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The atrial fibrillation paradox -connecting hypertension to atrial disease and stroke



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1. Introduction

A “double paradox” exists in the understanding of racial differences in the association between traditional cardiovascular (CV) risk factors, the incidence and prevalence atrial fibrillation (AF), and the increased incidence of ischemic stroke. Simply stated, Black persons have an increased number of CV risk factors yet less AF. Despite lower incidence of AF, Black individuals have higher rates of stroke and systemic embolism. This important public health challenge is notable, given that, despite a significant decline in overall stroke mortality rates since the 1950s, age-adjusted stroke death rates have remained higher in Black versus White individuals through 2008.[2]

The purpose of this review is to examine the risk of ischemic stroke in Black persons and provide a summary of options to improve the recognition of individual risk and reinforce preventive care. Consider the following concepts:

- Black individuals have more traditional CV risk factors and higher rates of ischemic stroke, than their non-Hispanic White counterparts, yet a lower incidence and prevalence of AF.
- The difference in the incidence of AF does not fully explain the differences in stroke risk
- The explanation for these differences is likely complex and leads to the following questions.
 - Should researchers and clinicians reassess the way atrial disease and embolic risk are defined in specific populations?
 - Do traditional risk factors for AF account for increased stroke risk in select patient populations which also needs to be re-evaluated in the context of stroke reduction.

As with prior work[1,17,18,19,21] which has addressed the “AF Paradox” this review supports the concept of atrial disease - including atrial fibrillation - as a continuum. There also appears to be a risk of stroke associated with this continuum in the absence of a diagnosis of

AF.[1,18,21] These factors alone do not account for the differences in overall stroke rates in Black persons. In addition to a revision on the views of atrial disease, there should be a renewed emphasis early and aggressive blood pressure control – as well as other risk factor management – in Black individuals to affect the differences in stroke rates. The objective of this review is to re-examine the specific role of hypertension in atrial disease and perceptions on stroke risk, AF and possible differences between Black and White individuals.

2. Risk factors and atrial fibrillation

There are a broad range of CV risk factors that predispose individuals to the development of AF. Of note, several of these characteristics are highlighted in the CHA₂DS₂-VASc (Congestive heart failure, Hypertension, Age ≥ 75, Diabetes, prior Stroke/TIA, Vascular disease, Age 65-74Sex category [female]) risk score used to determine the risk of ischemic stroke (and systemic embolism) in patients with diagnosed non-valvular AF for the purpose of treating with stroke reduction therapies.[3] Given the insidious onset of AF and disease progression, it may not be clear what the specific relationship between CV risk factors and AF may be at play in an individual patient.[4] There are multiple mechanisms associated with CV risk factors which may explain the development of AF. In addition, there are multiple considerations such as aging, left atrial enlargement, heart failure, hypertension, chronic obstructive pulmonary disease, and a previous history of cerebrovascular disease which are commonly associated with AF progression. These risk factors are not mutually exclusive, but cluster with additional risk factors including obesity, diabetes mellitus, and obstructive sleep apnea (OSA).[5] It is also recognized that risk factors may be classified as non-modifiable, modifiable, or disease processes that add to burden of AF. These risk factors lead to structural modifications as well as changes in substrate associated with fibrosis, inflammation, and cellular modifications of the atria, increasing the susceptibility to AF. It is also appreci-

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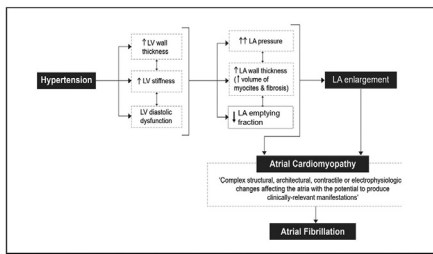


Fig. 1. Central illustration. Relationship between hypertension, LV changes, and atrial fibrillation (adapted from 8).

ated that also appreciate that AF begets AF resulting in further electrical and structural changes.[6]

