ARIC Manuscript Proposal #3920

PC Reviewed: 9/14/2021 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Burden and prognosis of diabetic foot infection: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Burden and prognosis of diabetic foot infection

2. Writing Group:
Writing group members: Michael Fang, Jiaqi Hu, Elizabeth Selvin, Kunihiro Matsushita, Caitlin Hicks

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

First author: Michael Fang
Address: 2024 E Monument Street, Baltimore, MD 21205
Phone: (410) 955-4156
Fax:
E-mail: mfang9@jh.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: Elizabeth Selvin
Address: 2024 E Monument Street, Baltimore, MD 21205
Phone: (410) 955-4156
E-mail: eselvin@jhu.edu

3. Timeline:

- Data cleaning and analysis: ~Aug-Sept 2021
- Manuscript drafting: ~Sept-Nov, 2021
- Manuscript revisions: ~Nov-Jan 2022
- Manuscript submission to ARIC: ~Feb 2022

4. Rationale:

Foot infections occur frequently among people with diabetes and significantly elevate the risk of lower-extremity amputations. The incidence of lower-extremity amputations among US adults with diabetes has experienced a dramatic resurgence, declining by 43% from 2000 to 2009 before increasing by 50% from 2009 to 2015.[1] Characterizing the burden of diabetic foot

infection (DFI) can enhance the prevention and management of foot complications, which may reduce rates of amputations at a population-level.

It is widely believed that 15-25% of people with diabetes will develop at least one foot infection during their lifetime.[2] However, these estimates are derived from older, retrospective studies of clinical populations. Contemporary estimates based on prospective data from the general population are lacking, and little is known about which populations have the highest risk of DFI.

The long-term consequences of DFI are also not well understood. Along with amputations, emerging evidence suggests DFI may be associated with an increased risk of other complications, including cardiovascular disease, mortality, and falls.[3-5] However, existing studies are based on small clinical samples with short follow-up and limited adjustment for confounding. As a result, it is unclear whether this association reflects a "causal" relationship or whether DFI is simply a marker of poor underlying health.

Drawing on over two decades of data from a large community-based study, our objectives were to (1) characterize the burden of and risk factors for DFI; and (2) assess the subsequent risk of cardiovascular disease and mortality following the onset of DFI.

5. Main Hypothesis/Study Questions:

Research question 1: What is the burden of and risk factors for DFI in older adults?

- Hypothesis: We hypothesize that the burden of DFI will be substantial, particularly among participants who are older, low socioeconomic status (SES), or Black and those with a long duration of diabetes and poor glycemic control.

Research question 2: What is the association between incident DFI and risk of cardiovascular disease and mortality?

- Hypothesis: We hypothesize DFI will be independently associated with an increased risk for cardiovascular disease and mortality.

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: For research question 1, we will characterize the crude rate and 5-, 10-, 15-, and 20-year cumulative incidence of DFI, overall and by key demographic (age, sex, race, SES) and clinical characteristics (duration of diabetes, glycemic control). We will also examine the burden of different types of DFI (e.g., infection with or without wound). We will estimate Cox regression models to examine the association between traditional and novel risk factors with DFI. Our analyses will progress from minimally adjusted (demographics only) to fully adjusted models (demographics + cardiometabolic risk factors + health behaviors + SES and health care utilization).

For research question 2, we will estimate Cox regression models to assess the association between incident DFI and subsequent risk of cardiovascular disease and mortality. Our analyses will similarly progress from minimally adjusted to fully adjusted models. For all analyses, we will examine effect modification by race, age, and sex, respectively.

We will conduct several sensitivity analyses. First, we will reconduct all analyses using only participants who were using Medicare fee-for-service (FFS, Part B). As we note in the limitations, one issue is that some participants may using health plans other than Medicare FFS and thus may not be captured in Medicare claims data. Second, we will compare baseline characteristics for participants using Medicare FFS with those using other health plans.

Inclusion/Exclusion: We will include all participants at ARIC visit 4 with (1) diabetes (self-reported diagnosis, use of glucose lower medication, or a fasting glucose ≥126 mg/dl); (2) no history of DFI; and (3) no missing information on key covariates. For analyses of incident cardiovascular events, we will exclude participants with prevalent cardiovascular disease in the main analyses. In sensitivity analyses, we re-run our analyses with these participants included.

