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Atrial fibrillation, not atrial cardiopathy, is associated with stroke: A single center retrospective study

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ABSTRACT

Background: Atrial fibrillation (AF) increases the risk of thromboembolism. Atrial cardiopathy, defined as structural left atrial enlargement (LAE), has been proposed to be a unifying risk factor for stroke, with or without atrial fibrillation (AF). We sought to understand the relative importance of LAE and AF as risk factors for stroke.
Methods: We performed a retrospective analysis of all patients who underwent echocardiography within the Henry Ford Health System between March and September 2016. Patients were categorized based on the degree of LAE (none, mild, moderate and severe). The diagnosis of prior stroke or AF was ascertained by the presence of these conditions in the electronic medical record (www.EPIC.com).
Results: Total of 8679 cases, 54% were female, 41% were African-American, and mean age was 65 ± 17 years. Fifteen percent had mild, 12% had moderate and 18% had severe LAE; the frequency of AF was 22%; and prior stroke was 18%. In multivariate analysis, the odds of AF increased progressively with severity of LAE (adjusted OR for mild 1.81, moderate 2.13 and severe 4.38, all $P < .001$) and AF was confirmed as a risk factor for prior stroke (aOR 1.34, CI 1.15–1.56, $p < .001$). By contrast, there was no association between LAE and stroke (aOR 0.98 CI 0.86–1.12, $p = .74$), regardless of the severity of LAE, and regardless of whether AF was present or not.
Conclusion: Structural LAE, found in almost half of this population, has a significant association with AF. While AF was confirmed to have a significant association with prior stroke, we found no association between stroke and LAE. AF, not LAE, appears to be the true atrial factor associated with stroke.

1. Introduction

Atrial fibrillation (AF) is a commonly diagnosed cardiac arrhythmia with an estimated prevalence of 49–96 cases per 1000 person-years. [1] AF increases the annual risk of thromboembolism to as high as 6%, which is about 7 times greater than seen with sinus rhythm [2]. AF is further associated with a four-fold increased prevalence of ischemic stroke, prompting an assessment for AF in all patients who present with stroke. [3,4]

Increased size of the left atrium, the prevalence of which is estimated to be about 32%, is associated with new onset AF. [5–7] Left atrial enlargement (LAE) has been reported as a risk factor for incident [8–10] and recurrent stroke [11,12], especially in cases of cryptogenic and cardioembolic stroke with documented AF. [13–15] The Cardiovascular Health Study data has called into question whether LAE is independently associated with stroke. [16] [17].

The significant stroke risk associated with AF is well documented, and while it is known that LAE is a risk factor for developing AF, it remains unclear to what extent structural atrial pathology may contribute to stroke risk in the absence of AF. Atrial cardiopathy, defined as left atrial enlargement (LAE) with associated structural and physiological changes, has been proposed to be the unifying risk factor for AF and cardioembolic stroke. Atrial cardiopathy is defined as LAE on echocardiography, increased p-wave terminal force in lead V1 (PTFV1) on electrocardiography, or increased serum levels of brain natriuretic peptide (NT-proBNP) [18,19].

The extent to which atrial cardiopathy is associated with stroke in the absence of AF has not been fully evaluated. In this study, we sought

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to better understand the relative associations of LAE and AF with stroke.

2. Methods

2.1. Study setting and population

This retrospective study was conducted between March 6th to September 6th, 2016 at Henry Ford Health System (HFHS) in South-East Michigan. The health system is composed of five acute care hospitals, four free-standing emergency departments, and over 38 outpatient facilities. All patients who underwent transthoracic echocardiography (TTE)within this period were included in the analysis, regardless of indication, and regardless of the clinical setting (i.e. inpatient versus outpatient). TTE were performed on patients seen in echocardiography labs within the Henry Ford Health System during the study period. Studies were performed and interpreted by board certified cardiologists and measurements as delineated in the 2015 American Society of Echocardiography recommendations [20]. In particular, left atrial anteroposterior diameter was measured using M-mode echocardiography or 2DE in parasternal long- axis view at the level of the aortic valve according to a leading edge–to–leading edge convention [20,21]. Left atrial size was categorized into four groups according to left atrial diameter and gender: normal left atrial size in mm (Women: ≤ 38, Men: ≤ 40), mild LAE (Women: 39–42, Men: 41–46), moderate LAE (Women: 43–46, Men: 47–51), and severe LAE (Women: ≥ 47, Men: ≥ 52) [22]. Echocardiographic findings, demographics, and active diagnoses listed in the problem list (including stroke and atrial fibrillation or flutter) were obtained from the electronic medical record (www.EPIC.com). $CHADS_2$-VaSC Scores were calculated as well. The study was approved by the HFHS Institutional Review Board.