3. Hypertension and AF

The relationship between hypertension and AF is not fully understood. Because of its higher prevalence in the Black patient population, hypertension exhibits a more consistent association with the development of AF than other risk factors. In the ARIC (Atherosclerosis Risk in Communities) study, hypertension was associated with approximately 20% of incident AF cases. In patients with known AF, hypertension is present in about 60% to 80% of those individuals. Experimental models indicate that hypertension may result in early and progressive changes in left atrial (LA) anatomy and function, which may promote AF through a variety of electrophysiological mechanisms. These data suggest the importance of an early control of BP in hypertensive patients as a preventive strategy leading to the progression of LA remodeling and development of AF.[7]

One mechanism that may be related to the development of AF in association with hypertension is described as atrial cardiomyopathy. This condition is associated with atrial cardiomyocyte hypertrophy and contractile dysfunction, arrhythmogenic changes in cardiomyocyte ion-channel and transporter function, atrial fibroblast proliferation, hyperinnervation, and thrombotic changes which in turn have a substantial impact on cardiac performance, arrhythmia occurrence, and stroke risk. As the diagram below (Fig. 1) demonstrates, hypertension is associated with hemodynamic mechanisms which include the increase in left ventricular (LV) wall thickness, the rise in LV stiffness, and the impairment in LV diastolic function. These changes in turn, may lead to a rise in LA stretch and pressure, with subsequent remodeling and dysfunction of the LA, ultimately predisposing to AF. In a unique electrophysiological study comparing hypertensive patients and normotensive controls, the former group showed slowing of global and regional conduction, an increase in areas of low voltage and, most notably, an easier inducibility of sustained AF.[8]

4. Distinct characteristics of hypertension and stroke in black individuals

Reductions in CV disease incidence and mortality in the United States have not been shared equally by all patient groups. Since the earliest studies in the 1950s, overall stroke mortality rates in Black patients remain 4.5-fold higher than among White patients. There is an age-risk correlation to stroke mortality where Black patients have a 2.6 fold higher risk than White patients ages 45 to 54 years of age but decreasing risk (1.8 times lower) for 55 to 64 years of age, 1.2 times lower for 65 to 74 years of age, 0.9 times lower for 75 to 84 years of age, and 0.8 times lower for ≥ 85 years of age.[2]. Data from the National Health Disparities survey for CV disease identified several factors linked to increase stroke risk, including Black race, poor health literacy, access to healthcare and overall economic status. These characteristics seem to be more prominent in the Southeastern United States which have less investment in

social safety programs and less healthful dietary practices. As reported by Reshetnyak and others, the effect of Social Determinants of Health (SDOH) are more impactful in younger Black patients and diminish after age 65, underscoring the need to identify both social and clinical characteristics earlier in life.[9] As summarized by Essien and others, many of the SDOH as related to AF including race, financial resources, access to care, social support, residential environment and health literacy are critical in the detection, evaluation, and management of AF. Much additional research is needed to assess the impact of SDOH on outcomes associated with AF. Issues such as physical environment, economic stability, education, and health care systems – including access to specialty care - have direct impacts on underdiagnosis and undertreatment of AF. For example, an individual who lives remotely with limited financial resources may not have access to a health care facility which provides specific diagnostic and specialty services. Patient level research which examines how the impact poor educational status may impact AF awareness, knowledge of symptoms leading to better diagnosis, and treatment are necessary. Understanding the patient care environment which examines the manner in which providers identify and communicate the importance of risk factor management, engaging in a meaningful description of AF, the risk of stroke, and management options, can result in a more complete shared decision-making process. Social support to improve trust in the health care system and willingness to seek medical services also play a role. Lastly, community-based research to examine how these SDOH are connected to access to care, social networks and health literacy will result in an improved understanding of how AF impacts disadvantaged patient populations.[10]

