ARIC Manuscript Proposal #2296

PC Reviewed: 1/14/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Temporal patterns associated with PAD-related encounters in both inpatient and outpatient settings

b. Abbreviated Title (Length 26 characters): Temporal PAD care patterns

2. Writing Group:
Writing group members: Corey Kalbaugh, MS, MA, Laura Loehr, MD, PhD, Gerardo Heiss, MD, PhD, Lisa Wruck, PhD, Lindsay Bengtson, PhD, Kunihiro Matsushita, MD, PhD, Anna Kucharska-Newton, 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 December 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, where the highest prevalence is expected [1]. Common PAD manifestations, intermittent claudication (pain with exercise) and critical limb ischemia (a limb- and life-threatening stage of PAD represented as rest pain or tissue loss, can result in significant physical disability [2]. The prevalence of claudication and critical limb ischemia is expected to rise as the population ages [3]. All forms of PAD are 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 [5, 6].

The majority of research on PAD-related care examines the course of the disease pertaining to inpatient care. However, a study by Hirsch et al (2008) found that only 6.4% (n=668) of those with PAD had an inpatient claim with a PAD-related diagnostic code, suggesting that more than 90% of care occurs in the outpatient setting [4]. Additional evidence is confirming that a significant proportion of the initial diagnoses and subsequent care now likely occurs in the outpatient setting [5, 7]. A study that includes outpatient encounters will allow us to examine the clinical course (i.e. temporal patterns) of PAD as it relates to <u>both</u> inpatient and outpatient care, an area of research that is missing in the existing literature.

The proposed analyses will, therefore, provide a longitudinal assessment of the temporal patterns associated with PAD-related encounters using administrative claims. Administrative claims allow characterization of the clinical course of PAD, including hospitalizations and outpatient care, from the first diagnosis thru the entire clinical course. The proposed research will also evaluate patient demographic factors associated with different patterns of PAD-related care. 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 [8].

5. Main Hypothesis/Study Questions:

Specific Aim 1: Estimate the temporal patterns associated with PAD-related encounters, according to the setting of initial encounter, among CMS Medicare Fee-for-Service beneficiaries residing in the Atherosclerosis Risk in Communities (ARIC) Study geographic regions.

Aim 1.1 Estimate monthly rates of PAD-related outpatient encounters and PAD-related inpatient encounters following an initial <u>outpatient</u> encounter.

Aim 1.2 Estimate monthly rates of PAD-related outpatient encounters and PAD-related inpatient encounters following an initial inpatient encounter.

Aim 1.3 Adjust estimated monthly rates of PAD-related encounters, using comparability ratios derived in ARIC MS #2260 ("The burden of peripheral artery disease: linkage of Medicare claims with the ARIC study", lead author: Kalbaugh).

Aim 1.4 Estimate time to PAD-related events: recurrent outpatient encounter, initial hospitalization, and revascularization following an initial outpatient encounter.

Aim 1.5 Estimate time to PAD-related events: first outpatient encounter, re-hospitalization, and revascularization following an initial inpatient encounter.

All analyses will be conducted overall and by age categories, race, gender, and race-gender subgroups.

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/Population: The CMS Medicare data available from 2003-2012 for residents of the four geographically defined areas of the ARIC Study: Washington County, Maryland (MD), Forsyth County, North Carolina (NC), the city of Jackson, Mississippi (MS), and the suburb cities of Minneapolis, Minnesota (MN).

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; 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. Beneficiaries must also remain in FFS for the duration of our observation period (2003-2012).

Individuals must be enrolled in Medicare FFS continuously for at least one year without a PAD diagnostic code prior to becoming eligible for the assessment of PAD events. 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, the initial event date will be the inpatient discharge date.

Estimates obtained from the 2000 US Census, indicate that nearly 450,000 individuals reside in the four ARIC regions, including approximately 103,000 individuals 65 years of age and older. Census data indicate that 57% of the ARIC population is female and 16% is black. Based on estimates of the penetrance of the Medicare Advantage program in the ARIC regions obtained from the ARIC cohort, approximately 40% (n=41,000) of individuals are estimated to be Medicare Advantage enrollees who will be excluded from our study. The remaining 60% (62,000) are Medicare beneficiaries with only fee-for-service coverage ages 65 years and older. Only these individuals are eligible for inclusion in the proposed study.