2.2. Covariates

Based on established literature [3,6–9,16,23], the following factors were considered as potential confounders in assessing the association between LAE, AF and stroke: baseline demographics (age, sex, and race-ethnicity) and comorbid medical risk factors (hypertension (HTN), diabetes mellitus (DM), hyperlipidemia (HLD), smoking, stroke/cerebrovascular accident (CVA), peripheral vascular disease (PVD), congestive heart failure (CHF) and use of antiplatelet and anticoagulation medications.

2.3. Statistical analysis

To assess the association of LAE with AF, stroke and the aforementioned potential confounders, chi-squared tests and analysis of variance (ANOVA) were used to compare the four LAE groups. Multivariate logistic regression analyses were done to assess the association of LAE with AF and stroke after adjusting for the effects of the other potential confounders. Adjusted odds ratios (aOR), and 95% confidence intervals were computed from the logistic regression models. The testing level was set at 0.05 and all analyses were performed using SAS version 9.4.

3. Results

A total of 8679 cases were included in the study. Mean age was 65 ± 17 years with a range from 16 to 103; 54% were female and 41% were African American. Fifty-five percent of patients had normal LA size, 15% had mild, 12% had moderate and 18% had severe LAE. Age, hypertension, diabetes, congestive heart failure, peripheral vascular disease, atrial fibrillation, CHADS2-Vasc scores, lower ejection fraction, and use of antiplatelet and anti-coagulation medications were all significantly associated with increasing severity of LAE (Table 1). Female gender and smoking were significantly associated with decreasing severity of LAE (Table 1). Also, the overall difference in the racial distributions among the LAE groups was significant (Table 1).

The prevalence of AF increased with degree of LAE (11% normal, 23% mild, 30% moderate and 49% severe). This pattern was also seen with the odds of AF increasing with severity of LAE (mild aOR 1.8, CI 1.49–2.16, $P < .001$; moderate aOR 2.13, CI 1.76–2.57, $P < .001$; and severe aOR 4.38, CI 3.71–5.17, $P < .001$) after adjusting for the other potential confounders.

In the multivariate analysis, age (adjusted odds ratio (aOR) 1.34 CI 1.27–1.40 $p < .001$ for increase in 10 years), history of CHF (aOR 2.61 CI 2.26–3.01 $p < .001$), history of HTN (aOR 1.36 CI 1.12–1.65 $p < .001$) and history of stroke (aOR 1.32 CI 1.14–1.54 $p < .001$) were associated with an increased risk of AF. Female gender (aOR 0.59 CI 0.52–0.67 $p < .001$), African American race (aOR 0.52 CI 0.46–0.60 $p < .001$) and smoking (aOR 0.73 CI 0.59–0.91 $p < .003$) were associated with a reduced risk of AF (Fig. 1).

The prevalence of stroke also increased with increasing degree of LAE (16% normal, 19% mild, 20% moderate and 22% severe), however the effect size was not as great as with AF. After adjusting for other potential confounders, the association of LAE with stroke was not found to be significant [normal LA size vs mild (aOR 0.97, CI 0.81–1.16, $P = .724$), moderate (aOR 0.92, CI 0.76–1.12, $P = .42$) and severe LAE (aOR 1.02, CI 0.86–1.22, $P = .791$)] nor for normal LA size vs any LAE (aOR 0.98 CI 0.86–1.12, $p = .74$). This analysis was repeated in both those with and without known AF and the findings were unchanged, with no increase odds of stroke among patients with none versus increasing levels of LAE severity. (Table 2).