The presence of high blood pressure in Black persons represents an important opportunity to improve overall cardiovascular health, including lowering the rate of ischemic stroke. The prevalence of hypertension in Black individuals over 20 years of age is among the highest in the world, and these differences appear in younger ages as well. Lessons from the Bogalusa Heart Study indicate the early onset of high blood pressure in youth persists into adulthood. While control rates for hypertension remain poor, fewer Black patients with hypertension achieve treatment goals than do their White counterparts. A 10-mm Hg difference in systolic blood pressure results in a 3-fold greater risk of stroke when Black and White patients are compared.[7] Consistent with these statistics is the observed increase in stroke incidence in younger individuals which is a notable public health issue given that younger people can carry a lifetime burden of risk and disability. As reported in 2005, the increase in stroke incidence rates occurred in both Black and White individuals when compared to earlier timelines.[11] In a more recently published analysis, increasing stroke rates in the young were associated with traditional risk factors, including hypertension and smoking. Of note, was the observed changes in stroke rates, particularly in young Black individuals as shown in the graphic below in Fig. 2.[11]

Data from the CARDIA (Coronary Artery Risk development in Young Adults Study) looked at the association between blood pressure changes over 30 years and the incident of stroke in a diverse population of more than 5000 study participants (Fig. 3). Stroke incidence was linked to high blood pressure categories which strengthened from young adulthood to middle age, with stroke incidence reported as 4 times greater in Black versus White patients. By age 40, the increase in stroke risk was observed at a level of systolic BP of 90 mm Hg ranging upward and so the blood pressure trajectory seen in young adulthood was associated with long term incidence of stroke. These data strongly endorse the concept of primordial prevention to reduce blood pressure - including at values of BP which are traditionally considered normal - in young adults, particularly in young Black persons given the remarkably high incidence of stroke.[12]

A promising observation was seen in the SPRINT (Systolic Blood Pressure Intervention Trial) which demonstrated the relationship between blood pressure control and the development of AF. (Table 1) The study which included more than 8000 participants and blood pressure

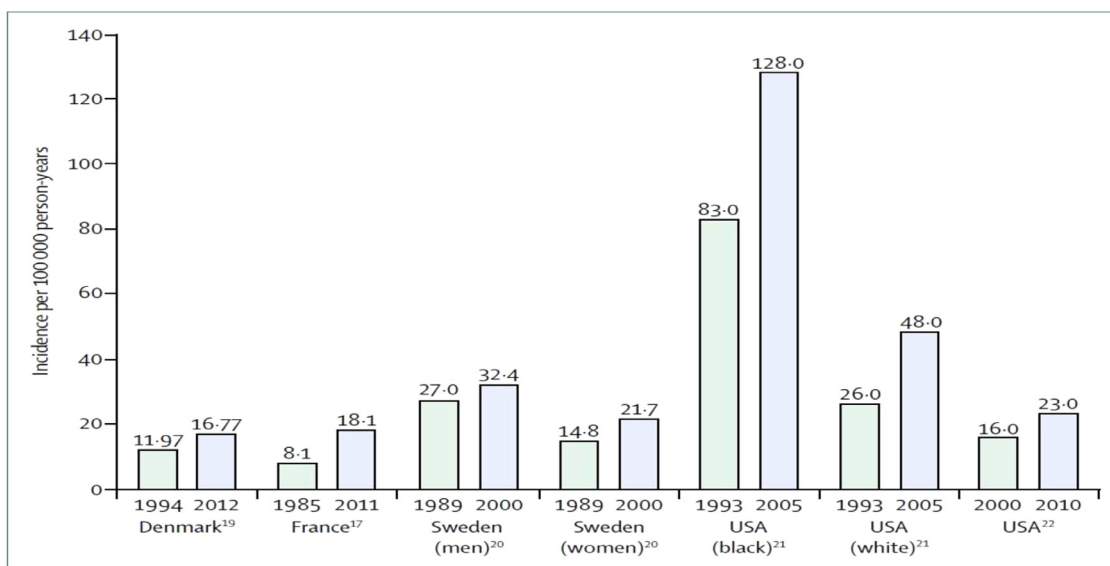


Fig. 2. The increasing incidence of stroke in young adults[11].

