ARIC Manuscript Proposal #2260

PC Reviewed: 11/12/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The burden of peripheral artery disease: linkage of Medicare claims with the ARIC study

b. Abbreviated Title (Length 26 characters): PAD using Medicare claims

2. Writing Group:
Writing group members: Corey Kalbaugh, MS, MA; Anna Kucharska-Newton, PhD; Lisa Wruck, PhD; Lindsay Smith, PhD; Elizabeth Selvin, PhD; Gerardo Heiss, MD, PhD; Laura Loehr, MD, PhD; others welcome

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

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3. Timeline: Data analysis to begin upon approval of proposal. Manuscript to be written by August 2014.

4. Rationale:

Peripheral artery disease (PAD) is estimated to affect more than 8 million individuals in the United States, including up to 20% of those over 65 years of age [1]. Common PAD manifestations, intermittent claudication (IC), or pain with exercise, and critical limb ischemia (CLI), a limb- and life-threatening disease that presents as rest pain or tissue loss, can result in significant physical disability [2]. The incidence of IC and CLI is expected to rise as the population ages [3]. PAD is associated with high overall costs, frequent re-hospitalizations and increased mortality [4]; five-year mortality is estimated at 25% for IC and 50% for CLI, the most severe form of PAD [5, 6].

Accurate measures of the population burden of PAD are essential for targeting public health prevention. Existing population burden measures of PAD rarely include information from outpatient clinics where the majority of initial encounters occur; therefore, current PAD prevalence and incidence estimates under-report actual events. Intermittent claudication, the initial presentation in more than 90% of those with PAD, is now managed primarily in the outpatient setting with medications, exercise training, and risk factor modification [3]. Recent advances in endovascular technology and wound care have further increased the frequency of outpatient management for advanced PAD [7, 8]. Consideration of PAD diagnoses made in the outpatient setting, in addition to hospitalized events, and is therefore critical to an accurate measure of the population burden of PAD.

The aim of the proposed study is to estimate the prevalence and incidence of clinically diagnosed PAD. This investigation will utilize CMS Medicare claims data available for Medicare beneficiaries living in the four geographically defined communities of the Atherosclerosis Risk in Communities (ARIC) Study, a large observational study that investigates the etiology of atherosclerotic diseases[9].

5. Main Hypothesis/Study Questions:

Overall Aim: To estimate prevalence and incidence of peripheral artery disease (PAD) in the inpatient and outpatient setting among CMS Medicare fee-for-service beneficiaries residing in the Atherosclerosis Risk in Communities (ARIC) Study communities.

Aim 1.1 Estimate the unadjusted annual prevalence, incidence proportion, and incidence rate of PAD in the inpatient and outpatient setting among CMS Medicare fee-for-service beneficiaries residing in the four ARIC communities. Analyses will be calculated overall and in age, gender, race, and race-gender strata.

Aim 1.2 Quantify diagnostic error among inpatient PAD events by validating the use of CMS Medicare fee-for-service claims to define inpatient PAD events using adjudicated events available from the ARIC cohort as the gold standard.

Aim 1.3 Quantify diagnostic error among outpatient PAD events by estimating concordance between self-report PAD events from ARIC annual follow-up questionnaires and outpatient PAD events in CMS claims data defined with ICD-9-CM/CPT-4 codes.

Aim 1.4 Estimate adjusted prevalence and incidence of PAD in the inpatient and outpatient setting among CMS Medicare fee-for-service beneficiaries residing in the four ARIC communities. Analyses will be calculated overall and in age, gender, race, and race-gender strata.

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: Incidence and prevalence study over 10 years of available CMS data

Inclusion/Exclusion: Medicare beneficiaries can opt to have additional coverage of their health care services provided by managed care programs, such as Medicare Advantage. Insurance agencies offering managed care programs are not required to submit claims for individual services and, consequently, information on health care utilization by beneficiaries in these programs is incomplete. Thus, we will only include CMS Medicare data available for all fee-for-service CMS Medicare beneficiaries ages 65 years and older residing in the four geographically defined areas of the ARIC Study. Analyses for Aim 1.2 and Aim 1.3 of this study will be conducted using CMS Medicare data which have been linked with data from the population-based ARIC Study cohort.