In multivariate analysis, the odds of stroke increased with older age (aOR 1.18, CI 1.13–1.24, $P < .001$ per increase of 10 years), African American race (aOR 1.42, CI 1.25–1.62, $P < .001$), hypertension (aOR 1.68, CI 1.38–2.04, $P < .001$), diabetes mellitus (aOR 1.20, CI 1.06–1.36, $P = .005$), smoking (aOR 1.22, CI 1.02–1.45, $P = .03$), peripheral vascular disease (aOR 1.59 CI 1.38–1.82 $p < .001$), AF (aOR 1.31, CI 1.1–1.56, $p = .002$) and use of antiplatelets (aOR 1.59 CI 1.4–1.81, $p < .001$). The odds of stroke were reduced with CHF (aOR 0.70 CI 0.6–0.82 $p < .001$) (Fig. 2).

4. Discussion

In this large retrospective cross-sectional study, we found that the LAE found on routine echocardiography is strongly associated with a previous diagnosis of AF. We also confirmed that AF is associated with a history of stroke. By contrast, structural enlargement of the left atrium, found in almost half of the population, had no association with stroke, regardless of its severity, and regardless of the presence or absence of AF. These findings challenge the concept of atrial cardiopathy as the unifying driving causative force behind cardioembolic strokes.

LAE is believed to be the underlying pathology behind recurrent AF [24] and is independently associated with recurrent cardioembolic and cryptogenic strokes [11]. However, the direct correlation of LAE to stroke risk, independent of AF, has been a debated one. While some prior studies have shown an association between the same [8,10], our results agree with the results of the recent study published by Kamel and colleagues [16] which showed no association of LA size with risk of ischemic stroke, casting doubt on the notion that LAE is responsible for stroke independent of AF.

In addition to providing insight into the relative associations between AF, LAE and stroke, our data provides other interesting insights. There has been significant heterogeneity in the literature on the association of AF with smoking [25,26]. The recently published REGARDS trial showed a higher risk of AF in smokers when compared to non-smokers [27]. However, this association was concluded to be confounded by cardiovascular risk factors [27]. Our study showed that while tobacco use was negatively associated with AF, it was positively associated with stroke, perhaps suggesting the etiology of stroke in this patient population to be non-embolic in nature.

Table 1
Clinical and demographic characteristics in relation to the severity of left atrial enlargement.

	None	Mild	Moderate	Severe	*P* value
	(*N* = 4732)	(*N* = 1264)	(*N* = 1083)	(*N* = 1600)	
Female	2685 (57%)	667 (53%)	548 (51%)	807 (50%)	< 0.001
Age	60 ± 17	68 ± 15	71 ± 14	73 ± 15	< 0.001
Race					
Caucasian	2058 (43%)	624 (49%)	573 (53%)	852 (53%)	< 0.001
African American	2042 (43%)	487 (39%)	383 (35%)	609 (38%)	
Other/unknown race	150 (13%)	153 (12%)	115 (11%)	125 (8%)	
Smoking	758 (16%)	167 (13%)	127 (12%)	156 (10%)	< 0.001
Hypertension	3202 (68%)	1034 (82%)	932 (86%)	1404 (88%)	< 0.001
Diabetes mellitus	1418 (30%)	456 (36%)	408 (38%)	556 (35%)	< 0.001
Congestive heart failure	842 (18%)	436 (34%)	435 (40%)	955 (60%)	< 0.001
Prior ischemic stroke	773 (16%)	243 (19%)	215 (20%)	356 (22%)	< 0.001
Peripheral vascular disease	913 (19%)	373 (30%)	373 (34%)	550 (34%)	< 0.001
Prior afib/aflutter	511 (11%)	296 (23%)	324 (30%)	789 (49%)	< 0.001
$CHADS_2$-VaSC score	2.9 ± 1.9	3.7 ± 1.9	4.0 ± 1.8	4.4 ± 1.9	< 0.001
LV ejection fraction	62 ± 9	58 ± 12	56 ± 14	52 ± 16	< 0.001
Antiplatelet use	1791 (38%)	619 (49%)	559 (52%)	863 (54%)	< 0.001
Anti-coagulation use	508 (11%)	224 (18%)	234 (22%)	566 (35%)	< 0.001

Data are N (%) or mean ± SD.