Outcomes: The main outcome for research question 1 is incident DFI. Consistent with prior research,[6] this event will be captured using ICD-9/10 codes in the primary diagnostic position from hospital discharge records collected from active ARIC study surveillance and hospitalizations, emergency department visits, and ambulance use from Medicare claims. A complete list of the ICD codes used to define this measure used are shown in Table 1. Data sources used to identify DFI are available until December 31, 2018.

Inpatient and outpatient claims were available for participants aged 65 or older using Medicare FFS. For participants enrolled in Medicare but not using FFS (i.e., Medicare Part C), inpatient claims were available after 2008. Because most DFIs are addressed in outpatient settings, we would significantly underestimate the burden of DFI without analyzing Medicare claims. Further, these data substantially increase our statistical power, enabling us to examine the association between DFI and different complications.

For research question 2, the primary outcomes are incident cardiovascular disease (any and different subtypes) and mortality (all-cause and cause-specific). Incident coronary heart disease will be defined as fatal and non-fatal coronary heart disease, definite or probable myocardial infraction, and silent myocardial infraction. Incident stroke will be defined as definite or probable ischemic or hemorrhagic stroke. Both coronary heart disease and stroke events were adjudicated by an expert panel. Heart failure was identified from ICD-9 codes (428) from hospitalization discharge records from 1988-2004, and by adjudication thereafter. Any cardiovascular disease will be defined as coronary heart disease, stroke or heart failure.

All-cause mortality will be determined through linkage to the National Death Index, phone interviews with participant proxies, and review of state records. Cause-specific mortality (cardiovascular, cancer, and infection mortality) will be identified using ICD-9/10 codes listed as the underlying cause of death in death certificates.

We will also consider two secondary outcomes as part of research question 2. The first is non traumatic lower-limb amputations (any amputation, major amputation, minor amputation), and

the second is falls (any fall, hospitalized fall, and fall with fracture). These events will be identified using ARIC hospitalization and CMS claims data.

Exposure: For research question 1, we will examine the following risk factors:

- Age, sex, race
- Household income (>$50,000; $25,000-$49,999; $12,000-$24,999; <$12,000)
- Education (graduate/professional school; college with or without completion; high school/GED/vocational school; <high school)
- Area deprivation index (quartiles)
- SES (composite measure based on household income, education, and area deprivation index)
- Health insurance type
- Health care utilization (access to routine care; frequency of care)
- Duration of diabetes
- Glycemic control (tertiles of fructosamine because HbA1c not available at visit 4)
- Peripheral artery disease based on ABI≤0.9
- Retinopathy based on fundus photography in visit 3
- Prevalent CVD
- Hypertension (>140/90 mm Hg or use of medication)
- Lipids (tertiles of HDL, LDL, triglycerides)
- Inflammation (CRP >3 mg/L)
- Obesity status
- Smoking and drinking
- Cognitive status (global cognitive z-score)
- Troponin I and T
- Elevated albuminuria (ACR>30)
- Reduced kidney function (eGFR<60)

For research question 2, the main exposure will be DFI, which will we treat as a time-varying measure. The defintion of DFI is described above.

Covariates: Our analyses will adjust for demographics (age, sex, race-center), health behaviors (alcohol consumption, smoking), cardiometabolic measures (body-mass index, hypertension status, HDL and LDL cholesterol levels, glycemic control) and SES and health care utilization.

Challenges/limitations: (1) Unmeasured confounding: Because this is an observational study, one of the main issues is unmeasured differences in those who do versus do not develop DFI.

(2) Measurement of DFI: Because DFI is measured from hospitalization discharge records and claims data, less severe cases will likely be missed. There may also be misclassification, as events were based on ICD codes and not adjudicated.

