

ARIC Manuscript Proposal #2184

PC Reviewed: 8/13/13
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Parathyroid hormone and CVD

b. Abbreviated Title (Length 26 characters): Parathyroid hormone and CVD

2. Writing Group:

Writing group members: Aaron Folsom, Elizabeth Selvin, Erin Michos, Alvaro Alonso, Jeff Misialek, John Eckfeldt, Josef Coresh, Jim Pankow, Pamela Lutsey

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

First author: Aaron Folsom

Address:

Phone:

Fax:

E-mail: folso001@umn.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).

Name:

Address:

Phone:

Fax:

E-mail:

3. Timeline: Analyses begin summer 2013

4. Rationale:

Parathyroid hormone (PTH) serves to regulate blood calcium and is altered in primary hyperparathyroidism (relatively rare) and secondarily in vitamin D deficiency, kidney disease and certain other conditions.

Elevated PTH is associated with increases in blood pressure and cardiac contractility, which may eventually lead to cardiomyocyte hypertrophy, apoptosis, and fibrosis of the

left ventricle and vascular medial smooth muscle tissue (1-4). PTH may also predispose to valvular and myocardial calcification, especially in patients with moderate to severe chronic kidney disease (CKD) (5). Proinflammatory effects of elevated PTH have also been posited, as it appears to stimulate cytokine release from vascular smooth muscle cells and lymphocytes (1, 6-8).

A recent meta analysis of 15 cohort studies reported that CVD incidence or mortality was increased about 1.5 fold with PTH excess (9). The Cardiovascular Health Study (CHS) reported a positive association with heart failure incidence but associations with CHD and CVD were not independent of renal function (10). Most prior studies, other than CHS, did not look at vitamin D simultaneously and data on African Americans are lacking. PTH has also been associated positively with high BP and echocardiographic outcomes (9).

As part of Pam Lutsey's ancillary study, PTH was measured in visit 2 samples, along with calcium and vitamin D. We propose to look at PTH and multiple CVD outcomes in ARIC.

5. Main Hypothesis/Study Questions:

Hypothesis: PTH is associated positively with incident CHD, heart failure, stroke, peripheral artery disease, atrial fibrillation, and CVD mortality, independent of vitamin D, calcium, and eGFR.

Hypothesis: There will be a race interaction.

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).

Design: cohort beginning at V2 forward

Inclusion: whites and Af Ams who attended V2 and had the main independent variables measured

Exclusions: For each disease outcome, those with prevalent disease will be excluded

Main exposure: PTH (Note: PTH was also measured in 1900 subjects at visit 3 in Erin Michos' project. We will consider using these duplicate measures for a subset in the analysis to improve precision.)

Outcomes: incident CHD, heart failure, stroke, PAD, atrial fibrillation, and CVD mortality

Other variables: age, race, sex, major CVD risk factors, season of exam, BP meds, vitamin supplement use, CRP, NT-proBNP, eGFR, serum Vit D, calcium, and phosphorous.

Analysis:

We will examine the interrelations of PTH with covariables, especially race, Vit D, calcium, phosphorous, and eGFR. We will explore the shape of the relation of PTH with outcomes using cubic splines, and use an appropriate form in Cox regression. (In CHS, there appeared to be nonlinear associations and so PTH was dichotomized.) As a preliminary step, we will also evaluate whether seasonality of blood draw and PTH levels are interrelated. If warranted, we will account for season of blood draw in all models.

We will run a series of models. Model 1 will adjust for demographics. Model 2 will further adjust for major CVD risk factors, some of which may be on the causal pathway between PTH and CVD (e.g. diabetes, hypertension, inflammation). We will also carefully explore confounding and interaction by Vit D, calcium, phosphorous, and eGFR. Depending on the findings, we will present stratified results or adjust for these in additional models. Likely, because of confounding by CKD, we will need to run an analysis restricted to those without CKD.

A sensitivity analysis will be run after excluding people with possible primary hyperparathyroidism (high PTH and high calcium).

Refs:

1. Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. *Prog Biophys Mol Biol* 2006;92(1):39-48.
2. Rostand SG, Drueke TB. Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. *Kidney Int* 1999;56(2):383-392.
3. Perkovic V, Hewitson TD, Kelynack KJ, Martic M, Tait MG, Becker GJ. Parathyroid hormone has a pro-sclerotic effect on vascular smooth muscle cells. *Kidney Blood Press Res* 2003;26(1):27-33.
4. Amann K, Tornig J, Flechtenmacher C, Nabokov A, Mall G, Ritz E. Blood-pressure-independent wall thickening of intramyocardial arterioles in experimental uraemia: evidence for a permissive action of PTH. *Nephrol Dial Transplant* 1995;10(11):2043-2048.
5. Andersson P, Rydberg E, Willenheimer R. Primary hyperparathyroidism and heart disease -- a review. *Eur Heart J* 2004;25(20):1776-1787.
6. Martin-Ventura JL, Ortego M, Esbrit P, Hernandez-Presa MA, Ortega L, Egido J. Possible role of parathyroid hormone-related protein as a proinflammatory cytokine in atherosclerosis. *Stroke* 2003;34(7):1783-1789.
7. Somjen D, Weisman Y, Kohen F, Gayer B, Limor R, Sharon O, Jaccard N, Knoll E, Stern N. 25-hydroxyvitamin D3-1alpha-hydroxylase is expressed in human

vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. *Circulation* 2005;111(13):1666-1671.

8. Rigby WF, Denome S, Fanger MW. Regulation of lymphokine production and human T lymphocyte activation by 1,25-dihydroxyvitamin D3. Specific inhibition at the level of messenger RNA. *J Clin Invest* 1987;79(6):1659-1664.
9. van Ballegooijen AJ. Reinders I. Visser M. Brouwer IA. Parathyroid hormone and cardiovascular disease events: A systematic review and meta-analysis of prospective studies. *Am Heart J* 2013;165(5):655-664.
10. Kestenbaum B, Katz R, de Boer I, *et al.* Vitamin D, parathyroid hormone, and cardiovascular events among older adults. *J Am Coll Cardiol* 2011;58(14):1433-1441.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes
 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 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.csc.unc.edu/ARIC/search.php>

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)?