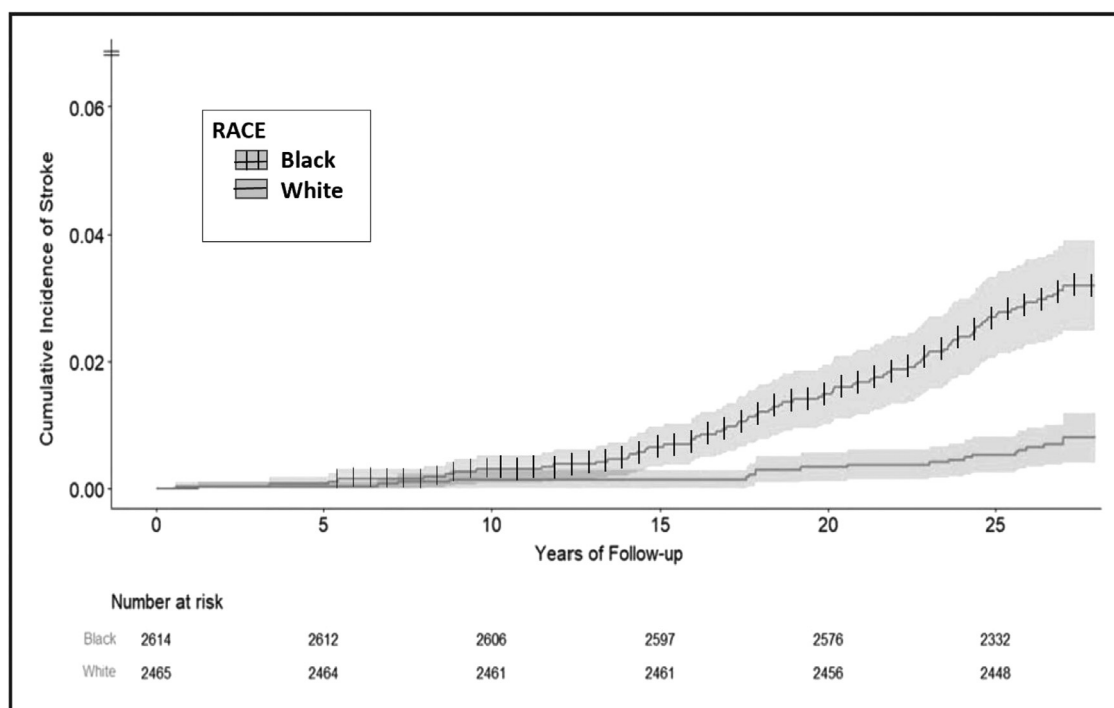


Fig. 3. Stroke incidence comparing Black and White patients from the CARDIA study[12].

Table 1
Effect of Intensive vs Standard BP Lowering on Incident AF in SPRINT[13].

Treatment arm	Participants (n)	Events (n)	Event Rate (1000 person-years)	HR (95% CI)*	PValue
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.

control targets (SBP < 120 mm HG) as compared to standard treatment (target SBP < 140 mm HG) for 5.2 years of follow up. Intensive BP was associated with 26% lower risk of developing AF, suggesting that more aggressive blood pressure control may be important as a preventive strategy for the development of AF.[13]

5. Atrial fibrillation, hypertension, and the intersection of risk

Despite having a higher burden of traditional risk factors for AF, Black patients have a lower incidence and prevalence of AF. As noted by multiple investigators, atrial size tends to be smaller in Black individ-

uals. In a recent report, the extent of atrial enlargement in the presence of hypertension was less in Black patients despite other similar parameters of ventricular wall thickness and echocardiographic measures of diastolic function. In contrast to their White counterparts, Black individuals had significantly lower levels of biomarkers associated with the development of extracellular matrix and atrial remodeling in response to hypertension which may explain lower rates of AF in black individuals. Yet the diagnosis of atrial fibrillation alone, does not account for the excess stroke rates, suggesting that other mechanisms are in play[14]

