ARIC Manuscript Proposal #2831

PC Reviewed: 09/13/16   **Status: _____**   **Priority: 2**
SC Reviewed: ___/___/___   **Status: _____**   **Priority: ____**

1.a. Full Title:

Associations of Lipoprotein(a) Levels with Incident Atrial Fibrillation and Stroke in Patients with Atrial Fibrillation Among Whites and Blacks: the ARIC Study.

b. Abbreviated Title (Length 26 characters):

Lipoprotein(a) and atrial fibrillation.

2. Writing Group:
    Writing group members:

Konstantinos N. Aronis	Johns Hopkins	First Author
Di Zhao	Johns Hopkins	Second author, analyst
Erin D. Michos	Johns Hopkins	Senior author
Seth S. Martin	Johns Hopkins	Co-author
Steven R. Jones	Johns Hopkins	Co-author
Eliseo Guallar	Johns Hopkins	Co-author
Saman Nazarian	University of Penn	Co-author
Salim S. Virani	Baylor College of Medicine	Co-author
Christie Ballantyne	Baylor College of Medicine	Co-author
Ron Cornelis Hoogeveen	Baylor College of Medicine	Co-author
Alvaro Alonso	Emory University	Co-author

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. *KNA* **[please confirm with your initials electronically or in writing]**

First author: **Konstantinos N. Aronis, MD**
Address: Zayed 7125, Division of Cardiology, Johns Hopkins Hospital, 1800 Orleans Street, Baltimore, MD 21287
         Phone: (cell) 201-716-9226   Fax: 410-502-0231
         E-mail: karonis1@jhmi.edu

Senior author: Erin D. Michos, MD, MHS, FACC
Address: Blalock 524-B, Division of Cardiology, Johns Hopkins Hospital, 600 N.
             Wolfe Street, Baltimore, MD 21287
             Phone: 410-502-6813 Fax: 410-502-0231
             E-mail: edonnell@jhmi.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

3.   Timeline:

Analyses for this proposal will take place in early fall of 2016 immediately following approval of this proposal, with goal to submit an abstract to the American College of Cardiology (ACC) on October 18th and to submit for journal publication by early 2017.

4.   Rationale:

Atrial fibrillation (AF) is a disease with increasing incidence and prevalence in the United States and Europe.[1] With improved survival and the overall aging of the population, it is estimated that the incidence of AF will increase from 1.2 million cases in 2010 to 2.6 million cases in 2030, with a corresponding rise in AF prevalence from 5.2 million in 2010 to 12.1 million in 2030.[2] AF is associated with increased morbidity, mortality, and healthcare-associated expenses.[3-5] AF increases the risk of stroke by 5-fold and strokes associated with AF have up to two times higher mortality, higher recurrence rate, and are associated with worse neurological and functional outcomes compared to non-AF strokes.[6, 7] Identifying and studying modifiable risk factors is a critical step for primary and secondary prevention of AF.[8]

Lp(a) is a lipoprotein moiety that has similar lipid composition to LDL and contains the distinguishing apolipoprotein(a) [apo(a)] covalently bound to apoB-100.[9] Apo(a) is structural homologous to plasminogen[10] and inhibits the tissue factor pathway inhibitor.[11] In several cohorts and meta-analyses, Lp(a) has been associated with an increased incidence of coronary artery disease and stroke.[12-15] Over the last two decades, Lp(a) has been considered an emerging cardiovascular risk factor,[16] now known to be causal of CHD by Medelian randomization.[17] It has a dual role in promoting cardiovascular disease: a pro-atherosclerotic and a pro-thrombotic.

Lp(a) has adverse effects on the cardiovascular system outside its role in atherosclerosis and atherothrombosis. Lp(a) has been causally related to calcific aortic sclerosis via Mendelian randomization.[18] There are no conclusive data on the association of Lp(a) and AF. In a case-control study from Spain, Lp(a) levels were not associated with AF (n=202).[19] Lp(a) levels were not associated with AF recurrence after electrical cardioversion in a cohort of 79 patients and 2 years of follow-up.[20] Prospective associations of Lp(a) levels with incident AF have not been studied to date. Lp(a) levels are associated with atherosclerotic cardiovascular disease, which in turn is associated

with incident AF.[21, 22] The role of Lp(a) as an independent risk factor for AF remains to be elucidated.

