ARIC Manuscript Proposal # 1915

PC Reviewed: 3/20/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Improvement of cardiovascular risk prediction using non-traditional risk factors in the chronic kidney disease (CKD) population

b. Abbreviated Title (Length 26 characters): CVD prediction in CKD

2. Writing Group:

Writing group members: Kunihiro Matsushita, Yingying Sang, Brad C. Astor, Ron Hoogeveen, Christie M. Ballantyne, Josef Coresh; others welcome

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

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3. Timeline: Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale: Chronic kidney disease (CKD) is a major global public health problem. CKD affects 10 to 16% of the adult population in Asia, Europe, and North America and increases the risk of cardiovascular disease for 2 to 30 fold according to the stage of CKD.[1, 2] Indeed, individuals with CKD are more likely to die of cardiovascular disease

than to develop kidney failure.[2] Despite that, effective strategy of cardiovascular disease (CVD) prevention for persons with CKD has not been established. First of all, data on effectiveness of medical therapies among CKD patients are sparse, since persons with CKD have been frequently excluded from major cardiovascular clinical trials. Additionally, a few trials explicitly focusing on patients on dialysis did not show benefits of conventional preventive approaches such as statin therapy,[3, 4] suggesting some differences in the clinical characteristics of CKD population which affect cardiovascular benefits and risks.

In June 2011, the SHARP Study demonstrated that low-density lipoprotein cholesterol reducing regimen with simvastatin and ezetimibe reduced the risk of cardiovascular disease approximately 20% in persons with CKD.[5] The SHARP Study has clearly shown that cardiovascular disease in CKD is, to some extent, preventable and has opened a door to the discussion as to who with CKD would benefit by the LDL-C lowering therapy. The US National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) currently recommends LDL-C lowering therapy for individuals with 10-year risk of coronary heart disease ≥20% predicted by the Framingham Risk Score.[6] However, the Framingham Risk Score (FRS) has been developed in a middle-aged general population and thus has been shown to poorly perform in individuals with CKD.[7] Therefore, an investigation about improvement in cardiovascular risk prediction using non-traditional risk factors for CKD population is warranted.

5. Main Hypothesis/Study Questions:

1. Existing CVD prediction tools do not perform well in the CKD subgroup of the ARIC population
2. Non-traditional risk factors improve CVD risk prediction beyond traditional CVD risk factors in the CKD subgroup of the ARIC population

Novel risk factors tested will be:

- Markers of kidney filtration function (GFR estimated [eGFR] by the CKD-EPI 2009 creatinine equation and cystatin C, β2-microglobulin [B2M], β-trace protein [BTP])
- Kidney damage marker (urinary albumin-to-creatinine ratio [ACR])
- Other lipid parameters (triglyceride, apolipoproteins A1 and B)
- Cardiac damage/overload markers (high-sensitivity troponin T [hsTnT] and N-terminal pro–B-type natriuretic peptide [NT-proBNP])
- Additional CVD measures: ankle-brachial index (ABI), and presence of atrial fibrillation

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).

Inclusions:

- All black and white ARIC subjects with data at visit 4 (the only visit for which urinary albumin data for CKD definition are available in the entire cohort)

Exclusions:
-Ethnicity other than black or white
-Individuals without data of serum creatinine and urinary albumin
-Prevalent CVD at visit 4

Exposure:
-Traditional risk factors:
We will define traditional risk factors as those used in multiple prediction tools as shown in table below. Specifically, these include age, blood pressure, antihypertensive medication use, total (or LDL) cholesterol, HDL cholesterol, diabetes, and smoking status. These existing tools usually are designed to predict risk for gender and racial groups separately. So, we will include gender and race into traditional risk factors.

