ARIC Manuscript Proposal # 3263

PC Reviewed: 11/13/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: High molecular weight kininogen (HK), Prekallikrein (PK) and Incident Heart Failure

b. Abbreviated Title (Length 26 characters): HK, PK and Heart Failure

2. Writing Group:

Writing group members: Romil Parikh, Aaron Folsom, Jeff Misialek, Wayne Rosamond, Patty Chang, Weihong Tang, Mary Cushman

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

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3. Timeline: Finished manuscript by Spring 2019

4. Rationale:

The contact activation system and the kallikrein/kinin system (KKS) play important roles in thrombosis and inflammation. Some evidence suggests associations with atherosclerosis and venous thrombosis[1,2], but evidence for a role in heart failure (HF) is lacking.

Two key components of these systems are kallikrein and high molecular weight kininogen (HK). Plasma and tissue kallikrein cleave HK to liberate bradykinin (BK). BK, through coupling of receptors B2R & B1R with endothelial and cytokine-inducible nitric oxide (NO) synthase respectively, is a potent stimulator of NO production, as well as prostacyclin (PGI2) production and tissue plasminogen activator release.[2] A study in knockout mice found production of kinin to be protective against cardiovascular remodeling.[3]

Cardiac remodeling is an important contributor to HF, although the underlying drivers of cardiac remodeling in heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) seem at least partially distinct. It has been proposed that systemic inflammation, through increased production of reactive oxygen species, causes limited availability of NO, resulting in low protein kinase G, which induces myocardial remodeling and diastolic LV dysfunction- the main cardiac dysfunction in HFpEF.[4] In the population based cohort Health ABC, inflammatory markers such as IL-6 & TNFα were significantly increased in patients who developed HFpEF, compared with those who did not develop HF, but were lower and not significantly increased in those who developed HFrEF.[5]

The LITE ancillary study of ARIC measured plasma HK and prekallikrein (PK) at ARIC visit 3 in venous thromboembolism cases and a cohort random sample. We propose to study these biomarkers and risk of incident HF in the cohort sample. Considering the potentially protective effects of BK against cardiac remodeling, we hypothesize participants with lower functioning KKS (or a lower HK and PK level) will be at an increased risk for developing HF, and specifically HFpEF compared with HFrEF.

1. Wu Y. Contact pathway of coagulation and inflammation. Thrombosis Journal. 2015;13:17.
2. Schmaier AH. The contact activation and kallikrein/kinin systems: pathophysiologic and physiologic activities. J Thromb Haemost 2016; 14: 28–39.
3. Liu YH, , Yang XP, Mehta D et al Role of kinins in chronic heart failure and in the therapeutic effect of ACE inhibitors in kininogen-deficient rats. Am. J. Physiol. Heart Circ. Physiol. 278: H507–H514, 2000.
4. Paulus WJ, Tschope C. A Novel Paradigm for Heart Failure With Preserved Ejection Fraction: Comorbidities Drive Myocardial Dysfunction and Remodeling Through Coronary Microvascular Endothelial Inflammation. J Am Coll Cardiol. Vol. 62, No. 4, 2013
5. Kalogeropoulos A, Georgiopoulou V, Psaty BM, et al. Inflammatory markers and incident heart failure risk in older adults: the Health ABC (Health, Aging, and Body Composition) study. J Am Coll Cardiol. 2010 May 11;55(19):2129-37.

5. Main Hypothesis/Study Questions:

Plasma HK and PK are inversely associated with risk of incident HF (stronger for HFpEF compared to HFrEF).

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, using visit 3 random sample with biomarkers measured (N~3900 without HF at baseline visit 3)

Exclusions: pre-visit 3 HF defined by Gothenburg criteria or incident hospitalized HF, anticoagulant use, missing key covariates

Exposure: HK and PK at visit 3

Outcome: incident hospitalized HF based on ICD codes through 2016 or 2017. After 2005, HF will be separated into HFpEF and HFrEF, based on ARIC review.

Confounding variables (taken from visit 3): age, race, sex, BMI, total cholesterol, HDL-C, TG, diabetes, CKD, prevalent CHD, smoking, alcohol, SBP and antihypertensive medications, atrial fibrillation, and inflammatory biomarkers (CRP).

We will examine correlates of HK and PK to assess potential confounders. We will use a cubic spline analysis to examine the shape of the associations with HF. The associations of HF with HK and PK will be assessed in the cohort random sample of N~4000. The approximate number of incident HF cases expected is 800. We will use quartiles or continuous representations of the biomarkers and use Cox proportional hazards regression to adjust for potential confounders.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _xx___ 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 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 _xx___ 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

___xx___ 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)?

3110. High molecular weight kininogen (HK) or prekallikrein and venous thromboembolism (VTE)—Folsom et al.

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

11.b. If yes, is the proposal

_xx__ A. primarily the result of an ancillary study (list number* ___2001.16 LITE__)

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