There are limited data on the associations of Lp(a) and the risk of AF-related stroke. In a case-control study, patients with AF and cardioembolic stroke had 2-fold higher Lp(a) levels compared to those with AF and non-cardioembolic stroke (n=40).[23] In patients with AF, Lp(a) levels were independently associated with the presence of left atrial thrombus[24] or a recent thromboembolic event[25] (n=150 and 172). Prospective associations of Lp(a) levels with incidence of AF-related stroke have not been studied to date. Whether potential associations of Lp(a) with stroke in patients with AF is related to adverse effects of Lp(a) on left atrial function, atrial endothelial dysfunction or solely to the pro-thrombotic action of Lp(a) remains unknown.

Last, it remains unknown whether the potential association between Lp(a) levels and AF risk varies by race or sex. Blacks have approximately 3-fold higher Lp(a) levels compared to whites and women have higher Lp(a) levels by 15-20% compared to men.[26] Blacks[27, 28] and women[29] have lower incidence of AF, and little is known on whether race or sex could exhibit effect modification on AF risk factors. Among patients with AF, the risk of stroke is higher in women compared to men[30, 31] and in blacks compared to whites.[31-33] In a recent analysis of ARIC, there was no effect modification by race or sex in the risk for coronary heart disease or stroke conveyed by Lp(a).[26]

Proposal Significance Summary:
The primary purpose of our study is to evaluate for independent associations between Lp(a) levels and incident AF and focus on potential interactions by race and sex. Our secondary aim is to assess for independent associations of Lp(a) levels and stroke in ARIC participants with AF and examine for potential interactions with race and sex.

5.   Main Hypothesis/Study Questions:

Hypotheses:
1. We hypothesize that elevated Lp(a) levels will be associated with a higher incidence of AF. The relationship will remain significant even after adjustment for traditional AF risk factors.
2. We hypothesize that being a black or woman will attenuate the AF risk conveyed by Lp(a).
3. We hypothesize that elevated Lp(a) levels will be associated with higher rates of incident ischemic stroke in participants with a history of prevalent or incident AF compared to those without an AF history. This association will remain significant even after adjusting for CHADS$_2$-VASc score.
4. We will examine for whether the associations of Lp(a) with stroke risk differ by sex and race among participants with a history of prevalent or incident AF. Given the paucity of data, we cannot hypothesize the direction (if any) of such an effect modification. From prior analysis in ARIC, it is possible that there is no effect

modification of Lp(a)-related stroke risk by race or sex. However, this has not been examined specifically in participants with AF.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design: Prospective cohort study. Baseline: ARIC visit 4, 1996-1998. Follow-up using most recent follow-up data files available (currently through 2013).

Inclusion/Exclusion

Inclusion: For the primary analysis of incident AF, we will include all ARIC participants who are free of prevalent AF at visit 4 and have Lp(a) levels at visit 4.

Inclusion: For the secondary analysis of incident ischemic stroke which is to be stratified by AF status (i.e. those with a history of prevalent or incident AF vs. those without an AF history), we will include all ARIC participants who are free of prevalent stroke at visit 4 and have Lp(a) levels at visit 4.

Exclusion: Those whose Lp(a) levels are not available. For primary analysis, we will exclude participants with prevalent AF history at visit 4 and for secondary analysis we will exclude participants with prevalent stroke history at visit 4. Participants of racial/ethnic group other than white or black, blacks from the MN and MD field centers and those with no information on their race. Participants with a low-quality or missing ECG and those with missing covariates.

Variables
 Exposure:
    Lp(a) levels (measured in visit 4 serum).

Lp(a) in visit 4 was measured using the Denka Seiken molar assay, apo (a) isoform independent.[34]

As per prior ARIC analyses,[26] Lp(a) levels will be examined in several ways as follows: (a) as a continuous variable and appropriate transformations will be applied to adjust for potential deviation from normality; (b) as Lp(a) quintiles and (c) as 5 pre-specified Lp(a) categories defined by the arbitrary thresholds of ≤ 10 mg/dL, > 10 to ≤ 20 mg/dL, >20 to ≤ 30 mg/dL, > 30 mg/dL to ≤ 50 and >50 mg/dL.

Outcome:
    Primary outcome: Incident AF through December 31, 2013. In ARIC AF is
    ascertained by 3 different sources: ECGs performed at study visits, hospital
    discharge ICD codes and death certificates.[28] The incidence date of AF will be

defined as the date for the first ECG showing AF, the first hospital discharge coded as AF or when AF was listed as a cause of death, whichever occurred earlier.

Secondary outcome: Incident ischemic stroke or systemic embolism.
All stroke-related hospitalizations and deaths occurring through December 31, 2013 in ARIC participants were identified by annual telephone follow-up call and community surveillance of all ARIC hospitalizations. Hospital records for all possible stroke-related hospitalizations were obtained (ICD-9 codes 430-438 until 1997 and ICD-9 codes 430-436 afterwards). Definite/probable hospitalized strokes were classified by a combination of computer algorithm and physician review, using standardized criteria. Strokes were sub-classified as ischemic versus hemorrhagic.

