1.a. Full Title: Glycemia and risk of hospitalization in persons with and without diabetes

b. Abbreviated Title (Length 26 characters): Glycemia and hospitalization

2. Writing Group: Rita Kalyani, Frederick L. Brancati, Jessica Yeh, Brad Astor, Elizabeth Selvin; others welcome

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

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3. Timeline: Data analysis to start in January 2008. Our goal will be to submit the manuscript for ARIC review by January 2009.
4. Rationale:

Individuals with diabetes are at increased risk for hospitalization and represent a significant burden of national hospitalization costs. Analyses of the CDC National Hospital Discharge Survey suggest that the number of hospital discharges with diabetes as any-listed diagnosis has more than doubled from 2.2 million discharges in 1980 to 5.1 million discharges in 2003. According to the American Diabetes Association, inpatient hospital care totaled $40.3 billion in 2002, representing one third of the total annual economic cost of diabetes ($132 billion). In sum, diabetes represents 11% of the U.S. health care expenditure. Expenditures incurred by patients with diabetes are substantial and identifying causes for inpatient hospitalization could help reduce this burden.

In addition to being at high risk for diabetes-related hospitalizations, individuals with diabetes are at a 60% greater risk of hospitalization for general medical conditions such as gastrointestinal illnesses and respiratory failure compared to their non-diabetic counterparts. A previous study demonstrated that nearly 16% of all hospitalized patients with diabetes had discharge diagnoses related to infection. The top five primary discharge diagnoses for patients with diabetes according to the CDC National Hospital Discharge Survey in 2003 were: circulatory diseases (31.3%), diabetes (10.9%), respiratory diseases (10.5%), digestive digestives (9.3%), and injury/poisoning (6.6%). In comparison, the top five discharge diagnoses for the general U.S. population in 2002 were: circulatory diseases (17.1%), pregnancy and childbirth (12.3%), newborns and perinatal conditions (11.3%), respiratory diseases (9.7%), and digestive diseases (8.6%) according to the Agency for Healthcare Research and Quality. These statistics support the observation that patients with diabetes are at increased risk for hospitalization due to general medical conditions.

Few studies have investigated the prospective association of glycemic control – as assessed by hemoglobin A1c (HbA1c) level - with risk of hospitalization in persons with diabetes. A positive association between HbA1c and overall hospitalization rates has been reported in single clinic settings. And virtually nothing is known about the association of HbA1c level in the normal and pre-diabetic range with hospitalization risk. Previous epidemiologic studies in persons with and without diabetes have demonstrated a graded, independent association of HbA1c level with risk of incident cardiovascular events including coronary heart disease, stroke, and peripheral arterial disease—all major causes of hospitalization. Nonetheless, information on the relation of glycemia and overall hospitalization rate, specific causes of hospitalization, and repeated hospitalizations in the presence and absence of a diabetes diagnosis is lacking.

Understanding the interplay between HbA1c, a diagnosis of diabetes and risk of hospitalization may inform treatment goals and interventions to prevent future hospitalization.

5. Main Hypothesis/Study Questions:

H1: Glycemia, as assessed by HbA1c, will be positively associated with risk of any-hospitalization and multiple hospitalizations in persons with and without diabetes.
H2: Glycemia will be positively associated with risk of hospitalization for conditions such as gastrointestinal illnesses, respiratory diseases, cardiovascular disease, infection, lower extremity disease (peripheral arterial disease, gangrene, amputation), retinopathy, renal disease, neuropathy, and metabolic disorders and the association for microvascular conditions (e.g., retinopathy, renal disease, neuropathy) may be stronger than that for macrovascular conditions (e.g., cardiovascular disease) in persons with and without diabetes.

H3: The HbA1c-hospitalization associations in persons with and without diabetes may be modified by age, gender, and/or race/ethnicity.

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).

Data Source and Study Population:

Inclusions: The study population will include all individuals both with and without diabetes at the second ARIC examination who had a valid hemoglobin A1c measurement. All ARIC visit 2 participants with stored blood will have HbA1c measured. Diabetes will be defined as fasting glucose of 126 mg/dl or higher, a non-fasting glucose of 200 mg/dl or higher, a self-reported physician diagnosis of diabetes, or treatment for diabetes at either ARIC visit 1 or visit 2. All analyses will be stratified by diabetes status (presence or absence of diabetes).

Exclusions: Persons with missing covariates of interest, missing information on fasting status, or incomplete fast of <8 hours will be excluded.

Exposure: Hemoglobin A1c

In persons with diabetes, HbA1c was previously measured from ARIC visit 2 stored whole blood samples as part of ARIC Ancillary Study #2003.5, “Glycemic control (HbA1c) at visit 2 as a predictor of coronary heart disease, kidney disease, and incident diabetes.” HbA1c is available for over 5,400 ARIC participants including all individuals with diabetes (diagnosed and undiagnosed).