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

Outcomes: PAD occurrence in the outpatient setting will be identified using the annual Carrier (Part B) and Outpatient files for the years 2003-2012. Evaluation and Management (E&M) codes, from Carrier (Part B) files, used to identify outpatient encounters are shown below in Table 1. From these outpatient encounters, a PAD-related ICD-9 code (Appendix 1) listed in any position will qualify as a PAD-related outpatient encounter.

Table 1: E&M codes for identification of outpatient encounters

ENCOUNTER TYPE	**CODE**
AMBULATORY CARE VISITS	
New office visit	99201-99205
Established office visit	99211-9215
Consultation	99241-99245
New preventive medicine visit	99385-99387
Established preventive medicine visit	99395-99397

Outpatient events can also be identified from the annual Outpatient files, which capture events occurring in the Federally Qualified Health Centers. Revenue Center codes 521 and 522 will be used to identify outpatient events.

PAD-related hospitalizations will be identified from CMS Medicare MedPAR files for years 2003-2012 using ICD-9 and CPT-4 codes based on the Mayo Clinic Algorithm, as shown in Appendix 1. Codes in the first position or in any position on the claim will be evaluated. A look-back period of at least 365 days will be used to establish the initial PAD occurrence. A sensitivity analysis will be conducted to determine the optimum look-back period.

Statistical Analyses:

Event rates

The rates of PAD-related care will be estimated using Poisson regression analysis. The denominator for our analyses will be estimated as person-months in fee-for-service

enrollment, incorporated into models using an offset term. Analyses will be calculated overall and in age, gender, race, and race-gender strata. Age will be categorized as follows: 65-74 years, 75-84 years, 85 years and older. We will evaluate Poisson models for overdispersion and use negative binomial regression if needed.

Time-to-Event

Time to events (first hospitalization, re-hospitalization, first outpatient visit, and first procedures) will be calculated from the date of the initial PAD diagnosis and will be examined by the setting of initial diagnosis (inpatient v outpatient). Events will be censored at the end of follow-up, as determined by enrollment in Medicare Advantage or at December 31st, 2012 (end of our observation period). Analyses will account for the competing risk of death. Patient death and death dates can be obtained from the Master Beneficiary Summary File. Multivariable Cox proportional hazards models will model hazard ratios to make comparisons between age, race, gender, and race-gender subgroups. For the purposes of our study age 65-74 will be the referent group for age, whites will be the referent group for race, males will be the referent group for gender, and white males will be the referent group for race-gender subgroups.

Adjustment of Estimates: Comparability ratios, obtained separately for hospitalizations and outpatient events, will be used as a calibration factor to adjust rates (as described in MS #2260-Kalbaugh). Comparability ratios are multiplied directly to unadjusted estimates as has been previously described in the ARIC population in relation to acute myocardial infarction [9]. Calculations are shown in Appendix 2.

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. It is also possible, given our choice of denominators (person-months in fee-for-service enrollment), that an individual will have PAD-related encounters in the months after they are no longer enrolled continuously in fee-for-service. Those encounters will not be captured. However, prior research shows that approximately 83% of people with FFS have continuous coverage. 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 # 2260: The burden of peripheral artery disease: linkage of Medicare claims with the ARIC study (Kalbaugh)

MS #2253: Linked measures of Outpatient and Inpatient Heart Failure (Heiss)

MS #2257: Patterns of healthcare utilization following an initial diagnosis of heart failure. The Atherosclerosis Risk in Communities (ARIC) Study (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.

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4. Hirsch, A.T., et al., *National health care costs of peripheral arterial disease in the Medicare population.* Vasc Med, 2008. **13**(3): p. 209-15.
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7. Taylor, S.M., et al., *Comparison of interventional outcomes according to preoperative indication: a single center analysis of 2,240 limb revascularizations.* J Am Coll Surg, 2009. **208**(5): p. 770-8; discussion 778-80.
8. Investigators, T.A., *The Atherosclerosis Risk in Communities (ARIC) Study: Design and Objectives.* American Journal of Epidemiology, 1989. **129**(4): p. 687-702.
9. Rosamond, W.D., et al., *Trends in the sensitivity, positive predictive value, false-positive rate, and comparability ratio of hospital discharge diagnosis codes for acute myocardial infarction in four US communities, 1987-2000.* American Journal of Epidemiology, 2004. **160**(12): p. 1137-1146.

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.

Appendix 2: Comparability Ratio calculations

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

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.