Main covariates (measured at visit 4):
Age, sex, race, study site, systolic blood pressure, diastolic blood pressure, hypertension treatment, heart rate, height, body mass index (BMI), electrocardiographic left ventricular hypertrophy, PR interval, LDL-C cholesterol, HDL-C cholesterol, triglycerides, NT-pro-BNP, diabetes, smoking, personal history of coronary heart disease, personal history of stroke, personal history of systemic embolism, personal history of heart failure, personal history of vascular disease. The CHADS2-VASc score will be calculated from the aforementioned covariates.

For secondary analysis (for outcome of incident stroke), we will create two groups: (1) those with a history of prevalent AF at visit 4 or who developed incident stroke during ARIC follow-up and (2) those with no history of AF documented at any time during ARIC follow-up.

Potential effect modifiers: Race, sex (for primary analysis) and AF status (for secondary analysis).

Data analysis
Visit 4 will serve as baseline for the current analysis. Baseline characteristics (1996-1998) of the study population will be described using means ± SD, medians [interquartile range], and proportions across quintiles of Lp(a) and by race.

Multivariable-adjusted Cox proportional hazards models will be used to estimate the hazard ratios (95% confidence intervals) for the association of Lp(a) levels with incident AF (primary outcome) and for ischemic stroke (secondary outcome). The proportional-hazards assumption will be checked using Schoenfeld residuals and graphic methods (ln[-ln] survival plots).

For the primary outcome: Multivariable analysis will be performed in three pre-specified Cox models. Model 1: Lp(a), age, sex, race, and site. Model 2: Model 1 + smoking, systolic and diastolic blood pressure, treatment for hypertension, heart rate, height, BMI, electrocardiographic left ventricular hypertrophy, PR interval, prevalent heart failure, coronary artery disease, and diabetes. Model 3: Model 2 + LDL-C, HDL-C, triglycerides and NT-pro-BNP. Model 4: Model 1 + CHADS2-VASc score. Model 5: Model 4 +

smoking, heart rate, height, BMI, electrocardiographic left ventricular hypertrophy, PR interval. Model 6: Model 5 + LDL-C, HDL-C, triglycerides and NT-pro-BNP. The purpose for Models 4-6 is the fact that CHADS2-VASc score is associated with incident AF.[35, 36]

We will formally test for two-way multiplicative interactions of Lp(a) levels by race and sex as well as for three-way interactions of Lp(a) levels by race*sex using Wald tests and stratified analyses if there is any evidence for interaction. However, *a priori* we plan to present results overall and stratified by race and sex based on prior studies and inherent interest, regardless if a significant race or sex interaction is present.

For the secondary outcome: Multivariable analysis will be performed in three pre-specified Cox models. Model 1: Lp(a), age, sex, race, and site. Model 2: Model 1 + CHADS$_2$-VASc score. Model 3: Model 2 + LDL-C, HDL-C and triglycerides.

For the secondary outcome, AF will be included in the analysis as a time-dependent covariate. We will formally check for interaction by history of AF status. However *a priori,* we plan to stratify results among those with a history of AF (prevalent or incident during ARIC) vs those with no AF history, to see if the association of Lp(a) with incident ischemic stroke is stronger among those with an AF history.

We will use Kaplan-Meyer curves and restricted cubic splines to visually depict the associations between Lp(a) levels and risk for AF and stroke. Analysis will be performed in the whole sample as well as race and sex stratified.

7.a. Will the data be used for non-CVD analysis in this manuscript?
___ Yes   _X_ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?
(N/A)
____ Yes   ____ No
(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?
____ Yes   _X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
(N/A)
____ Yes   ____ No

9. **The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.** ARIC Investigators have access to the publications lists under the Study Members Area of the web site at:
http://www.cscc.unc.edu/ARIC/search.php

__X____ Yes _____ No

10. **What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?**

#1610 (Virani): Associations between lipoprotein(a) levels and cardiovascular outcomes in African Americans: The Atherosclerosis Risk In Communities (ARIC) Study. ***This proposal evaluated LP(a) with CHD and stroke. Manuscript was published in Circulation 2012. Did not include AF outcomes, so no overlap with our primary analysis. For our secondary analysis of ischemic stroke, there is some overlap. The difference is that we are going to stratify by those with a history of AF vs those without such a history when examining the association of Lp(a) with incident ischemic stroke. Furthermore, we have invited Dr. Virani to be a co-author to avoid overlap.*