In persons without diabetes, HbA1c is currently being measured from ARIC visit 2 stored whole blood samples as part of ARIC Ancillary Study # 2006.15, “Hemoglobin A1c (HbA1c), Incident Diabetes, and Major Causes of Morbidity and Mortality in Non-Diabetic Participants.”

Outcome: Hospitalizations
Hospitalizations are assessed via self-report by participants during the annual follow-up phone calls. Data are currently available through the year 2004. ICD9 codes for all discharge diagnoses associated with hospitalization events will be obtained from the hospital record abstraction forms.

*Any-hospitalization* will include all hospitalizations during the study period regardless of the ICD9 code. However, all these persons with a discharge diagnosis of diabetes (any 250) listed as either a primary or secondary diagnosis will be considered to have diagnosed diabetes at the time of hospitalization.

*Diabetes-related hospitalizations* will include any hospitalization with at least one of the ICD9 codes listed in Appendix A.

*General medical hospitalizations* will be classified by ICD9 codes as follows (excluding any ICD9 codes from Appendix A that falls into these categories):

- Neoplasms (140-239)
- Other Endocrine, Nutritional, and Metabolic Disease and Immunity Disorders (249-279, not 250)
- Diseases of the Blood and Blood-Forming Organs (280-289)
- Mental Disorders (290-319)
- Diseases of the Nervous System and Sense Organs (320-389)
- Respiratory Diseases (460-519)
- Digestive Diseases (520-579)
- Genitourinary Diseases (580-629)
- Diseases of the Skin and Subcutaneous Tissue (680-709)
- Musculoskeletal System and Connective Tissue (710-739)
- Injury and Poisoning (800-999)

**Covariates**

Covariates of interest include: age, gender, race, center, education level, income, marital status, health insurance status, LDL- and HDL-cholesterol, triglycerides, blood pressure, hypertension medication, body mass index, and waist circumference. Diabetes medication use will also be of interest for subgroup analyses.

**Data Analysis**

We will assess the risk relationship by modeling HbA1c as a continuous variable, in quartiles and using clinically relevant cutpoints (<6, 6-7, 7-8, 8-9, and >9 in persons with diabetes). We will use Cox proportional hazard models to characterize the association of HbA1c with risk of first hospitalization (any hospitalization, diabetes-related hospitalization, general medical hospitalization) after adjustment for potential confounding factors. We will use Poisson models with consideration of over-dispersion (negative binominal distribution) to characterize the association of HbA1c with multiple (repeated) hospitalizations. All analyses will be stratified by diabetes status using diabetes as defined earlier and include all individuals both with and without diabetes.
Among patients with diabetes, analyses will also be stratified by diagnosed versus undiagnosed diabetes.

We will conduct subgroup analyses examining the relationship between hemoglobin A1c and hospitalization outcomes by age (< 60 years of age versus ≥ 60 years of age); gender (male versus female); race (black versus white) and formally test for interactions by age, gender, and race in our multivariable models. Among persons with diabetes, we will also compare individuals with diagnosed versus undiagnosed diabetes status.

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 ICTDER02 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   ___X___ No

(This file ICTDER02 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?  
___X__ 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 ICTDER02 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  
___X__ Yes   ___X__ 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   ___X__ 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 #1333  Association between obesity and hospitalizations.

Selvin E, et al. Long-term stability of hemoglobin A1c (HbA1c) measurements from frozen whole blood samples stored over a decade, Diabetic Medicine. [MS #1011]


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:2003.5, 2006.15)

___ ___  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/](http://www.cscc.unc.edu/aric/forms/)

12. 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.