Existing prediction tools to be used as a basic model:

	FRS 1998[8]	**FRS 2008**[9]	**ARIC CHD**[10]	**ARIC Stroke**[11]	**Reynolds**[12, 13]
Age	**x**	**x**	**x**	**x**	**x**
Blood pressure	**x**	**x**	**x**	**x**	**x**
Antihypertensive Medications		**x**	**x**	**x**	
Total (or LDL) Cholesterol	**x**	**x**	**x**		**x**
HDL cholesterol	**x**	**x**	**x**		**x**
Diabetes	**x**	**x**	**x**	**x**	**x**
Smoking	**x**	**x**	**x**	**x**	**x**
Left Ventricular Hypertrophy				**x**	
Family History of premature CHD					**x**
High-Sensitivity CRP					**x**

-Non-traditional risk factors:
A group of other CVD risk factors will be tested. Factors included in one risk prediction tool listed in the table but not in others, i.e., left ventricular hypertrophy by electrocardiogram, family history of premature CHD, and high-sensitivity C-reactive protein (hsCRP)[11-13] will be categorized as non-traditional risk factors. The selection of other non-traditional risk factors will be based on literature and availability at visit 4 for the entire ARIC participants. Following risk factors will be tested: various markers of kidney filtration function (GFR estimated [eGFR] by the CKD-EPI 2009 creatinine equation[14, 15] and cystatin C, β2-microglobulin [B2M], β-trace protein [BTP][16]), kidney damage marker (urinary albumin-to-creatinine ratio [ACR]),[1] other lipid parameters (triglyceride, apolipoproteins A1 and B),[17] cardiac damage/overload markers (high-sensitivity troponin T [hsTnT] and N-terminal pro–B-type natriuretic peptide [NT-proBNP]),[18, 19] ankle-brachial index (ABI),[20] and presence of atrial fibrillation.[21]

Outcome (All events that occurred after visit 4 and before January 1, 2009 will be included)**:**
-Incident coronary heart disease (CHD) including a hospitalized myocardial infarction (MI), fatal CHD, or cardiac procedure
-Incident stroke: definite and possible incident stroke
-Incident HF: the first HF hospitalization coded 428 according to the ICD-9 or death from HF (coded 428 for ICD-9 and I50 for ICD-10)[22, 23]
-Incident peripheral artery disease (PAD): ICD-9 diagnosis codes for symptomatic PAD: 443.9 (intermittent claudication, peripheral vascular disease not otherwise specified), 707.1-707.19 (lower extremity ulcers), 785.4 (gangrene) and ICD-9 procedure codes for symptomatic PAD: 84.11 (toe amputation), 84.12 (foot amputation), 84.15 (below knee amputation), 84.17 (above knee amputation), 38.18 (leg endarterectomy), 39.29 (leg bypass), 39.50 (leg angioplasty).

Since there is a trend to predict general CVD[9] rather than specific type of CVD, our primary outcome will be composite CVD. We will evaluate each subtype of CVD separately as a sensitivity analysis. Secondary analyses will examine all-cause mortality.

Statistical Analysis:

1. Evaluation of existing prediction tools
   Among various existing risk prediction tools shown in the above table,[8-11] we will primarily assess the Framingham Risk Score (FRS) for CVD published in 2008 (FRS2008)[9] The reasons are 1. FRS2008 has been shown to perform better than FRS1998, which is used in the NCEP-ATP III clinical guidelines,[6] 2. NCEP ATP IV seems to adopt risk prediction of global CVD (lecture at AHA 2011), 3. FRS1998 has been already shown to poorly perform in CKD population in ARIC and the Cardiovascular Health Study.[7]

   We will evaluate calibration and discrimination to assess the performance of FRS2008 in participants with CKD (defined as eGFR <60 ml/min/1.73m^2 and/or ACR ≥30 mg/g) and without CKD. Calibration assesses whether predicted risk and actual risk agree. Individuals with and without CKD will be divided into quintiles of predicted risk based on FRS2008, respectively, and plots of 10-year predicted and actual CVD events will be produced to visually evaluate calibration. Differences between predicted and actual risk will be compared using a modified Hosmer-Lemeshow chi-square statistic. High χ^2 values indicate poor calibration. Discrimination is the ability of a prediction model to separate those who had events from those who did not have events and was quantified by the concordance or C-statistic, analogous to the area under a receiver operating characteristic curve but able to account for censoring, as is typically met in cohort studies. Utilizing coefficients developed by the Framingham investigators to calculate the FRS2008 for each individual, we will compute C-statistics for FRS2008 in our CKD and non-CKD populations.