#2566 (Garg) Lipoprotein-associated Phospholipase A2 and risk of incident atrial fibrillation: Findings from The Atherosclerosis Risk in Communities Study (ARIC), The CardiovascularHealth Study (CHS), and The Multi-Ethnic Study of Atherosclerosis (MESA).
**This proposal is evaluation Lp-PLA2 not Lp(a)

We have also included as a coauthor Dr. Hoogeveen, who is the PI of the visit 4 Lp(a) ancillary, to ensure no overlap with other planned proposals using visit 4 Lp(a) data.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____X Yes ____ No

11.b. If yes, is the proposal
__X_ **A. primarily the result of an ancillary study (list number* __see above_____**

AS#2010.12
Ancillary PI: Dr. Hoogeveen who is included as a co-author on this proposal

___ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____)**

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If amanuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central**whenever the journal does not and be in compliance with this policy. Four files about the public access policy fromhttp://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms.http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

Reference List

1.   Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB, American Heart Association Statistics C and Stroke Statistics S. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation*. 2016;133:e38-e360.
2.   Colilla S, Crow A, Petkun W, Singer DE, Simon T and Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *The American journal of cardiology*. 2013;112:1142-7.
3.   Magnani JW, Rienstra M, Lin H, Sinner MF, Lubitz SA, McManus DD, Dupuis J, Ellinor PT and Benjamin EJ. Atrial fibrillation: current knowledge and future directions in epidemiology and genomics. *Circulation*. 2011;124:1982-93.
4.   Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB and Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946-52.
5.   Kim MH, Johnston SS, Chu BC, Dalal MR and Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circulation Cardiovascular quality and outcomes*. 2011;4:313-20.
6.   Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ and D'Agostino RB. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke*. 1996;27:1760-4.
7.   Steger C, Pratter A, Martinek-Bregel M, Avanzini M, Valentin A, Slany J and Stollberger C. Stroke patients with atrial fibrillation have a worse prognosis than patients without: data from the Austrian Stroke registry. *Eur Heart J*. 2004;25:1734-40.

8.   Van Wagoner DR, Piccini JP, Albert CM, Anderson ME, Benjamin EJ, Brundel B, Califf RM, Calkins H, Chen PS, Chiamvimonvat N, Darbar D, Eckhardt LL, Ellinor PT, Exner DV, Fogel RI, Gillis AM, Healey J, Hohnloser SH, Kamel H, Lathrop DA, Lip GY, Mehra R, Narayan SM, Olgin J, Packer D, Peters NS, Roden DM, Ross HM, Sheldon R and Wehrens XH. Progress toward the prevention and treatment of atrial fibrillation: A summary of the Heart Rhythm Society Research Forum on the Treatment and Prevention of Atrial Fibrillation, Washington, DC, December 9-10, 2013. *Heart rhythm : the official journal of the Heart Rhythm Society*. 2015;12:e5-e29.

9.   Fless GM, Rolih CA and Scanu AM. Heterogeneity of human plasma lipoprotein (a). Isolation and characterization of the lipoprotein subspecies and their apoproteins. *J Biol Chem*. 1984;259:11470-8.

10.   McLean JW, Tomlinson JE, Kuang WJ, Eaton DL, Chen EY, Fless GM, Scanu AM and Lawn RM. cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. *Nature*. 1987;330:132-7.

11.   Caplice NM, Panetta C, Peterson TE, Kleppe LS, Mueske CS, Kostner GM, Broze GJ, Jr. and Simari RD. Lipoprotein (a) binds and inactivates tissue factor pathway inhibitor: a novel link between lipoproteins and thrombosis. *Blood*. 2001;98:2980-7.

12.   Danesh J, Collins R and Peto R. Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective studies. *Circulation*. 2000;102:1082-5.

13.   Emerging Risk Factors C, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG and Danesh J. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA*. 2009;302:412-23.

14.   Smolders B, Lemmens R and Thijs V. Lipoprotein (a) and stroke: a meta-analysis of observational studies. *Stroke*. 2007;38:1959-66.

15.   Nave AH, Lange KS, Leonards CO, Siegerink B, Doehner W, Landmesser U, Steinhagen-Thiessen E, Endres M and Ebinger M. Lipoprotein (a) as a risk factor for ischemic stroke: a meta-analysis. *Atherosclerosis*. 2015;242:496-503.

16.   Expert Panel on Detection E and Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-97.

17.   Kamstrup PR, Tybjaerg-Hansen A, Steffensen R and Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA*. 2009;301:2331-9.

18.   Kamstrup PR, Tybjaerg-Hansen A and Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. *J Am Coll Cardiol*. 2014;63:470-7.