Variables of interest: age, center, gender, and race.

Outcomes: ICD-9-CM and CPT-4 codes will be examined to determine PAD events using the Mayo Clinic Algorithm, as shown in Appendix 1.

Data Analysis: We will estimate the unadjusted and adjusted annual prevalence, incidence proportion, and incidence rate of PAD in the inpatient and outpatient setting among CMS Medicare fee-for-service beneficiaries residing in the four ARIC communities. Analyses will be calculated overall and in age, gender, race, and race-gender strata.

Prevalence Calculations

$$Annual\ Prevalence = \frac{\#\ PAD\ events_{year\ i,age,gender,race}}{population\ at\ risk_{year\ i,age,gender,race}}$$

Numerator: For hospitalized PAD, prevalent events will include all annual listings of any of the selected PAD codes in the primary or secondary position. Diagnostic codes in the CMS Medicare claims for outpatient services are not ordered and identification of a primary diagnosis for outpatient events is not possible from outpatient claims data. I will use an established administrative claims convention to identify disease diagnoses and consider a diagnosis of PAD as present if the Medicare beneficiary has had a hospitalization for PAD (inpatient PAD diagnosis) or if the Medicare beneficiary has had at least two claims for outpatient visits (at least 3 days apart) with a PAD code listed on the claim within 12 consecutive months (outpatient PAD diagnosis). If an outpatient event precedes an inpatient event within 365 days, the prevalent event date will be the outpatient date of service. If an inpatient event occurs more than 365 days after a singular outpatient event the prevalent event date will be the date of inpatient discharge.

Denominator: To minimize reporting error, proposed analyses will be limited to Medicare beneficiaries with continuous fee-for-service Part A and Part B coverage for at least 12 months prior to the observation period and throughout the observation period. The denominator for the assessment of PAD rates will be calculated as person-years of follow-up. The method of denominator calculation for this proposal is known as "full coverage" and includes only those with FFS coverage during the entire surveillance period [10].

Incidence Calculations

$$Incidence\ proportion = \frac{\#\ new\ PAD\ events_{year\ i,age,gender,race}}{population\ at\ risk_{year\ i,age,gender,race}}$$

$$Incidence\ rate = \frac{\#\ new\ PAD\ events_{\ year\ i,age,gender,race}}{person\ months\ at\ risk_{year\ i,age,gender,race}}$$

Numerator: Estimation of incidence will begin in 2004. Administrative claims will be examined for at least one year prior (year 2003) as a minimum washout period to ensure that any events captured in 2004 are truly incident events. Any individual with presence of a PAD-related code in outpatient and inpatient claims for the year 2003 will be excluded from incidence analyses moving forward. Also, individuals must be enrolled in Medicare FFS continuously for at least one year before becoming eligible for the assessment of PAD incidence. Incident PAD diagnoses will be defined as the earliest occurrence of a PAD-related hospitalization with no PAD hospitalizations in the preceding 365 days (inpatient PAD diagnosis) or as the first two consecutive occurrences of the selected PAD-specific ICD-9-CM codes occurring within 365 days of each other and at least three days apart (outpatient PAD diagnosis). If one outpatient event precedes an inpatient event within 365 days, the incident event date will be the inpatient discharge date. If an inpatient event occurs more than 365 days after a singular outpatient event the incident event date will be the date of inpatient discharge.

Denominator: The denominator for calculating incidence proportion by year will be the same as described above for annual prevalence with one additional condition: those with an incident event will be excluded from the denominator in follow-up years. The denominator for calculating incidence rates over years 2004-2012 will factor the number of person-months that each person is included in FFS during each year. Each individual will contribute 12 person months per year to the denominator of interest, unless they died during the year of interest. Confidence intervals will be reported for each prevalence and incidence estimate.

