ARIC Manuscript Proposal #2253

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1.a. Full Title:

b. Abbreviated Title (Length 26 characters): Inpatient and Outpatient HF

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __GH__

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3. Timeline: Analysis to begin upon approval. Complete the manuscript within eight months of approval by ARIC.

4. Rationale and Overview The goal of this proposal is to derive estimates of the rates of linked outpatient (OP) and inpatient (IP) heart failure events. We build on the methods developed in ARIC that identify first hospitalizations classified as ADHF per ARIC criteria, to then identify the HF-related outpatient encounters preceding and following the sentinel event during a pre-establish observation period. To fully characterize burden of clinically manifest HF during the observation period we further consider readmissions for HF and deaths following a first hospitalization for HF.

Included in this proposal is a sequence of analytic steps that draws on ARIC heart failure classification methods, on ARIC Surveillance data, and on CMS-Medicare datasets for the ARIC Surveillance communities to estimate (a) monthly rates of OP HF medical care visits up to 365 days

prior to a first hospitalized ADHF; (b) monthly rates of OP HF medical care visits up to 365 days following a first hospitalized ADHF; (c) monthly rates of readmissions up to 365 days following a first hospitalized ADHF; (d) monthly case fatality up to 365 days following a first hospitalized ADHF; and (e) annual rates of the OP and IP HF events by age, sex and race, adjusted for case fatality. Details are provided in the section on analyses.

We propose to apply these estimates to two population frames, the first of which is the set of geographically defined populations under epidemiologic surveillance by the ARIC Study. Annual rates of ADHF derived by ARIC will be supplemented with the above OP and readmission estimates to derive annual rates of OP+IP HF by age, sex and race (adjusted for case fatality) for the geographic areas under surveillance by ARIC. These statistics are seen as a complement to the annual event rates and trends prepared by ARIC Surveillance according to its standardized protocol.

A second step will apply the above OP and HF hospitalization estimates to the U.S. population aged 65 years and older who were hospitalized for ADHF during 2005-2010, based on the National Inpatient Sample (NIS) of hospital discharges from the US. HF hospitalizations will be calibrated to ADHF per ARIC Surveillance criteria as derived in ARIC Ms#1996 (Agarwal SK et al.) by demographic categories, ICD-9 discharge code, the position of the ICD-9 code, type of hospital and calendar year. After adjusting for multiplicities to account for hospital readmissions and for case fatality, ADHF hospitalizations will be multiplied by the demographic stratum-specific annual HF-related OP encounters calculated from the CMS-Medicare data, to estimate rates of HF occurrence that combine inpatient and outpatient manifestations of HF.

5. Main Study Questions

(a) Using CMS Medicare data for the ARIC Study communities, estimate calibration factors for the assessment of the occurrence of heart failure in the outpatient setting.

   i. Estimate the probability that the first HF hospitalization observed in any given calendar year constitutes the first-ever (incident) HF hospitalization. These estimates will be provided for age, race, and gender groups as well as *a priori* identified algorithms of HF discharge codes.

   ii. Estimate monthly rates of outpatient encounters coded as heart failure / heart failure-related symptoms or signs occurring within 365 days prior to a first hospitalized heart failure event, by patient demographics.

   iii. Estimate monthly rates of outpatient encounters coded as heart failure / heart failure-related symptoms or signs occurring during the 365 days following a first hospitalized heart failure event, by patient demographics.

(b) Using the ARIC CMS Medicare data and ARIC cohort heart failure surveillance data, estimate the annual rate of heart failure hospitalizations following the incident heart failure-related hospitalization.

(c) Estimate the monthly case fatality up to 365 days following a first hospitalized heart failure event, by patient demographics.
(d) Estimate the annual rate of heart failure-related outpatient encounters occurring prior to and following the first heart failure hospitalization in the ARIC (geographic) study areas, by calendar year and patient demographics.

(e) Estimate the annual rates of first heart failure hospitalization, of readmissions and of case fatality in the Nationwide Inpatient Sample (NIS) of yearly hospital discharges, by calendar year and patient demographics.

(f) Adjust the estimated annual rates of first heart failure hospitalization in the NIS to acute decompensated heart failure (ADHF) events, using calibration factors derived in ARIC MS#1996.

(g) Estimate the annual rate of heart failure-related outpatient encounters occurring prior to and following a first heart failure hospitalization defined as ADHF in the NIS, by calendar year and patient demographics.

(h) Estimate the annual rate of inpatient and outpatient heart failure-related medical events in the NIS, by calendar year and patient demographics.

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 methodological limitations or challenges if present).

