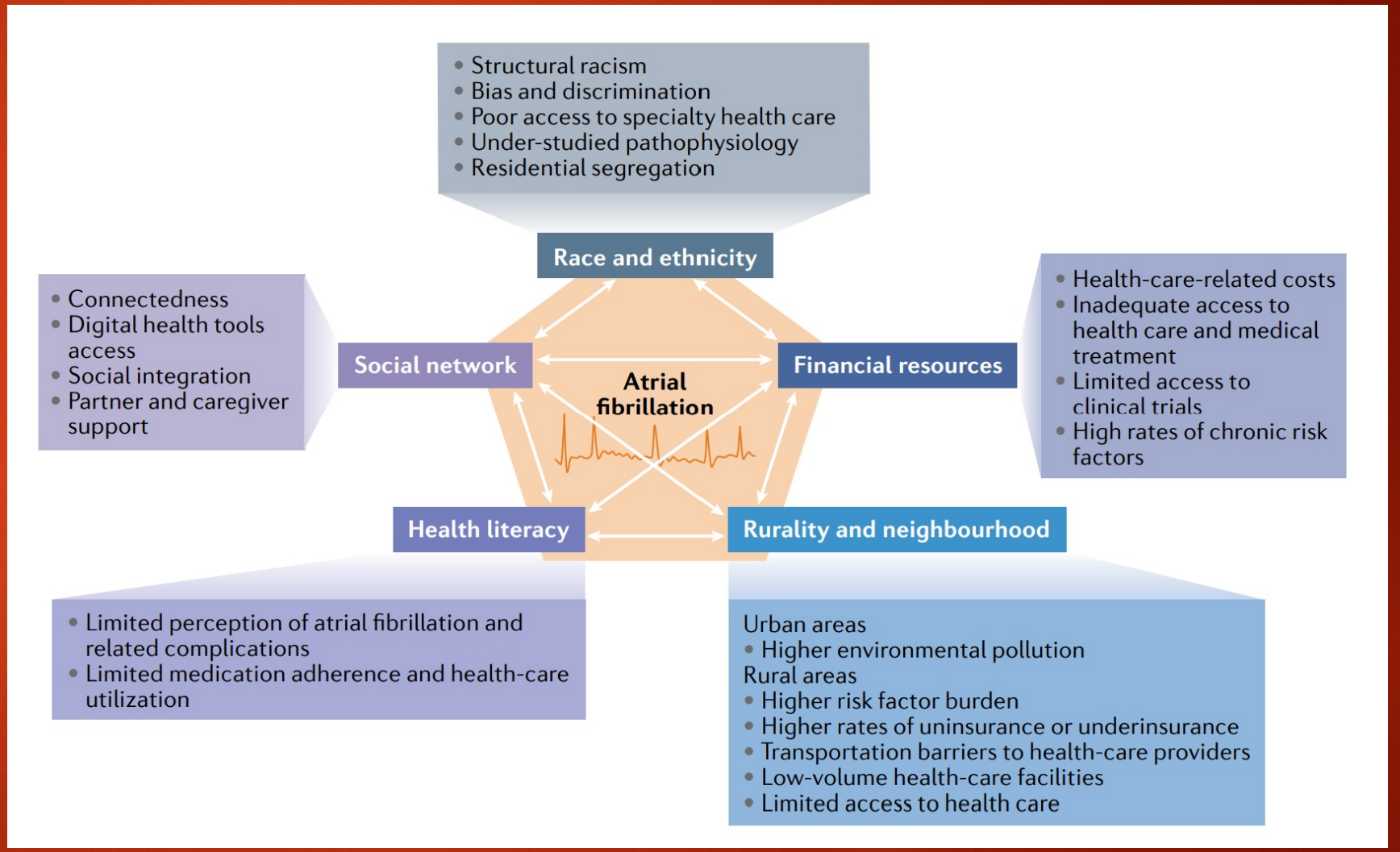
DOI: 10.1212/WNL.0000000000011197

Social determinants of atrial fibrillation

- Social determinants — such as **race and ethnicity**, financial resources, social support, access to health care, rurality and residential environment, local language proficiency and health literacy — have prominent roles in the evaluation, treatment and management of atrial fibrillation



Impact of Health Literacy and Atrial Fibrillation

- Low health literacy is associated with reduced knowledge of AF, its treatment and related outcomes.
- Individuals with limited health literacy have decreased understanding of AF and the importance of anticoagulation for stroke prevention.
- Health literacy and LLLP have not been included as factors in AF clinical trials or registry-based studies, their importance is underscored by an international survey of physicians in which 46% of respondents considered their patients to be unable to explain AF adequately1
- Low health literacy and local language proficiency are associated with decreased patient-centred communication and, in turn, diminished shared decision-making

Summary recommendations

- Earlier recognition and aggressive management of hypertension as well as other cardiovascular risk factors - notably diabetes mellitus - should become a standard of practice to reduce the burden of stroke and the potential development of atrial disease.
- Hypertension, particularly in younger individuals, may play a unique role in the development of atrial disease. It also underscores that there is a progression of atrial disease leading to an increased burden of atrial arrhythmias, which along the progression represents increased thromboembolic risk.
- More research is needed to evaluate changes in P-wave indices, as a marker for atrial disease, particularly in Black patients. This may add to the understanding and interpretation of risk of stroke and its relationship to progressive atrial disease.
- Along with aggressive management of the risk factors, we should determine whether anticoagulation or other preventive therapies may help reduce the risk of thromboembolic events in a range of conditions that lead to AF, including atriopathy.
- Additional research is needed in determining the impact of social determinants of health as it relates to stroke prevention and overall CV health outcomes.