Calibration Studies

Inpatient Validation Study: A validation study that is part of an ongoing ancillary study (2012.19) will be completed to quantify sensitivity, specificity, positive predictive value, and negative predictive value associated with using ICD-9-CM codes to capture inpatient PAD events. These performance results will be reported to complement the comparability ratios (see below) we will use to adjust the burden of hospitalized PAD.

Outpatient Concordance Study: A concordance study will be completed to assess using CMS data to quantify outpatient PAD events. We will examine the agreement between PAD events identified using CMS claims and PAD events identified from two PAD-related questions asked of ARIC cohort participants at annual follow-up telephone surveys: "Since we last contacted you has a doctor said that you have peripheral vascular disease or intermittent claudication?" and "Do you have pain in your legs caused by a blockage of the arteries?" Kappa statistics and 95% confidence intervals will be reported to complement the comparability ratios (see below) we will use to adjust the burden of outpatient PAD.

Adjustment for Error: Comparability ratios, obtained separately for hospitalizations and outpatient events, will be used as a calibration factor to adjust prevalence and incidence estimates. Comparability ratios are multiplied directly to unadjusted estimates as has been previously described in the ARIC population in relation to acute myocardial infarction [11].

$$Formula: Comparability\ Ratio => c_{PAD(Hospitalization,Outpatient)} = \frac{E_{PAD,ARIC}}{E_{PAD,Claims}}$$

Hospitalizations: In the formula $E_{PAD,ARIC}$ is the number of events classified as definite PAD according to adjudication of ARIC participants' medical records for hospitalizations and $E_{PAD,Claims}$ represents the number of hospitalized events classified as PAD from ARIC participants' administrative claims.

Outpatient Events: In the formula $E_{PAD,ARIC}$ is the number of events classified as outpatient PAD according to ARIC participants' positive answers to the annual telephone survey questions and $E_{PAD,Claims}$ represents the number of events classified as PAD from ARIC participants' outpatient administrative claims.

Limitations: The study has several limitations, the strongest of which is its reduced generalizability due to enrollment of Medicare beneficiaries in the Medicare Advantage programs. The level of enrollment in Medicare Advantage varies across the ARIC study communities from less than 10% in Washington County to greater than 40% in Forsyth and it has changed over the years for which Medicare data are available in ARIC. The proposed analyses will be limited to Medicare beneficiaries not enrolled in Medicare Advantage plans, limiting

inferences to fee-for-services enrollees. Other potential study limitations, specific to the use of administrative claims data, include lack of detailed information on comorbidities, and illness severity, coding inconsistencies, and data missingness, specifically missing information on self-reported race.

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 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 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)?

MS #1997: Incidence of atrial fibrillation using the Centers for Medicare and Medicaid Services data (Smith)

MS #1528: Concordance of heart failure diagnostic codes comparing medical records and Medicare administrative claims in ARIC cohort participants (Kucharska-Newton)

AS #2012.19: Population-Based Prevalence and Natural History of Peripheral Artery Disease (Kalbaugh)

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
_____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)* 2012.19)

*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.

Appendix 1 : Mayo Clinic Algorithm

International Classification of Diseases, Clinical Modification, version 9 (ICD-9-CM) hospital discharge codes - The Mayo Clinic algorithms for identifying peripheral artery disease events.

ICD-9-CM Diagnosis Codes For PAD

440.2×, 440.3×, or 440.8×.

Procedure Codes Related To PAD

One of the ICD-9-CM/CPT-4 procedure codes for lower extremity artery angiography: 88.48, 75710, 75711, 75712, 75716, 75717, 75718, 75630, 75631 ***PLUS*** one **(concurrent)** of the codes below for non coronary vessel stents: 39.50, 39.90, 37205, 37206, 37207, 37208, 37184, 37185, 37186.