Study design

The CMS Medicare data for the ARIC Surveillance geographic areas will be used, recognizing the limitation of the non-ignorable Medicare Advantage coverage in three of those areas and the subset of Zip codes used to define the CMS data for ARIC areas that straddle the boundaries of the ARIC surveillance areas. Since any rate estimates for these areas use denominators appropriate to the zip-code-defined areas, the rates will be valid, but will be for slightly larger areas than the ARIC surveillance areas.

Confirmation of the estimated annual proportions of outpatient heart failure events relative to first HF hospitalizations will be obtained from the University of North Carolina Healthcare System, an integrated healthcare system of the UNC-Chapel Hill Hospital and affiliated with it clinics, and from a national sample of CMS-Medicare claims data. We will seek similar information from Kaiser Permanente, a managed care consortium affiliated with the Cardiovascular Research Network (CVRN). Both the UNC healthcare data and the CVRN data lack a population denominator. Estimates from those sources will therefore be used only as corroboration of estimates from the CMS Medicare data.

Study population

For estimates of heart failure-related outpatient encounters we will use CMS Medicare data available for the ARIC Surveillance areas for the years 2003-2012, provided as part of the NHLBI-CMS Medicare Interagency Agreement. The first hospitalized HF event will be defined as a HF hospitalization with no prior HF hospitalizations occurring in the preceding 365 days. Participation in fee-for service Medicare for at least 365 days prior to the first HF hospitalization and continuous fee-for-service Medicare enrollment following the first HF hospitalization will be a requirement for the assessment of inpatient and outpatient events prior to and following that hospitalization. Use of CMS Medicare data from beneficiaries with partial-year Medicare enrollment eligibility could lead to biased estimates of prior rates, as rates of HF events in the 365 days prior to the index event are not expected to be uniform over time. Since we will also estimate time dependent rates, specifically, rates in each of the 12 months prior to the index event, an alternative analysis may allow use of index events with less than a full prior 365 days of non-Advantage Medicare eligibility.

In the analysis of in-patient or outpatient HF events occurring in the 365 days after index event, similar exclusion issues arise as with prior-year analysis, with additional consideration of death within the 365 days. Since no HF events after death can occur, for the estimation of annual HF health care burden after a first HF hospitalization there is no reason to exclude index events among those who die within 365 days.

Variables of interest

Heart failure-related hospitalizations will be identified from CMS Medicare MedPAR files available for the years 2003-2012 on the basis of ICD-9-CM code 428.x located in first position and in any position on the claim. The first occurrence of ICD-9-CM code 428.x in annual MedPAR files will be considered as the first inpatient heart failure diagnosis. A “look-back” period of 365 days will be used to ascertain lack of HF-related hospitalizations in the year preceding the observation year.

Occurrence of heart failure in the outpatient setting will be ascertained from annual Carrier (Part B) and Outpatient files for the years 2000-20012. Outpatient claims representing outpatient healthcare encounters will be identified from the Carrier (Part B) files using the following Evaluation and Management (E&M) codes:

Table 1. E&M codes for the identification of outpatient events

E&M code	Code explanation
99201 - 99205	New office visit
99211 - 99215	Established office visit
99241 - 99245	Consultation
99385 - 99387	New preventive medicine visit
99395 - 99397	Established preventive medicine visit
99441 - 99444	Telephone and online physician services

Additionally, outpatient events occurring in Federally Qualified Health Centers will be identified from annual Outpatient files using Revenue Center codes 521 and 522.

Heart failure events occurring in the outpatient setting will be identified on the basis of the presence of ICD-9-CM code 428.x in any position in the selected outpatient claims. Additionally, outpatient encounters with a record of the following symptoms of heart failure: acute lung edema ICD-9-CM: 518.4), dyspnea (ICD-9-CM: 786.0x) and fatigue (ICD-9-CM: 780.79) will be identified.

Frequency of outpatient visits with ICD-9 codes reflecting presence of heart failure symptoms, without the presence of heart-failure specific ICD-9 codes, will be assessed as part of the accompanying proposal on patterns on healthcare utilization in heart failure. Subsequent sensitivity analyses will evaluate the rate of outpatient HF encounters with consideration of outpatient visits for heart failure symptoms without the presence of ICD-9 code 428.xx.

Statistical Analyses:

Event rates

Event rates will be calculated for demographically defined groups (race, gender, age-group categories) and by calendar year as number of events in a sub-group for a given calendar year of the event type of interest divided by the total available fee-for-service Medicare observation time for that sub-group for the given calendar year. The following age categories will be considered in the analyses: 65-74 years; 75-84 years; 85 years and older. Age-adjusted rates will also be presented, adjusted by Poisson regression.

