ARIC Manuscript Proposal #4082

PC Reviewed: 7/12/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The association of blood urea nitrogen with incident heart failure in the community: the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Association between BUN and HF

2. Writing Group:

Writing group members: Hairong Liu, Junichi Ishigami, Lena Mathews, Suma Konety, Michael Hall, Patricia P. Chang, Chiadi Ndumele, Wayne Rosamond, Kunihiro Matsushita

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

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3. Timeline: 2022.5-2022.11 data analysis
2022.8-2022.12 manuscript preparation

4. Rationale:

Blood urea nitrogen (BUN) is a common laboratory test in clinical practice. It mainly reflects kidney function but also represents other clinical conditions such as gastrointestinal bleeding[1]and hyperthyroidism.[2] Previous studies have shown that BUN levels were often elevated in patients with heart failure (HF)[3], and higher levels of BUN were predictive of poor

prognosis in this clinical population.[4-11] For example, a large US study with more than 50,000 patients with HF identified BUN as one of the most potent prognostic predictors in this clinical population.[11] However, little is known about whether BUN is associated with incident HF in the community.[8] One study from China investigating 5,000 adults observed that BUN levels were not associated with incident HF once accounting for potential confounders. However, this study has a few important caveats: including only adults aged 60 years or older, relatively short follow-up time of four years, and enrolling only Asians.

To overcome these caveats, we will examine the association of BUN with the subsequent risk of HF using data from the Atherosclerosis Risk in Communities (ARIC) Study. If BUN is robustly associated with HF risk in our study, our results would have clinical implications since BUN is widely measured in clinical settings but not specifically used to classify HF risk. Also, the value of HF risk prediction is greater than ever given the availability of new medications reducing the risk of HF (e.g., SGLT2 inhibitors[13]) and the growing interest in a risk-centered approach for guiding HF prevention. [14,15,16]

5. Main Hypothesis/Study Questions:

Hypothesis 1: BUN is associated with incident HF, independently of potential confounders such as kidney function.

Hypothesis 2: BUN improves the risk prediction of HF beyond conventional predictors of HF

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: A prospective cohort study.

Inclusion: All Black and White ARIC participants with data of BUN but without a history of HF at visit 1.

Exclusion criteria:

-Self-reported race and ethnicities other than Black or White

-Participants with prevalent HF at baseline are defined by the Gothenburg criteria that require the presence of specific cardiac and pulmonary symptoms as well as medical treatment of HF at previous visit[17-19]

-Participants without data on BUN or relevant covariates

Exposure:

At ARIC visit 1, BUN levels were measured using the DART blood urea nitrogen reagent with a method based on the modification of the Talke and Schubert method.[21]

Outcomes:

Primary outcome: Incident HF

The first HF hospitalization. Classification of Diseases Code, Ninth Revision (ICD-9) or death from HF (coded 428 for ICD-9 and I50 for ICD-10).[18]

Secondary outcomes: Although our primary interest is HF, we will also explore myocardial infarction, stroke, atrial fibrillation, and peripheral artery diseases, as secondary outcomes.

Other variables of interest and covariates:
Sociodemographic: age, race, gender, education attainement, annual housholde income
Physical information: blood pressure, body mass index, estimated glomerular filtration rate.
Lifestyle: smoking status and alcohol habit
Comorbidities: hypertension, dyslipidemia, diabetes, history of coronary heart disease, anemia.

Statistical Analysis Plan:

We will first compare baseline characteristics according to the quartiles of BUN. Then, using the Kaplan-Meier method, we will estimate the cumulative incidence of HF across these BUN groups. Their difference will be tested using a log-rank test. Subsequently, using Cox proportional hazards models, we will quantify the independent associations of BUN with incident HF. We will run the following models to evaluate the impact of potential confounders.

Model 1 will adjust for demographic variables age, race/ethnicity, gender, and ARIC center.

Model 2 will further adjust for sociodemographic variables: education and income

Model 3 will additionally account for lifestyle factors: smoking status and alcohol habit.

Model 4 will further adjust for clinical conditions such as blood pressure, antihypertensive medication use, body mass index, kidney function (eGFR by using CKD-EPI equation[23]), total cholesterol, high-density lipoprotein cholesterol, diabetes, and history of coronary heart disease, anemia.

