ARIC Manuscript Proposal #1949

PC Reviewed: 5/29/12   Status: **A**   Priority: **2**
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: Validation of inter-visit kidney events

 b. Abbreviated Title (Length 26 characters): Kidney event validation

2. Writing Group:
     Writing group members: Morgan Grams, Josef Coresh, W.H. Linda Kao, Brad Astor. Others are welcome to join.

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

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3. Timeline: Data analysis to start after approval of this manuscript proposal, preliminary abstract available by June 2012, first draft available by December 2012.

4. Rationale:

Kidney disease is an increasingly common condition in the United States.[1] Both reduced glomerular filtration rate (GFR) and albuminuria are independently and continuously associated with poor outcomes such as cardiovascular disease and death,[2-4] and the Atherosclerosis Risk in Communities (ARIC) cohort has provided valuable evidence for these associations. To date, however, only a subset of the kidney disease events in ARIC has been rigorously measured – namely, those defined at study visits, when kidney function was assessed using laboratory data. By incorporating intervening (inter-visit) kidney disease events, we improve estimation in time-to-event analyses, capture outcomes among participants who do not attend subsequent follow-up visits, and retrieve information on acute kidney injury, an often transient but potent predictor for adverse future outcomes. Inter-visit kidney events (including acute kidney injury, chronic kidney disease, and end stage renal disease) are captured through hospitalization discharge ICD-9-CM codes, and they have not been adjudicated. Thus, the validity of ICD-9-CM-identified kidney hospitalizations (which comprise the majority of kidney events in the cohort) is not known.

5. Main Hypothesis/Study Questions:

Aim 1: To estimate the sensitivity and specificity of three overlapping categories of kidney disease-related ICD-9-CM codes compared with a gold standard of physician adjudication in a large population-based cohort using sampling weights.
Hypothesis 1: Sensitivity and specificity varies based on severity of disease. The presence of more than one kidney disease code improves sensitivity.

Aim 2: To differentiate between the development of kidney failure as an acute injury event and that as a result of chronic kidney disease progression; to further classify kidney failure as a permanent or transient occurrence.
Hypothesis 2: Half the incidence of kidney failure occurs after an acute insult.

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).

Methodological challenges:
Since ARIC visit 4, there have been 34,140 hospitalizations among surviving participants. Reviewing all hospitalizations to ascertain the validity of kidney disease events is not feasible. By ICD-9-CM-coded type of hospitalization, there were 1,375 hospitalizations for acute kidney injury (AKI), 4,777 hospitalizations for chronic kidney disease (CKD), and 1,354 for end stage renal disease (ESRD); however, there is

Table 1: Overlap among kidney hospitalizations

	single code	+ CKD or ESRD	+both
AKI	669	621	85
CKD	3015	1677	
ESRD	137		

substantial overlap by category (Table 1), with 5,621 ICD-9-CM-coded kidney disease events overall. The remaining hospitalizations include 15,247 with cardiovascular disease codes, and 13,272 with non-cardiovascular codes.

Sampling Frame
In order to validate ICD-9-identified events, we will sample from the pool of hospitalizations among ARIC participants from 1996 (the last study visit) to 2009. Records were randomly selected (using a random number generator function) without replacement from nine ICD-9-CM hospitalization code-classified strata, oversampling from hospitalizations including kidney disease ICD-9-CM codes. The nine mutually exclusive ICD-9-CM identified strata are: 1) AKI code only, 2) AKI and CKD codes only, 3) AKI and ESRD code only, 4) AKI, CKD, and ESRD codes, 5) CKD code only, 6) CKD and ESRD codes only, 7) ESRD code only, 8) cardiovascular diagnosis but no kidney code, and 9) no kidney or cardiovascular code. Stratum 8 and 9 are separate because a priori we believe the probability of finding a false negative in strata 8 to be much higher than that in strata 9.