19.   Diaz-Peromingo JA, Alban-Salgado A, Garcia-Suarez F, Sanchez-Leira J, Saborido-Frojan J and Iglesias-Gallego M. Lipoprotein(a) and lipid profile in patients with atrial fibrillation. *Med Sci Monit*. 2006;12:CR122-5.

20.   Naji F and Sabovic M. Lipoprotein(a) and inflammation in patients with atrial fibrillation after electrical cardioversion. *J Negat Results Biomed*. 2011;10:15.

21.   Chamberlain AM, Agarwal SK, Folsom AR, Soliman EZ, Chambless LE, Crow R, Ambrose M and Alonso A. A clinical risk score for atrial fibrillation in a biracial

prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). *The American journal of cardiology*. 2011;107:85-91.

22.　　Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, Sr., Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM, Kannel WB, Wang TJ, Ellinor PT, Wolf PA, Vasan RS and Benjamin EJ. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet*. 2009;373:739-45.

23.　　Okura H, Inoue H, Tomon M, Nishiyama S and Yoshikawa T. Increased plasma lipoprotein(a) level in cardioembolic stroke with non-valvular atrial fibrillation. *Intern Med*. 1998;37:995.

24.　　Igarashi Y, Yamaura M, Ito M, Inuzuka H, Ojima K and Aizawa Y. Elevated serum lipoprotein(a) is a risk factor for left atrial thrombus in patients with chronic atrial fibrillation: a transesophageal echocardiographic study. *American heart journal*. 1998;136:965-71.

25.　　Igarashi Y, Kasai H, Yamashita F, Sato T, Inuzuka H, Ojima K and Aizawa Y. Lipoprotein(a), left atrial appendage function and thromboembolic risk in patients with chronic nonvalvular atrial fibrillation. *Jpn Circ J*. 2000;64:93-8.

26.　　Virani SS, Brautbar A, Davis BC, Nambi V, Hoogeveen RC, Sharrett AR, Coresh J, Mosley TH, Morrisett JD, Catellier DJ, Folsom AR, Boerwinkle E and Ballantyne CM. Associations between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2012;125:241-9.

27.　　Perez MV, Wang PJ, Larson JC, Soliman EZ, Limacher M, Rodriguez B, Klein L, Manson JE, Martin LW, Prineas R, Connelly S, Hlatky M, Wassertheil-Smoller S and Stefanick ML. Risk factors for atrial fibrillation and their population burden in postmenopausal women: the Women's Health Initiative Observational Study. *Heart*. 2013;99:1173-8.

28.　　Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ and Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *American heart journal*. 2009;158:111-7.

29.　　Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB and Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119-25.

30.　　Friberg J, Scharling H, Gadsboll N, Truelsen T, Jensen GB and Copenhagen City Heart S. Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (The Copenhagen City Heart Study). *The American journal of cardiology*. 2004;94:889-94.

31.　　Shroff GR, Solid CA and Herzog CA. Atrial fibrillation, stroke, and anticoagulation in Medicare beneficiaries: trends by age, sex, and race, 1992-2010. *J Am Heart Assoc*. 2014;3:e000756.

32.　　Kabra R, Cram P, Girotra S and Vaughan Sarrazin M. Effect of race on outcomes (stroke and death) in patients >65 years with atrial fibrillation. *The American journal of cardiology*. 2015;116:230-5.

33.   Magnani JW, Norby FL, Agarwal SK, Soliman EZ, Chen LY, Loehr LR and Alonso A. Racial Differences in Atrial Fibrillation-Related Cardiovascular Disease and Mortality: The Atherosclerosis Risk in Communities (ARIC) Study. *JAMA Cardiol*. 2016;1:433-41.
34.   Dati F, Tate JR, Marcovina SM, Steinmetz A, International Federation of Clinical C, Laboratory M and Standardization IWGfLA. First WHO/IFCC International Reference Reagent for Lipoprotein(a) for Immunoassay--Lp(a) SRM 2B. *Clin Chem Lab Med*. 2004;42:670-6.
35.   Sciacqua A, Perticone M, Tripepi G, Tassone EJ, Cimellaro A, Mazzaferro D, Sesti G and Perticone F. CHADS2 and CHA2DS2-VASc scores are independently associated with incident atrial fibrillation: the Catanzaro Atrial Fibrillation Project. *Intern Emerg Med*. 2015;10:815-21.
36.   Yin L, Ling X, Zhang Y, Shen H, Min J, Xi W, Wang J and Wang Z. CHADS2 and CHA2DS2-VASc scoring systems for predicting atrial fibrillation following cardiac valve surgery. *PLoS One*. 2015;10:e0123858.