ARIC Manuscript Proposal # 1323r

PC Reviewed: 01/15/08	**Status: _A___**	**Priority: __2_**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

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[1]. 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[2], 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[3]. A previous study demonstrated that nearly 16% of all hospitalized patients with diabetes had discharge diagnoses related to infection[4]. 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%)[1]. 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[5]. 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[6-7]. 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[8-12]. 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 binomial 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 ____ 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? ____ 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"?
____ 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 #1333 Association between obesity and hospitalizations.

Selvin E, et al. Long-term stability of hemoglobin A_{1c} (HbA_{1c}) measurements from frozen whole blood samples stored over a decade, *Diabetic Medicine*. [MS #1011]

Selvin E, Coresh J, Golden SH, Brancati FL, Folsom A, Steffes M. Glycemic control and coronary heart disease risk in persons with and without diabetes. *Arch Intern Med* 2005; 165: 1910-1916. [MS #1024]

Selvin E, Wattanakit K, Steffes MW, Coresh J, Sharrett AR. HbA1c and peripheral arterial disease in diabetes: the Atherosclerosis Risk in Communities study. *Diabetes Care*.2006; 29:877-82.

Selvin E, Coresh J, Shahar E, Zhang L, Steffes M, Sharrett AR. Glycaemia (haemoglobin A1c) and incident ischaemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Lancet Neurol*. 2005; 4:821-6.

Vitelli LL, Shahar E, Heiss G, McGovern PG, Brancati FL, Eckfeldt JH, Folsom AR. Glycosylated hemoglobin level and carotid intimal-medial thickening in nondiabetic individuals. The Atherosclerosis Risk in Communities Study. Diabetes Care 1997;20:1454-8.

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/

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

1) Centers for Disease Control and Prevention (CDC), National Center for Health Statistics, Division of Health Care Statistics, data from the National Hospital Discharge Survey. *http://www.cdc.gov/diabetes/statistics/hospitalization_national.htm*

2) Gagliardino JJ, Martella A, Etchegoyen GS, Caporale JE, Guidi ML, Olivera EM, Gonzalez C. Hospitalization and re-hospitalization of people with and without diabetes in La Plata, Argentina: comparison of their clinical characteristics and costs. *Diab Res Clin Prac* 2004; 65: 51-59.

3) Ray NF, Thamer M, Taylor T, Fehrenbach SN, Ratner R. Hospitalization and expenditures for treatment of general medical conditions among the U.S. diabetic population in 1991. *J Clin Endocrinol Metab* 1996; 81: 3671-3679.

4) Cook CB, Tsui C, Ziemer DC, Naylor DB, Miller WJ, Hentz JG. Common reasons for hospitalization in urban diabetes patients. *Ethn Dis*. 2006;16:391-7.

5) Merrill CT, Elixhauser A. Hospitalization in the United States, 2002. Rockville, MD: Agency for Healthcare Research and Quality 2005. HCUP Fact Book No.6 AHRQ Publication No. 05-0056. ISBN 1-58763-217-9.

6) Graber AL, Davidson P, Brown AW, Gaume JA, McRae JR, Wolff K. Hospitalization of patients with diabetes. *Endocrine Practice* 1995; 1: 399-403.

7) Cook CB**,** Hentz JG**,** Tsui C**,** Ziemer DC**,** Naylor DB**,** Miller WJ**.** Poor glycemic control increases risk of hospitalization in urban African Americans with diabetes. *Ethn Dis.* 2006;16: 880-5.

8) Khaw KT, Wareham N**,** Bingham S**,** Luben R**,** Welch A**,** Day N**.** Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med.* 2004; 141:413-20.

9) Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med*. 2004; 141:421-31.

10) Selvin E, Coresh J, Golden SH, Brancati FL, Folsom A, Steffes M. Glycemic control and coronary heart disease risk in persons with and without diabetes. *Arch Intern Med* 2005; 165: 1910-1916.

11) Selvin E, Wattanakit K, Steffes MW, Coresh J, Sharrett AR. HbA1c and peripheral arterial disease in diabetes: the Atherosclerosis Risk in Communities study. *Diabetes Care*.2006; 29:877-82.

12) Selvin E, Coresh J, Shahar E, Zhang L, Steffes M, Sharrett AR. Glycaemia (haemoglobin A1c) and incident ischaemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Lancet Neurol*. 2005; 4:821-6.

13) Gary TL, Batts-Turner M, Bone LR, Yeh HC, Wang NY, Hill-Briggs F, Levine DM, Powe NR, Hill MN, Saudek C, McGuire M, Brancati FL. A randomized controlled trial of the effects of nurse case manager and community health worker team interventions in urban African-Americans with type 2 diabetes. *Control Clin Trials*. 2004; 25: 53-66.

Appendix A: ICD9 Codes for Diabetes-related Complications

Adapted from Project SUGAR 2
Previous study results published by Gary et al., 2004[13]

CONDITIONS	ICD-9 CODES
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) 377 Disorders of optic nerve and

	visual pathways 379.21 (vitreous degeneration) 379.23 (vitreous hemorrhage)
Cardiovascular disease	410 (acute MI) 410 – 414 (ischemic heart disease) 413 (angina) 430 – 438 (stroke) 39.25, 39.29 (bypass) 39.50, 39.90 (Angioplasty) 415 – 429 (nonischemic) 785.5 Shock without mention of trauma 402 Hypertensive heart disease
Infections	001 – 139 Infectious And Parasitic Diseases 320 – 321 Bacterial meningitis 326 Late effects of intracranial abscess or pyogenic infection 380.1 Infective otitis externa 421 Acute and subacute endocarditis 460 – 466 Acute Respiratory Infections 480 – 487 Pneumonia And Influenza 510 Empyema 513 Abscess of lung and mediastinum 567 Peritonitis 590 Infections of kidney 599 Urinary tract infection, site not specified 680 – 686 Infections Of Skin And Subcutaneous Tissue 707 Chronic ulcer of skin 711 Arthropathy associated with infections 730 Osteomyelitis, periostitis, and other infections involving bone
Neurologic	250.6 Diabetes with neurologic complications 337.0 Idiopathic peripheral autonomic neuropathy 354.0 – 355.9 Carpal tunnel syndrome Mononeuritis of lower limb 356.9 Hereditary and idiopathic peripheral neuropathy, Unspecified 357.2 Inflammatory and toxic neuropathy 357.9 358.1 Myoneural disorders 536.0 Achlorhydria 558.9 Other noninfectious

	gastroenteritis and colitis 591.0 Hydronephrosis 593.7 Other disorders of kidney and ureter Vesicoureteric reflux 596.4 Atony of bladder 596.5 Other functional disorders of bladder 607.8 Disorders of penis Other 647.21 Infective and parasitic conditions in the mother classifiable elsewhere but complicating pregnancy, childbirth, or the puerperium 713.5 Arthropathy associated with neurological disorders
Renal	250.4 Diabetes with renal manifestations 274.1 Gouty nephropathy 275.4 Disorders of calcium metabolism 403 Hypertensive renal disease 404 Hypertensive heart and renal disease 580 – 589 Nephritis, Nephrotic Syndrome, And Nephrosis 590 Other Diseases Of Urinary System 591 Hydronephrosis 592 Calculus of kidney and ureter 593 Other disorders of kidney and ureter 596 Other disorders of bladder 600 Hyperplasia of prostate 753.1 Cystic kidney disease 791 Nonspecific findings on examination of urine
Diabetes-related metabolic disorders	251.1, and 251.2 Hypoglycemia 250.2 Hyperosmolar syndrome 250.1 Ketoacidosis 250.3 Diabetes with other coma