We will conduct a few sensitivity analyses. First, we will conduct subgroup analysis by age, sex, race, BMI, and other covariates to see whether there are different hazard ratios in each group. We will test potential effect modification with the likelihood ratio test. Second, we will see whether the results are similar when we use adjudicated HF cases after 2005. Finally, we will also run Fine-Gray models with death as a competing endpoint.

If there is a significant association between BUN value and incident HF in the analysis noted above, we will assess whether the addition of BUN improves the prediction of incident HF. We will include the following predictors as the base model: BUN, age, blood pressure, body mass index, hypertension,diabetes, and anemia. We will evaluate Harrell's c-statistics and calibration.[22]

We will repeat the analysis for the secondary outcomes listed above.

Limitations:

HF cases prior to 2005 not adjudicated

Only data from Blacks and Whites

BUN was measured only at visit 1

Although adjusting for other covariates, there may still have residual confounding.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __√__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No

(The file ICTDER 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 ___√_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 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/aricproposals/dtSearch.html

___√___ 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)?

To the best of our knowledge, there is no ARIC proposal exploring BUN and the subsequent risk of HF.

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.

Reference:

1. Tomizawa, M., Shinozaki, F., Hasegawa, R., Shirai, Y., Motoyoshi, Y., Sugiyama, T., Yamamoto, S., & Ishige, N. (2015). Patient characteristics with high or low blood urea nitrogen in upper gastrointestinal bleeding. World journal of gastroenterology, 21(24), 7500–7505. https://doi.org/10.3748/wjg.v21.i24.7500
2. Aizawa T, Hiramatsu K, Ohtsuka H, Kobayashi M, Koizumi Y, Miyamoto T, Niwa A, Yamada T. An elevation of BUN/creatinine ratio in patients with hyperthyroidism. Horm Metab Res. 1986 Nov;18(11):771-4. doi: 10.1055/s-2007-1012432. PMID: 3792996.
3. Jujo, K., Minami, Y., Haruki, S., Matsue, Y., Shimazaki, K., Kadowaki, H., Ishida, I., Kambayashi, K., Arashi, H., Sekiguchi, H., & Hagiwara, N. (2017). Persistent high blood urea nitrogen level is associated with increased risk of cardiovascular events in patients with acute heart failure. ESC heart failure, 4(4), 545–553. https://doi.org/10.1002/ehf2.12188
4. Zhu X, Cheang I, Liao S, Wang K, Yao W, Yin T, Lu X, Zhou Y, Zhang H, Li X. Blood Urea Nitrogen to Creatinine Ratio and Long-Term Mortality in Patients with Acute Heart Failure: A Prospective Cohort Study and Meta-Analysis. Cardiorenal Med. 2020;10(6):415-428. doi: 10.1159/000509834. Epub 2020 Oct 28. PMID: 33113531.
5. Aronson D, Mittleman MA, Burger AJ. Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure. Am J Med. 2004 Apr 1;116(7):466-73. doi: 10.1016/j.amjmed.2003.11.014. PMID: 15047036.
6. Filippatos G, Rossi J, Lloyd-Jones DM, Stough WG, Ouyang J, Shin DD, O'connor C, Adams KF, Orlandi C, Gheorghiade M. Prognostic value of blood urea nitrogen in patients hospitalized with worsening heart failure: insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) study. J Card Fail. 2007 Jun;13(5):360-4. doi: 10.1016/j.cardfail.2007.02.005. PMID: 17602982.
7. Lin HJ, Chao CL, Chien KL, Ho YL, Lee CM, Lin YH, Wu YW, Hsu RB, Chou NK, Wang SS, Chen CY, Chen MF. Elevated blood urea nitrogen-to-creatinine ratio increased the risk of hospitalization and all-cause death in patients with chronic heart failure. Clin Res Cardiol. 2009 Aug;98(8):487-92. doi: 10.1007/s00392-009-0025-1. Epub 2009 May 26. PMID: 19468780.
8. Gotsman I, Zwas D, Planer D, Admon D, Lotan C, Keren A. The significance of serum urea and renal function in patients with heart failure. Medicine (Baltimore). 2010 Jul;89(4):197-203. doi: 10.1097/MD.0b013e3181e893ee. PMID: 20616658.
9. Sliwa K, Davison BA, Mayosi BM, Damasceno A, Sani M, Ogah OS, Mondo C, Ojji D, Dzudie A, Kouam Kouam C, Suliman A, Schrueder N, Yonga G, Ba SA, Maru F, Alemayehu B, Edwards C, Cotter G. Readmission and death after an acute heart failure event: predictors and outcomes in sub-Saharan Africa: results from the THESUS-HF registry. Eur Heart J. 2013 Oct;34(40):3151-9. doi: 10.1093/eurheartj/eht393. Epub 2013 Sep 18. PMID: 24048728.
10. Parrinello G, Torres D, Testani JM, Almasio PL, Bellanca M, Pizzo G, Cuttitta F, Pinto A, Butler J, Paterna S. Blood urea nitrogen to creatinine ratio is associated with congestion and mortality in heart failure patients with renal dysfunction. Intern Emerg Med. 2015 Dec;10(8):965-72. doi: 10.1007/s11739-015-1261-1. Epub 2015 Jun 3. PMID: 26037394.