   We will also assess the impact of each predictor in FRS2008 by comparing coefficients for the CKD and non-CKD populations from best fitting models and the original Framingham cohort. These coefficients will be compared using a 2-tailed z statistic, where z = (β in the original Framingham Study – β in

the our CKD or non-CKD population)/(standard error). Here β is the log of the hazard ratio. The standard error (SE) is defined as ([SE in the original Framingham study]^2+ [SE in our CKD or non-CKD population]^2)$^{1/2}$.[7] Given that FRS2008 provides gender-specific predictions, we assessed their performance in males and females separately.

2. Assessment of additional prognostic value of non-traditional risk factors
Once we confirm that the performance of FRS2008 is not optimal in CKD population, we will use a model incorporating FRS2008 predictors with refitted coefficients and baseline hazard as basic model to assess additional prognostic information by non-traditional risk factors. As done in FRS2008,[9] we will log-transform traditional risk factors. Even if FRS2008 performs well in our CKD population, it is clinically important whether non-traditional risk factors provide additional prognostic information or not.

A. General approach: Using the model with traditional risk factors as a basic model, the improvement in model performance through addition of non-traditional risk factors in Cox proportional hazards regression models will be tested using metrics described below. Continuous non-traditional risk factors will be log-transformed. First, each non-traditional risk factor will be tested on the top of traditional risk factors ("univariable" analysis). Factors not associated with incident CVD in this analysis (P >0.1) will not be carried over the next "multivariable" analysis. Factors that are not significantly associated with incidence CVD in the multivariable analysis will be dropped from the model.

B. Statistics to evaluate model performance
    a. Discrimination: Concordance statistics (C statistics) and integrated discrimination improvement (IDI)[24] will be computed as measures of discrimination.
    b. Calibration: We will compare the observed vs. predicted risk of outcomes of interest for each quintile of predicted risk and determined the magnitude of the deviation using the Hosmer-Lemeshow test.
    c. Goodness of Fit: Overall model fit for sequential models will be compared using the Akaike Information Criterion (AIC), which takes into account both the statistical goodness of fit and the number of parameters required to achieve this particular degree of fit, by imposing a penalty for increasing the number of parameters.
    d. Reclassification: Reclassification refers to movement of patients from one class to another based on changes to assignment to risk categories. Reclassification improvement will be quantified using the net reclassification improvement (NRI) statistic. [24] To evaluate the effect of definition of risk categories on reclassification, we will calculate NRI using an alternative method that does not require categories (continuous NRI).

Limitations:

The number of participants with CKD in ARIC may be a concern. However, ARIC investigators developed risk prediction tool of coronary heart disease for persons with

diabetes (n=~1,500).[25] We will have similar number of participants with CKD at visit 4. Also, we will have more events since our primary outcome is composite CVD. As with any observational study, we will not be able to rule out the possibility of residual confounding. Identification of HF cases relied entirely on ICD codes abstracted from hospital records and death certificates.[26] Reliance on hospital discharge codes may underestimate HF incidence.[27]

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? ____ 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"?
____ 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)?
There are several manuscript proposals aiming to investigate the association of non-traditional risk factors listed in this manuscript proposal and incidence CVD. However, none of them, to our best knowledge, focus on the CKD population.