For the analyses in part (a) above, the analyses for any given calendar year will be limited to only those persons with a first hospitalized HF event in that year. Additional exclusions were discussed above. Poisson regression will be used to estimate the desired event rates, overall for the year, and for each of the 12 months prior to and following the index event, since this likely varies by time from index event, and to explore the variation in these rates by the factors considered.

Estimation of the national burden of heart failure

In concordance with methods used in ARIC MS# 1996, we plan to estimate the national overall burden of inpatient and outpatient heart failure using data on HF hospitalizations from the Nationwide Inpatient Sample (NIS). The NIS is a database of discharge data from 1,045 hospitals currently located in 46 States, approximating a 20% stratified sample of U.S. community hospitals. Hospitals participating in the NIS survey are selected annually through stratified, single-stage random cluster sampling of all community hospitals located in the US. All discharges per year are included from each selected hospital. The NIS data from 2003-2012 will be used in the proposed analyses.

Heart failure hospitalizations will be identified from the NIS data using ICD-9 codes 428.xx in any position and in the first position on the hospital discharge record. The NIS contains up to 25 diagnoses (15 prior to 2009), however the number of diagnoses recorded varies by state. The number of diagnoses used in the assessment of heart failure hospitalizations in the proposed study will be consistent across the years of observation and determined based on observed distributions.

The number of first HF hospitalizations will be estimated from the number of all HF hospitalizations

identified in the NIS hospitalization records for each calendar year, by age, race, and gender groups as well as *a priori* identified algorithms of HF discharge.

Estimates of annual rates of outpatient and inpatient HF events relative to annual estimates of all HF hospitalizations identified from the NIS data will be calculated using the calibration factors obtained from the ARIC CMS Medicare data as outlined in the preceding sections.

As outlined in (e) we will apply calibration factors derived as part of ARIC MS# 1996 to identify ADHF events in annual NIS hospitalization records and estimate the annual rate outpatient HF events preceding and following sentinel acute decompensated HF hospitalizations.

Standard methods for a stratified, single-stage cluster sample without replacement will be used to calculate respective variances. Sampling weights reflecting the NIS sampling design will be obtained from the Hospital Weights files provided by NIS. SUDAAN and STATA programs for survey analyses will be used to provide rate estimates.

All estimates will be provided overall, by year, and by race and gender and in the following categories of age at time of the first observed heart failure hospitalization: 65-74 years; 75-84 years; 85 year and older. Additional specific sub-groups will be defined from hospital discharge codes. Estimates will be presented at a priori defined levels of sub-group aggregations. The algebraic summary presented below of the estimation from NIS data of the rate of outpatient HF visits in the 365 days prior to (imputed) first HF hospitalization applies to the finer sub-grouping considered. However, although the calibration factors considered are specific to identified sub-groups, in the equation below, we will not subscript the factors to account for this dependence, or for the specific year being considered. We will also ignore all weighting issues in the summary below (but not in the real analysis), considering all counts as weighted with respect to the sampling.

The number of outpatient HF events per year occurring in a 365 day period prior to the date of the associated incident HF hospitalization is $N_{OPHF} = f2 \cdot f1 \cdot N1$, where:

N1 = the total number of HF hospitalizations
f1 = proportion of hospitalizations estimated from CMS data to be incident HF hospitalizations
f2 = annual rate of outpatient HF hospitalizations estimated from CMS data to occur within 365 days prior to an incident HF hospitalization

Limitations:

Potential limitations to the proposed analyses can occur as a result of applying estimates based on CMS Medicare data to a population of individuals with varying levels of enrollment in Medicare. Furthermore, the proposed coefficients derived from CMS Medicare data pertain only to healthcare encounters for fee-for-service CMS Medicare beneficiaries. Preliminary estimates from the ARIC cohort suggest a lack of systematic differences in health status and healthcare utilization between fee-for-service and Medicare Advantage beneficiaries. Potential for differences however, may exist across geographic locations. Geographic differences in practice patterns intrinsic to individual hospitals, outpatient clinics, and individual healthcare practitioners may further affect the error in the

application of calibration factors derived from CMS Medicare data to nationwide estimates of the occurrence of heart failure.

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)?

MP#1996 – Agarwal et al.: Estimated burden of acute decompensated heart failure hospitalization in the United States: Applying model from the ARIC study to National Databases

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ No

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study
___ 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.

References

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Hospital discharges with heart failure code at any position: National Inpatient Sample 1993 through 2010 . [cited 2012; Available from: http://hcupnet.ahrq.gov/

Rosamond, W.D., et al., Classification of heart failure in the atherosclerosis risk in communities (ARIC) study: a comparison of diagnostic criteria. Circ Heart Fail, 2012. 5 (2): p. 152 - 9