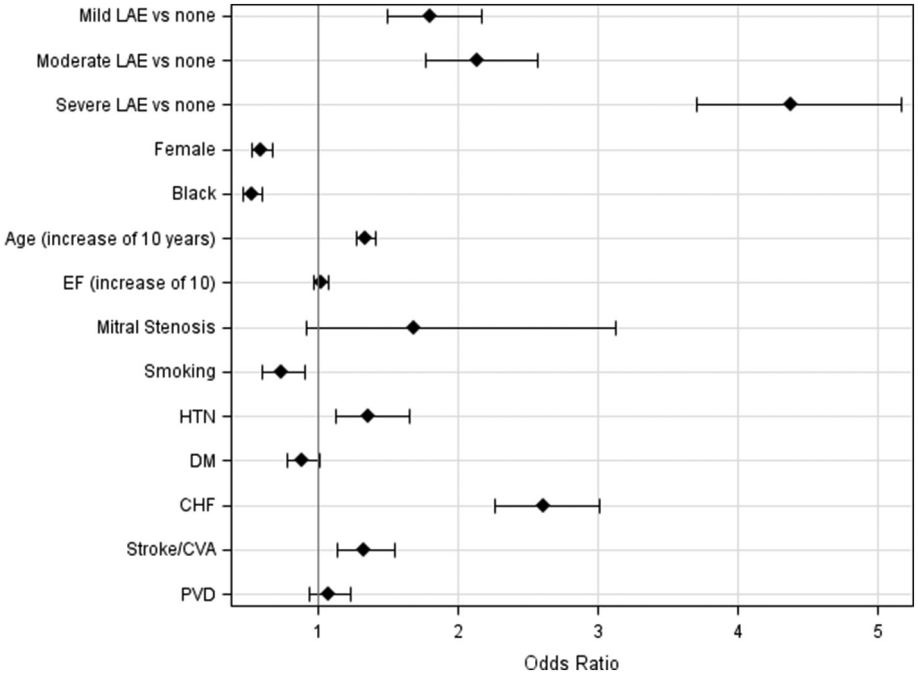

Fig. 1. Forest plot from multivariate logistic regression model for atrial fibrillation (Odds ratios with 95% confidence intervals).

Table 2
Odds of ischemic stroke according to severity of LAE in patients with and without atrial fibrillation.

LAE group	Patients with atrial fibrillation*		Patients without atrial fibrillation†	
	aOR (95% CI)	*P*-value	aOR (95% CI)	P-value
Mild	1.04 (0.74, 1.47)	0.813	1.00 (0.81, 1.22)	0.961
Moderate	1.21 (0.87, 1.67)	0.258	0.88 (0.70, 1.10)	0.269
Severe	1.19 (0.92, 1.56)	0.189	1.00 (0.80, 1.26)	0.996

Odds are calculated against the no LAE as the reference group.

* Prevalence of stroke: 22% Normal, 23% Mild, 25% Moderate and 25% Severe.

† Prevalence of stroke: 16% Normal, 18% Mild, 18% Moderate and 19% Severe.

Our analysis delved into the phenomenon previously described as the "AF racial paradox" [28], in which African Americans are described to have a reduced risk of AF [29] but an increased risk of stroke, despite a higher burden of associated risk factor [30] Our study showed the same discordance as mentioned in the literature previously. We hypothesize the presence of one or a combination of the following as possible explanations for this phenomenon: an inheritable susceptibility to developing dysrhythmias, socio-economic factors leading to less intensive screening for AF among African American, biological factors such as larger LA size in Caucasians compared to African Americans or shorter life expectancy and therefore, higher opportunities for AF to manifest in Caucasians with age. [31]. Our study showed that females were less likely to have AF which is consistent with other studies [1,32,33] although they are at higher risk of stroke and mortality from AF [32].Given our results, African Americans with LAE along with selected risk factors (including greater age, history of stroke, HTN or