Manuscript proposals investigating the association of non-traditional risk factors listed in this manuscript proposal and incident CVD
#172: Levels of Albumin, Creatinine, and Incident Coronary Heart Disease; Heiss, G
#364: Family history of coronary heart disease predicts incident coronary heart disease through its association both pre-clinical atherosclerosis and risk factors: the ARIC and FHS Studies: Tyroler, H
#575: Ankle-Brachial Index and Ischemic Stroke Incidence: The ARIC Study; Tsai, A

#758: Serum creatinine and risk of CVD: Atherosclerosis Risk in Communities (ARIC) Study; Ibrahim H
#952: Kidney function and anemia as risk factors for coronary heart disease and mortality: The ARIC Study; Astor, BC
#1028: Cardiovascular risk among adults with chronic kidney disease, with or without prior myocardial infarction; Wattanakit, K
#1058: Kidney Function and Risk of Peripheral Arterial Disease: Results from the Atherosclerosis Risk in Communities (ARIC) Study; Wattanakit, K
#1118: Reduced Kidney Function as a risk factor for incident heart failure: The ARIC Study; Kottgen, A
#1123: Albuminuria and Kidney Function as Predictors of Cardiovascular Events and Mortality; Astor B
#1244: Kidney Dysfunction and Sudden Cardiac Death among Participants in the ARIC Study; Deo, R
#1348: Chronic kidney disease and risk of hospitalization: The Atherosclerosis Risk in Communities Study; Bash, LD
#1423: Cystatin C-based estimated GFR and albuminuria as predictors of coronary heart disease (CHD) events and mortality; Astor B
#1475: Hypertension, left ventricular hypertrophy, and risk of incident hospitalized heart failure: The ARIC study; Chang P
#1485: Risk stratification in African Americans using C-reactive protein – an analysis from the ARIC study; Virani S
#1581: Novel markers of kidney function and prediction of incident chronic kidney disease and end-stage renal disease: the Atherosclerosis Risk in Communities (ARIC) Study; Astor B
#1623: Apolipoprotein B, Apolipoprotein A1 and Standard Lipid Measures in the Prediction of Incident Coronary Heart Disease: The Atherosclerosis Risk in Communities (ARIC) Study; Ndumele, C
#1754: Association of estimated glomerular filtration rate and albuminuria with ischemic and hemorrhagic strokes; Mahmoodi, BK
1808: The utility high sensitivity cardiac troponin t in the prediction of heart failure risk; Nambi, V
1811: Association of high sensitive Troponin T (hs-cTnT),N- Terminal pro- brain natriuretic peptide (NT-proBNP) and high sensitivity C- reactive protein (hs-CRP) with cause- specific mortality: ARIC study; Oluleye O
#1840: New-onset atrial fibrillation and risk of all-cause mortality and cardiovascular disease in whites and African Americans: the ARIC study; Alonso, A
#1873: Combined association of Cystatin C-based and Creatinine-based estimated Glomerular filtration rate (eGFR) with Mortality, Cardiovascular and Renal Outcomes, Waheed, S

<u>Manuscript proposals to develop risk prediction of CVD</u>
#611: ARIC CHD Risk Prediction; Chambless, LE
#824: Ischemic Stroke Risk Prediction; Chambless, LE
#1004: ARIC CHD Risk Prediction from Behavioral, Psychosocial, and Socioeconomic Factors; Chambless, LE

#1095: Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) Study using a genetic risk score; Morrison, A
#1110: Risk Prediction of Coronary Heart Disease and Stroke using Retinal Arteriolar and Venular Signs; McGeechan, K
#1832: A risk prediction model for incident PAD in the ARIC cohort; Kalbaugh, CA
1904: Cardiovascular Disease Risk Prediction in Combined Cohort Studies; D'Agostino, R

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)
_X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2006.16 and 2008.10_____ _____ _____)

*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 a manuscript 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, 2008 which 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 from http://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.