OR

One of the ICD-9-CM/CPT-4 procedure codes for lower extremity artery surgical and percutaneous vascular interventions: 38.18, 39.50, 39.25, 39.29, 38.08, 38.38, 38.48, 39.49; 39.56, 39.57, 39.58, 39.90, 35302, 35303, 35304, 35305, 35306, 35331, 35351, 35355, 35361, 35363, 35371, 35372, 35381, 35452, 35454, 35456, 35459, 35470, 35472, 35473, 35474, 35481, 35482, 35483, 35485, 35491, 35492, 35493, 35495, 35521, 35533, 35537, 35538, 35539, 35540, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35571, 35582, 35583, 35585, 35587, 35621, 35623, 35637, 35638, 35641, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 35226, 35256, 35286, 35700, 35721, 35741, 35876, 35879, 35881, 35883, 35884, 37184, 37185, 37186, 37205, 37206, 37207, 37208.

Exclude if one of the following ICD-9-CM codes for alternate reasons for surgery is also present: 736.3×, 736.4×, 736.5, 736.6, 736.7×, 736.8×, 736.9, 735.×, 754.3×, 754.4×, 754.5×, 754.6×, 754.7×, 755.02, 755.13, 755.14, 755.3, 755.4, 755.6×, 755.8, 759.7, 759.89, 895.××, 896.××, 897.××, 820.××, 821.××, 822.××, 823.××, 824.××, 825.××, 826.××, 827.××, 828.××, 829.××, 835.××, 836. ××, 837.××, 838.××, 904.××, 928.××, 929.××, 959.6, 959.7, 996.4×, 996.66, 996.67, 996.77, 996.78.

OR

One of the ICD-9-CM/CPT-4 procedure codes for lower extremity amputation: 84.1×, 84.91, 27295, 27590, 27591, 27592, 27598, 27880, 27781, 27782, 27888, 27889, 28800, 28805.

Exclude if one of the following ICD-9-CM codes for non-vascular amputation is also present: 170.6, 170.7, 170.8, 170.9, 171.3, 172.7, 173.7, 198.5, 344.1, 711.0, 728.86, 733.2, 736.3×, 736.4×, 736.5, 736.6, 736.7×, 736.8×, 736.9, 735. ×, 754.3×,754.4×,754.5×,754.6×,754.7×,755.02, 755.13, 755.14, 755.3, 755.4, 755.6×, 755.8, 759.7, 759.89, 820.××, 821.××, 822.××, 823.××, 824.××, 825.××, 826.××, 827.××, 828.××, 829.××, 835.××, 836. ××, 837.××, 838.××, 890. ××, 891, 895.××, 896.××, 897.××, 904.××, 905.4, 928.××, 929.××,959.6, 959.7,996.4×, 996.66, 996.67, 996.77, 996.78.

In identifying PAD events, occurrences of non-atherosclerotic causes of PAD should be excluded. That exclusion requires at least two occurrences of the following ICD-9-CM codes: 747.22, 237.7, 443.1, 446.0, 446.4, 446.5, 446.6, 446.7, 447.6, 710.1, 747.1, 747.64.

Validation Study:

Table: Agreement between ICD-9 codes and reviewer classification to identify hospitalized PAD

	Adjudicated Event		
ARIC ICD-9 Code	Yes	No	Row sum
Yes	a	b	r_1
No	c	d	r_2
Column sum	c_1	c_2	N

Formula Sensitivity $= \frac{a}{c_1}$ Formula: Specificity $= \frac{d}{c_2}$

Formula: Positive predictive value $= \frac{a}{r_1}$ Formula: Negative predictive value $= \frac{d}{r_2}$

Concordance Study:

Table: Agreement between CMS outpatient claims and ARIC Cohort outpatient events

	CMS Claim		
ARIC Questionnaire	Yes	No	Row sum
Yes	a	b	r_1
No	c	d	r_2
Column sum	c_1	c_2	N

Formula: Kappa (K) $= \frac{p_0 - p_e}{1 - p_e}$ Where: $p_0 = (a+d)/N$

$p_e = ((a+c)(a+b) + (b+d)(c+d))/N^2$

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