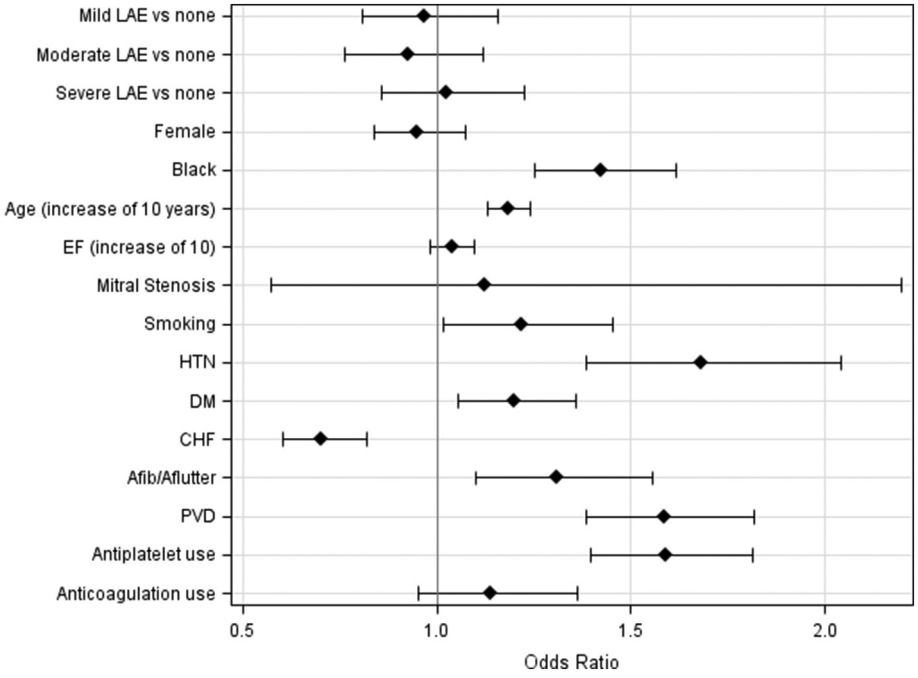

Fig. 2. Forest plot from multivariate logistic regression model for Stroke/CVA (Odds ratios with 95% confidence intervals).

CHF) would likely benefit from careful stroke risk screening.

A strength of our study is the availability of data on a wide range of potential confounding risk factors for the association between LAE, AF and stroke. Prolonged cardiac monitoring significantly increases the detection of AF in cryptogenic strokes [34,35], which account for approximately one-third of all ischemic strokes, and results in increased rates of anticoagulation. These results do not suggest substitution of occult AF for identification of left atrial cardiopathy, rather it highlights the importance of identifying AF in high risk patients like those with LAE. As these patients appear to be commonly identified on echocardiography done for various reasons, it would be reasonable to consider cardiac monitoring on patients identified with LAE.

Cryptogenic stroke comprises approximately one-third of all strokes and up to one-third of those patients are identified as having occult AF [36]. Treatment trials for cryptogenic stroke, such as RESPECT-ESUS and NAVIGATE-ESUS [37,38] have relied on the favorable risk profiles of the direct oral anti-coagulants (DOACs) and the presumed treatment of occult AF or other embolic sources to reduce recurrent stroke rates yet failed to show stroke risk reduction. The ongoing ARCADIA trial refines the enrollment criteria by adding LAE as a means to target a higher risk patient population for occult AF and cardio embolism. [39] Our findings may predict a fate similar to the other ESUS trials if the occult AF rate is lower than expected in this study.

Our study has several limitations. It is a retrospective single center study based on electronic medical record (EMR) data that may suffer from potential bias caused by the availability of accurately recorded information. While our study includes a large sample size, the incomplete information on stroke etiology limits our ability to further analyze relationships between associated risk factors and stroke subtypes. Echocardiography is operator and imaging protocol dependent. The patients included in this study had to have a reason for needing an echocardiogram which perhaps suggests a selection bias. Finally, the retrospective nature of our study limits our ability to comment on causal relationships.

5. Conclusion

Presence of LAE found on routine echocardiography is strongly associated with prevalent AF. Structural LAE, found in almost half of the population, represents a significant increasing association with occult AF, however, AF, not LAE, appears to be the true atrial factor associated with stroke.