References

1. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: A collaborative meta-analysis. *Lancet*. 2010;375:2073-2081
2. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW. Kidney disease as a risk factor for development of cardiovascular disease: A statement from the american heart association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Circulation*. 2003;108:2154-2169
3. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Gronhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Suleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wuthrich RP, Gottlow M, Johnsson E, Zannad F. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. 2009;360:1395-1407

4. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, Ritz E. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005;353:238-248
5. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellstrom B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Gronhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R. The effects of lowering ldl cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (study of heart and renal protection): A randomised placebo-controlled trial. *Lancet*. 2011;377:2181-2192
6. Expert Panel on Detection E, 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: The Journal of the American Medical Association*. 2001;285:2486-2497
7. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, Sarnak MJ. The framingham predictive instrument in chronic kidney disease. *J Am Coll Cardiol*. 2007;50:217-224
8. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837-1847
9. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: The framingham heart study. *Circulation*. 2008;117:743-753
10. Chambless LE, Folsom AR, Sharrett AR, Sorlie P, Couper D, Szklo M, Nieto FJ. Coronary heart disease risk prediction in the atherosclerosis risk in communities (aric) study. *J Clin Epidemiol*. 2003;56:880-890
11. Chambless LE, Heiss G, Shahar E, Earp MJ, Toole J. Prediction of ischemic stroke risk in the atherosclerosis risk in communities study. *American Journal of Epidemiology*. 2004;160:259-269
12. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: The reynolds risk score. *JAMA: The Journal of the American Medical Association*. 2007;297:611-619
13. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: The reynolds risk score for men. *Circulation*. 2008;118:2243-2251, 2244p following 2251
14. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604-612
15. Matsushita K, Selvin E, Bash LD, Astor BC, Coresh J. Risk implications of the new ckd-epi equation as compared to the mdrd study equation for estimated glomerular filtration rate: The atherosclerosis risk in communities (aric) study. *Am J Kidney Dis.* 2010;55:648-659
16. Astor BC, Shafi T, Hoogeveen RC, Matsushita K, Ballantyne CM, Inker LA, Coresh J. Novel markers of kidney function as predictors of esrd, cardiovascular disease, and mortality in the general population. *Am J Kidney Dis*. 2012
17. Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA: The Journal of the American Medical Association*. 2009;302:1993-2000
18. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, Folsom AR, Heiss G, Coresh J, Ballantyne CM. Cardiac troponin t measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the atherosclerosis risk in communities study. *Circulation*. 2011;123:1367-1376
19. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, Hashim I, Berry JD, Das SR, Morrow DA, McGuire DK. Association of troponin t detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA*. 2010;304:2503-2512
20. Potier L, Abi Khalil C, Mohammedi K, Roussel R. Use and utility of ankle brachial index in patients with diabetes. *Eur J Vasc Endovasc Surg*. 2011;41:110-116
21. Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH, Hart RG, Hinchey JA, Howard VJ, Jauch EC, Levine SR, Meschia JF, Moore WS, Nixon JV, Pearson TA. Guidelines for the primary prevention of stroke: A guideline

for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2011;42:517-584
22. Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, Chambless LE, Coresh J. Reduced kidney function as a risk factor for incident heart failure: The atherosclerosis risk in communities (aric) study. *J Am Soc Nephrol*. 2007;18:1307-1315
23. Pazin-Filho A, Kottgen A, Bertoni AG, Russell SD, Selvin E, Rosamond WD, Coresh J. Hba(1c) as a risk factor for heart failure in persons with diabetes: The atherosclerosis risk in communities (aric) study. *Diabetologia*. 2008;51:2197-2204
24. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: From area under the roc curve to reclassification and beyond. *Stat Med*. 2008;27:157-172; discussion 207-112
25. Folsom AR, Chambless LE, Duncan BB, Gilbert AC, Pankow JS. Prediction of coronary heart disease in middle-aged adults with diabetes. *Diabetes Care*. 2003;26:2777-2784
26. Matsushita K, Blecker S, Pazin-Filho A, Bertoni A, Chang PP, Coresh J, Selvin E. The association of hemoglobin a1c with incident heart failure among people without diabetes: The atherosclerosis risk in communities study. *Diabetes*. 2010;59:2020-2026
27. Khand AU, Shaw M, Gemmel I, Cleland JG. Do discharge codes underestimate hospitalisation due to heart failure? Validation study of hospital discharge coding for heart failure. *Eur J Heart Fail*. 2005;7:792-797