11. Lan Q, Zheng L, Zhou X, Wu H, Buys N, Liu Z, Sun J, Fan H. The Value of Blood Urea Nitrogen in the Prediction of Risks of Cardiovascular Disease in an Older Population. Front Cardiovasc Med. 2021 May 20;8:614117. doi: 10.3389/fcvm.2021.614117. PMID: 34095242; PMCID: PMC8173137.
12. Fonarow GC, Adams KF, Abraham WT, Yancy CW, Boscardin WJ, ADHERE Scientific Advisory Committee, Study Group, and Investigators FT. Risk Stratification for In-Hospital Mortality in Acutely Decompensated Heart Failure: Classification and Regression Tree Analysis. JAMA. 2005;293(5):572–580. doi:10.1001/jama.293.5.572
13. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM; DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008. doi: 10.1056/NEJMoa1911303. Epub 2019 Sep 19. PMID: 31535829.
14. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022 May 3;145(18):e895-e1032. doi: 10.1161/CIR.0000000000001063. Epub 2022 Apr 1. Erratum in: Circulation. 2022 May 3;145(18):e1033. PMID: 35363499.
15. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, Wainford RD, Williams B, Schutte AE. 2020 International Society of Hypertension global hypertension practice guidelines. J Hypertens. 2020 Jun;38(6):982-1004. doi: 10.1097/HJH.0000000000002453. PMID: 32371787.
16. Massimo F Piepoli, Arno W Hoes, Stefan Agewall, Christian Albus, Carlos Brotons, Alberico L Catapano, Marie-Therese Cooney, Ugo Corrà, Bernard Cosyns, Christi Deaton, Ian Graham, Michael Stephen Hall, F D Richard Hobbs, Maja-Lisa Løchen, Herbert Löllgen, Pedro Marques-Vidal, Joep Perk, Eva Prescott, Josep Redon, Dimitrios J Richter, Naveed Sattar, Yvo Smulders, Monica Tiberi, H Bart van der Worp, Ineke van Dis, W M Monique Verschuren, Simone Binno, ESC Scientific Document Group, 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), European Heart Journal, Volume 37, Issue 29, 1 August 2016, Pages 2341–2365, https://doi.org/10.1093/eurheartj/ehw106
17. Blood urea nitrogen (BUN) test - Mayo Clinic". www.mayoclinic.org. Retrieved 2019-05-13.
18. Eriksson H, Caidaul K, Larsson B, et al. Cardiac and pulmonary causes of dyspnoea--validation of a scoring test for clinical-epidemiological use: The Study of Men Born in 1913. Eur Heart J. 1987;8(9):1007-1014.

19. Wilhelmsen L, Eriksson H, Svardsudd K, Caidahl K. Improving the detection and diagnosis of congestive heart failure. Eur Heart J. 1989;10 Suppl C:13-8.
20. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). Am J Cardiol. 2008;101(7):1016-22.
21. Manual 10 clinical chemistry determinations. National Library of Medicine 1987.10.15 https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/document.cgi?study_id=phs000090.v1.p1&phd=227#sec154
22. Rahimi, K., Bennett, D., Conrad, N., Williams, T. M., Basu, J., Dwight, J., ... & MacMahon, S. (2014). Risk prediction in patients with heart failure: a systematic review and analysis. JACC: Heart Failure, 2(5), 440-446.
23. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604-12. doi: 10.7326/0003-4819-150-9-200905050-00006. Erratum in: Ann Intern Med. 2011 Sep 20;155(6):408. PMID: 19414839; PMCID: PMC2763564.