(3) Differences in Medicare eligibility and utilization: Medicare claims data may not fully capture DFI in the study population because (1) some participants were under age 65 at baseline

(visit 4) and thus were ineligible for Medicare during some portion of the follow up; and (2) some participants aged ≥65 elected to use other health plans (e.g., HMOs) rather than Medicare FFS. For research question 1, missing these events likely means we will understate the true burden of DFI. For research question 2, it is unclear how these issues may affect the true association between DFI and cardiovascular disease and mortality.

As we note above, we will reconduct all analyses only including participants who were enrolled in Medicare FFS. We will also compare baseline characteristics for all participants over age 65 at baseline that did versus did not use Medicare FFS. Consistent with prior ARIC analyses, we do not expect to find major between the two groups.

(4) Race/geography: Our analyses will examine differences in DFI risk between Black and White participants. However, racial differences are confounded by study sites, as only Forsyth recruited both Black and White participants. Thus, we cannot determine whether any differences are related to race or region. We also will not assess for racial differences beyond Black/White.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes X 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 X 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/aric/mantrack/maintain/search/dtSearch.html

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 3215: Traditional and Novel Risk Factors for Peripheral Neuropathy in the ARIC Study

MS 3531: Lifetime risk estimate and prognostic impact of nontraumatic lower-extremity amputation

Both papers examine risk factors for related but different lower-extremity outcomes. Additionally, the first and senior author of MS3215 and the senior author of M3531 are collaborators for our current paper.

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* _____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2009.16**)**

*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.

References

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2. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005;293(2):217-228.
3. Dietrich I, Braga GA, de Melo FG, da Costa Silva ACC. The diabetic foot as a proxy for cardiovascular events and mortality review. Current atherosclerosis reports 2017;19(11):1-5.
4. Saluja S, Anderson S, Hambleton I, et al. Foot ulceration and its association with mortality in diabetes mellitus: a meta-analysis. Diabetic Medicine 2020;37(2):211-218.
5. Wallace C, Reiber GE, LeMaster J, et al. Incidence of falls, risk factors for falls, and fall-related fractures in individuals with diabetes and a prior foot ulcer. Diabetes Care 2002;25(11):1983-1986.
6. Fincke BG, Miller DR, Turpin R. A classification of diabetic foot infections using ICD-9-CM codes: application to a large computerized medical database. BMC Health Services Research 2010;10(1):1-9.

Table 1: List of ICD-9/10 codes used to define DFI

	ICD-9 codes	ICD-10 codes
Any diabetic foot infection	040.0	A480
	440.23	E0852
	440.24	E0952
	680.7	E1052
	682.7	E1152
	681.1	E1352
	681.10	I70233
	681.11	I70234
	707.13	I70235
	707.14	I70238
	707.15	I70239
	730.07	I70243
	730.17	I70244
	730.27	I70245
	730.97	I70248
	785.4	I70249
		I70261
		I70262
		I70263
		I70269
		I70333
		I70334
		I70335
		I70343
		I70344
		I70345
		I70361
		I70362
		I70363
		I70369
		I70433
		I70434
		I70435
		I70443
		I70444
		I70445
		I70461
		I70462
		I70463
		I70469
		I70533
		I70534
		I70535
		I70543
		I70544
		I70545

		I70561 I70562 I70563 I70569 I70633 I70634 I70635 I70643 I70644 I70645 I70661 I70662 I70663 I70669 I70733 I70734 I70735 I70743 I70744 I70745 I70761 I70762 I70763 I70769 I96 L02611 L02612 L02619 L02621 L02622 L02629 L02631 L02632 L02639 L03031 L03032 L03039 L03041 L03042 L03049 L97301 L97302 L97303 L97304 L97309 L97311 L97312 L97313

		L97314 L97319 L97321 L97322 L97323 L97324 L97329 L97401 L97402 L97403 L97404 L97409 L97411 L97412 L97413 L97414 L97419 L97421 L97422 L97423 L97424 L97429 L97501 L97502 L97503 L97504 L97509 L97511 L97512 L97513 L97514 L97519 L97521 L97522 L97523 L97524 L97529 M86071 M86072 M86079 M86171 M86172 M86179 M86271 M86272 M86279 M86371 M86372

		M86379 M86471 M86472 M86479 M86571 M86572 M86579 M86671 M86672 M86679 M868X7