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References

[1] R.B. Schnabel, X. Yin, P. Gona, M.G. Larson, A.S. Beiser, D.D. McManus, et al., 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study, Lancet 386 (9989) (2015) 154–162.
[2] P. Petersen, Thromboembolic complications in atrial fibrillation, Stroke 21 (1) (1990) 4–13.
[3] W.B. Kannel, E.J. Benjamin, Status of the epidemiology of atrial fibrillation, Med. Clin. North Am. 92 (1) (2008) 17–40 (ix).
[4] W.N. Kernan, B. Ovbiagele, H.R. Black, D.M. Bravata, M.I. Chimowitz, M.D. Ezekowitz, et al., Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 45 (7) (2014) 2160–2236.
[5] C. Cuspidi, M. Rescaldani, C. Sala, Prevalence of echocardiographic left-atrial enlargement in hypertension: a systematic review of recent clinical studies, Am. J. Hypertens. 26 (4) (2013) 456–464.
[6] S.M. Vaziri, M.G. Larson, E.J. Benjamin, D. Levy, Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study, Circulation 89 (2) (1994) 724–730.
[7] B.M. Psaty, T.A. Manolio, L.H. Kuller, R.A. Kronmal, M. Cushman, L.P. Fried, et al., Incidence of and risk factors for atrial fibrillation in older adults, Circulation 96 (7) (1997) 2455–2461.
[8] E.J. Benjamin, R.B. D'Agostino, A.J. Belanger, P.A. Wolf, D. Levy, Left atrial size and the risk of stroke and death. The Framingham Heart Study, Circulation 92 (4) (1995) 835–841.
[9] M.R. Di Tullio, R.L. Sacco, R.R. Sciacca, S. Homma, Left atrial size and the risk of ischemic stroke in an ethnically mixed population, Stroke 30 (10) (1999) 2019–2024.