Additional considerations which warrant further investigation into the increased risk of stroke in Blacks include the association of European ancestry, lipoprotein little a -Lp(a), and proinflammatory cytokines such as IL-[15,16] Solimon et al documented several issues related to AF detection – modalities and AF subtypes (higher rates of paroxysmal AF in Black patients), access to care and competing mortality from myocardial infarction as rationale for fewer case identifications for AF in Black individuals. Considerations related to atrial size and P-wave indices were also theorized as possible explanations for the “AF paradox”. [17] Kamel et al. suggest that the progressive nature of atrial disease, such that AF is the consequence of atrial cardiomyopathy, and that thromboembolic events may precede the development of established AF. Given that AF is associated with atrial abnormalities including endothelial dysfunction, myocyte dysfunction and fibrosis - these derangements, not the arrhythmia itself, may be responsible for the thromboembolic event. [17] Further analysis by Solimon et. al. examined the relationship between AF and atrial flutter (AFL), noting that AFL is more common in Black individuals than their White counterparts. This suggests that these entities which have been combined in many population studies and might be considered as a continuum of atrial disease which may impact assessment of patients differently based on race. [19]

An important observation on the relationship between P-wave abnormalities and hypertension in a subset of patients aged younger than 60 years or less revealed a higher incidence of stroke in these individuals. The abnormal PTFV1 (P-wave terminal force in lead V₁) indicated a greater than two-fold increase in stroke occurred in those with a normal baseline PTFV1. In adjustment for other risk factors - sex, history of stroke or transient ischemic attack, ischemic heart disease or diabetes, baseline creatinine and in treatment systolic blood pressure, abnormal PTFV1 remained associated with a greater than two-fold increased risk of incident stroke. Okin et al. conclude that abnormal PTFV1, a marker of left atrial abnormality which was strongly associated with incident stroke. In hypertensive patients, PTFV1 as an index of atrial disease, may be an association of left atrial thrombus formation and stroke without clinically determined AF. [20]

Left atrial structure and function play a role in thromboembolism independently of AF. The characteristics of left atrial size, mechanical function, fibrosis, myocyte stress, and structural morphology have been associated with the risk of ischemic stroke in patients with and without AF, underscoring the fact that mechanisms other than the arrhythmia contribute to stroke risk. An analysis of the Greater Cincinnati Northern Kentucky Stroke Study (N=3426) was conducted to assess possible racial variation of these risk considerations in patients with a history of ischemic stroke. It was determined that Black patients had smaller left atrial size on echocardiography but more evidence of left atrial fibrosis and impaired interatrial conduction on ECG, as determined by PTFV₁. Even after adjustment for other demographic characteristics and CV risk factors, the racial variation in stroke risk persisted. In comparison to their White counterparts, Black patients have smaller atrial diameter but have a higher prevalence of left atrial abnormality on EKG. Prior to this analysis, few data exist which considered both of these characteristics together because prior studies have not examined the link between race, atrial substrate, systemic risk factors, and ischemic stroke. This study provided new findings indicating that the same pattern of Black-White differences in atrial substrate seen in the general population are also seen in patients with prior ischemic stroke, with Black patients having more fibrosis and impaired interatrial conduction and less dilation.

These characteristics of atrial dimensions accompanied by EKG changes indicating left atrial abnormality may in part, explain the AF paradox such that Black patients have a greater burden of recognized AF risk factors, these risk factors do not result in the development of AF. [21]

6. Concluding remarks

Despite the decline in stroke mortality overall, racial differences in ischemic stroke rates have not changed substantially since the 1950's. It is well established that AF, a condition which increases the risk and severity of ischemic stroke, is strongly related to poor control and/or an under-recognition of CV risk factors. The diagnosis of hypertension – a condition of high prevalence in black individuals - has the most powerful population-based association for AF, yet a paradox exist between risk of stroke, hypertension, and the clinical diagnosis of AF.

Given the ongoing challenge of appropriately identifying and managing CV risk factors - and changing views on the relationship between atrial disease and progression to atrial fibrillation, the approach to reducing the risk of stroke in Black persons can be complex. As a result, several clinical protocols must be addressed.

- 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 atrioopathy.
- Additional research is needed in determining the impact of social determinants of health as it relates to stroke prevention and overall CV health outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Dr. Mendys is an employee of Pfizer, Inc as a Senior Director, North American Medical Affairs

Dr. Ferdinand serves as a consultant for Amgen, Novartis, Medtronic ,Pfizer

Disclosures

Dr. Ferdinand serves as a consultant for Amgen, Novartis, Medtronic ,Pfizer Dr. Mendys is an employee of Pfizer, Inc as a Senior Director, North American Medical Affairs

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