References


## Appendix A: ICD9 Codes for Diabetes-related Complications

*Adapted from Project SUGAR 2*

*Previous study results published by Gary et al., 2004*

<table>
<thead>
<tr>
<th>CONDITIONS</th>
<th>ICD-9 CODES</th>
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| Amputation, leg/foot          | 895.0 – 895.1 amputation of toe  
                                  | 896.0 – 896.3 amputation of foot  
                                  | 897.0 – 897.7 amputation of leg |
| Gangrene                      | 785.4 Gangrene  
                                  | 682.6 Cellulites, leg  
                                  | 040.0 Gas gangrene  
                                  | 440.2 Atherosclerosis of native arteries of the extremities  
                                  | 038.9 unspecified septicemia |
| Lower extremity infection     | 457.2 Lymphangitis  
                                  | 680.6 Carbuncle and furuncle of leg  
                                  | 680.7 Carbuncle and furuncle of foot  
                                  | 682.6 cellulites, leg  
                                  | 682.7 cellulites, foot |
| Peripheral vascular disease   | 250.7 Diabetes with peripheral circulatory disorders  
                                  | 440 Atherosclerosis  
                                  | 441 Aortic aneurysm  
                                  | 443 Other peripheral vascular disease  
                                  | 444 Arterial embolism and thrombosis  
                                  | 447 Other disorders of arteries and arterioles  
                                  | 459 Other disorders of circulatory system  
                                  | 557.1 Vascular insufficiency of intestine (Chronic)  
                                  | 557.9 (Unspecified)  
                                  | 785.4 Symptoms involving cardiovascular system, Gangrene  
                                  | V43.4 Organ or tissue replaced by other means, blood vessel |
| Retinopathy                   | 250.5 Diabetes with ophthalmic manifestations  
                                  | 362.0, 362.01 – 362.02 (diabetic retinopathy)  
                                  | 362.1 Other background retinopathy and retinal vascular changes  
                                  | 362.81 Other retinal disorders  
                                  | 366.4 diabetic cataract  
                                  | 368 Visual disturbances  
                                  | 369.0-369.9 (blindness)  
                                  | 361.00 (retinal detachment)  
                                  | 361.9 (Unsp detachment)  
<pre><code>                              | 377 Disorders of optic nerve and |
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<table>
<thead>
<tr>
<th>Visual Pathways</th>
<th>Cardiovascular Disease</th>
<th>Infections</th>
<th>Neurologic</th>
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<tbody>
<tr>
<td>visual pathways</td>
<td>379.21 (vitreous degeneration)</td>
<td>410 (acute MI)</td>
<td>250.6 Diabetes with neurologic complications</td>
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<tr>
<td>379.23 (vitreous hemorrhage)</td>
<td>410 – 414 (ischemic heart disease)</td>
<td>320 – 321 Bacterial meningitis</td>
<td>337.0 Idiopathic peripheral autonomic neuropathy</td>
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<td>413 (angina)</td>
<td>326 Late effects of intracranial abscess or pyogenic infection</td>
<td>354.0 – 355.9 Carpal tunnel syndrome Mononeuritis of lower limb</td>
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<td>430 – 438 (stroke)</td>
<td>380.1 Infective otitis externa</td>
<td>356.9 Hereditary and idiopathic peripheral neuropathy, Unspecified</td>
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<td>39.25, 39.29 (bypass)</td>
<td>421 Acute and subacute endocarditis</td>
<td>357.2 Inflammatory and toxic neuropathy</td>
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<td>39.50, 39.90 (Angioplasty)</td>
<td>460 – 466 Acute Respiratory Infections</td>
<td>357.9</td>
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<td>415 – 429 (nonischemic)</td>
<td>480 – 487 Pneumonia And Influenza</td>
<td>358.1 Myoneural disorders</td>
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<td>785.5 Shock without mention of trauma</td>
<td>510 Empyema</td>
<td>536.0 Achlorhydria</td>
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<td>402 Hypertensive heart disease</td>
<td>513 Abscess of lung and mediastinum</td>
<td>558.9 Other noninfectious</td>
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<td>Gastroenteritis and colitis</td>
<td>591.0 Hydronephrosis</td>
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<td>593.7 Other disorders of kidney and ureter Vesicoureteric reflux</td>
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<td>596.4 Atony of bladder</td>
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<td>Renal</td>
<td>596.5 Other functional disorders of bladder</td>
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<td>607.8 Disorders of penis Other</td>
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<td>647.21 Infective and parasitic conditions in the mother classifiable elsewhere but complicating pregnancy, childbirth, or the puerperium</td>
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<td>713.5 Arthropathy associated with neurological disorders</td>
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<td>Renal</td>
<td>250.4 Diabetes with renal manifestations</td>
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<td>274.1 Gouty nephropathy</td>
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<td>275.4 Disorders of calcium metabolism</td>
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<td>403 Hypertensive renal disease</td>
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<td>404 Hypertensive heart and renal disease</td>
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<td>580 – 589 Nephritis, Nephrotic Syndrome, And Nephrosis</td>
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<td>590 Other Diseases Of Urinary System</td>
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<td>591 Hydronephrosis</td>
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<td>592 Calculus of kidney and ureter</td>
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<td>593 Other disorders of kidney and ureter</td>
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<td>596 Other disorders of bladder</td>
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<td>600 Hyperplasia of prostate</td>
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<td>753.1 Cystic kidney disease</td>
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<td>791 Nonspecific findings on examination of urine</td>
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<td>Diabetes-related metabolic disorders</td>
<td>251.1, and 251.2 Hypoglycemia</td>
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<td>250.1 Ketoacidosis</td>
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<td>250.3 Diabetes with other coma</td>
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