[10] M.E. Barnes, Y. Miyasaka, J.B. Seward, B.J. Gersh, A.G. Rosales, K.R. Bailey, et al., Left atrial volume in the prediction of first ischemic stroke in an elderly cohort without atrial fibrillation, Mayo Clin. Proc. 79 (8) (2004) 1008–1014.
[11] S. Yaghi, Y.P. Moon, C. Mora-McLaughlin, J.Z. Willey, K. Cheung, M.R. Di Tullio, et al., Left atrial enlargement and stroke recurrence: the Northern Manhattan Stroke Study, Stroke 46 (6) (2015) 1488–1493.
[12] J. Xue, Y. Lin, W. Huang, X. Chen, Q. Li, Z. Cai, et al., Left atrial size and risk of recurrent ischemic stroke in a Chinese population, Brain Behav. 7 (5) (2017) e00702.
[13] H.Y. Shin, I.H. Jeong, C.K. Kang, D.J. Shin, H.M. Park, K.H. Park, et al., Relation between left atrial enlargement and stroke subtypes in acute ischemic stroke patients, J. Cerebrovasc. Endovasc. Neurosurg. 15 (3) (2013) 131–136.
[14] S. Fujii, K. Shibazaki, K. Kimura, K. Sakai, J. Aoki, A simple score for predicting paroxysmal atrial fibrillation in acute ischemic stroke, J. Neurol. Sci. 328 (1–2) (2013) 83–86.
[15] R. Stahrenberg, F. Edelmann, B. Haase, R. Lahno, J. Seegers, M. Weber-Kruger, et al., Transthoracic echocardiography to rule out paroxysmal atrial fibrillation as a cause of stroke or transient ischemic attack, Stroke 42 (12) (2011) 3643–3645.
[16] H. Kamel, T.M. Bartz, M.S.V. Elkind, P.M. Okin, E.L. Thacker, K.K. Patton, et al., Atrial cardiopathy and the risk of ischemic stroke in the CHS (Cardiovascular Health Study), Stroke 49 (4) (2018) 980–986.
[17] S.T. Broughton, W.T. O'Neal, T. Salahuddin, E.Z. Soliman, The influence of left atrial enlargement on the relationship between atrial fibrillation and stroke, J. Stroke Cerebrovasc. Dis. 25 (6) (2016) 1396–1402.
[18] H. Kamel, P.M. Okin, W.T. Longstreth Jr., M.S. Elkind, E.Z. Soliman, Atrial cardiopathy: a broadened concept of left atrial thromboembolism beyond atrial fibrillation, Futur. Cardiol. 11 (3) (2015) 323–331.
[19] H. Kamel, J.S. Healey, Cardioembolic stroke, Circ. Res. 120 (3) (2017) 514–526.
[20] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J. Am. Soc. Echocardiogr. 28 (1) (2015) 1–39 (e14).
[21] M.H. Picard, D. Adams, S.M. Bierig, J.M. Dent, P.S. Douglas, L.D. Gillam, et al., American Society of Echocardiography recommendations for quality echocardiography laboratory operations, J. Am. Soc. Echocardiogr. 24 (1) (2011) 1–10.
[22] R.M. Lang, M. Bierig, R.B. Devereux, F.A. Flachskampf, E. Foster, P.A. Pellikka, et al., Recommendations for chamber quantification, Eur. J. Echocardiogr. 7 (2) (2006) 79–108.
[23] E.J. Benjamin, D. Levy, S.M. Vaziri, R.B. D'Agostino, A.J. Belanger, P.A. Wolf, Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study, JAMA 271 (11) (1994) 840–844.
[24] T. Ogata, R. Matsuo, F. Kiyuna, J. Hata, T. Ago, Y. Tsuboi, et al., Left atrial size and long-term risk of recurrent stroke after acute ischemic stroke in patients with nonvalvular atrial fibrillation, J. Am. Heart Assoc. 6 (8) (2017).
[25] I. Watanabe, Smoking and risk of atrial fibrillation, J. Cardiol. 71 (2) (2018) 111–112.
[26] A.D. Krahn, J. Manfreda, R.B. Tate, F.A. Mathewson, T.E. Cuddy, The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study, Am. J. Med. 98 (5) (1995) 476–484.
[27] M. Imtiaz Ahmad, C.D. Mosley, W.T. O'Neal, S.E. Judd, L.A. McClure, V.J. Howard, et al., Smoking and risk of atrial fibrillation in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, J. Cardiol. 71 (2) (2018) 113–117.
[28] M.K. Amponsah, E.J. Benjamin, J.W. Magnani, Atrial fibrillation and race - a contemporary review, Curr. Cardiovasc. Risk Rep. 7 (5) (2013).
[29] H. Kamel, D.O. Kleindorfer, P.D. Bhave, M. Cushman, E.B. Levitan, G. Howard, et al., Rates of atrial fibrillation in black versus white patients with pacemakers, J. Am. Heart Assoc. 5 (2) (2016).
[30] G. Howard, F. Peace, V.J. Howard, The contributions of selected diseases to disparities in death rates and years of life lost for racial/ethnic minorities in the United States, 1999–2010, Prev. Chronic Dis. 11 (2014) E129.
[31] T.A. Manolio, J.S. Gottdiener, T.S. Tsang, J.M. GardinCardiovascular Health Study Collaborative Research G, Left atrial dimensions determined by M-mode echocardiography in black and white older (> or =65 years) adults (The Cardiovascular Health Study), Am. J. Cardiol. 90 (9) (2002) 983–987.
[32] D. Ko, F. Rahman, R.B. Schnabel, X. Yin, E.J. Benjamin, I.E. Christophersen, Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis, Nat. Rev. Cardiol. 13 (6) (2016) 321–332.
[33] Y. Miyasaka, M.E. Barnes, B.J. Gersh, S.S. Cha, K.R. Bailey, W.P. Abhayaratna, et al., Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence, Circulation 114 (2) (2006) 119–125.
[34] V.N. Thijs, J. Brachmann, C.A. Morillo, R.S. Passman, T. Sanna, R.A. Bernstein, et al., Predictors for atrial fibrillation detection after cryptogenic stroke: results from CRYSTAL AF, Neurology 86 (3) (2016) 261–269.
[35] D.J. Gladstone, M. Spring, P. Dorian, V. Panzov, K.E. Thorpe, J. Hall, et al., Atrial fibrillation in patients with cryptogenic stroke, N. Engl. J. Med. 370 (26) (2014) 2467–2477.
[36] M. Marnane, C.A. Duggan, O.C. Sheehan, A. Merwick, N. Hannon, D. Curtin, et al., Stroke subtype classification to mechanism-specific and undetermined categories by TOAST, A-S-C-O, and causative classification system: direct comparison in the North Dublin population stroke study, Stroke 41 (8) (2010) 1579–1586.
[37] H.C. Diener, J.D. Easton, C.B. Granger, L. Cronin, C. Duffy, D. Cotton, et al., Design of Randomized, double-blind, evaluation in secondary Stroke Prevention comparing the EfficaCy and safety of the oral Thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS), Int. J. Stroke 10 (8) (2015) 1309–1312.
[38] R.G. Hart, M. Sharma, H. Mundl, S.E. Kasner, S.I. Bangdiwala, S.D. Berkowitz, et al., Rivaroxaban for stroke prevention after embolic stroke of undetermined source, N. Engl. J. Med. 378 (23) (2018) 2191–2201.
[39] S.V. Mitchell, M. Elkind, AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke (ARCADIA), [updated February 20, 20184/19/2018]. Available from, June 20, 2017. https://clinicaltrials.gov/ct2/show/NCT03192215.