Event Adjudication
All inpatient blood work, as well as the admission note, nephrology consultation (if performed), and discharge summary for each of the selected hospitalizations will be retrieved and adjudicated by two independent, blinded physicians. Adjudication will proceed according to a standardized algorithm as to whether it contains an AKI event, a CKD diagnosis, or an ESRD diagnosis. There will be possible overlap between the three kidney events. (In other words, a CKD patient could undergo AKI and then progress to ESRD in a hospitalization.) The following outcomes definitions will be used: **CKD**, chart mention or, if creatinine available, eGFR $\leq$ 30 (CKD Stage 4+) or $\leq$ 60 ml/min/ 1.73m^2 (CKD Stage 3+) by the CKD-Epi equation; **AKI**, chart mention or, if creatinine available, 50% increase in baseline creatinine with or without requirement for RRT; **ESRD**, renal replacement therapy requirement at admission and/or discharge, or death from kidney disease stemming from chronic progression of kidney disease (admission kidney function at CKD Stage 3 or worse). Sensitivity to alternative definitions will be examined.

Analysis plan
For each type of adjudicated event, we will estimate the total number of events in each of the nine strata by scaling by the inverse probability of being selected (1/number sampled/number in strata). Sample weights used in the pilot study are shown in Table 2. Depending on the strata, we will classify events and non-events by whether they have a corresponding ICD-9-CM-code. For example, for adjudicated AKI:

Table 2: Sample weights used in pilot study			
Strata	Strata Description	N, pilot	Weight
1	AKI only	12	55.8
2	AKI + CKD	17	34.3
3	AKI-D	6	6.3
4	AKI-D + CKD	11	7.6
5	CKD only	27	111.7
6	CKD + dialysis	42	25.9
7	Dialysis only	16	8.6
8	CVD only	30	508.2
9	No CVD, no kidney	30	442.4

ICD-9-CM-identified AKI-containing strata (1-4):
     total (weighted) events = A
     total (weighted) non-events = B
All other strata (5-9):
     total (weighted) events = C
     total (weighted) non-events = D
This will allow calculation of the sensitivity (A/(A+C))
and specificity (D/(D+B)) (Table 3).

Table 3: Validation example

	True AKI	No AKI
AKI code	A	B
No AKI code	C	D

We will also look at patient-, hospital-, ancd center-level factors associated with misclassification (e.g., false positives and false negatives).

Limitations
Older medical records may be more difficult to obtain, and the validity of ICD-9-CM codes for kidney disease events may vary based on year of hospitalization. For example, definitions of CKD and AKI have evolved over time, and historical physician-documented CKD or AKI may not match 2012 laboratory data-based definitions. We will perform subgroup analysis by time period to investigate this potential bias.

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 ICTDER03 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)?

Any proposal evaluating kidney disease as an outcome or predictor is related to this proposal and will stand to benefit from improved ascertainment of kidney disease.

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
   __x_   A. primarily the result of an ancillary study (list number* _ 2012.13_)
   ___   B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*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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2. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT: Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: A collaborative meta-analysis. *Lancet* 375: 2073-81, 2010
3. Grams ME, Astor BC, Bash LD, Matsushita K, Wang Y, Coresh J: Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. *J Am Soc Nephrol* 21: 1757-1764, 2010
4. Astor BC, Matsushita K, Gansevoort RT, van der Velde M, Woodward M, Levey AS, Jong PE, Coresh J, de Jong PE, El-Nahas M, Eckardt KU, Kasiske BL, Wright J, Appel L, Greene T, Levin A, Djurdjev O, Wheeler DC, Landray MJ, Townend JN, Emberson J, Clark LE, Macleod A, Marks A, Ali T, Fluck N, Prescott G, Smith DH, Weinstein JR, Johnson ES, Thorp ML, Wetzels JF, Blankestijn PJ, van Zuilen AD, Menon V, Sarnak M, Beck G, Kronenberg F, Kollerits B, Froissart M, Stengel B, Metzger M, Remuzzi G, Ruggenenti P, Perna A, Heerspink HJ, Brenner B, de Zeeuw D, Rossing P, Parving HH, Auguste P, Veldhuis K, Wang Y, Camarata L, Thomas B, Manley T: Lower estimated glomerular

filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int* 2011