ARIC Manuscript Proposal # 952

PC Reviewed: 08/07/03	**Status: __A__**	**Priority: __2__**
SC Reviewed: 08/07/03	**Status: __A__**	**Priority: __2__**

1. Full Title: Anemia and kidney dysfunction as predictors of cardiovascular disease.

Abbreviated Title: Anemia and cardiovascular disease

2. Writing Group

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3. Timeline: The data are available as part of ARIC visits 1 through 4. We project that analyses and manuscript preparation will take place over the next year.

4. Rationale:

Studies in patients on chronic dialysis have found anemia to be strongly related to poorer outcomes, including left ventricular growth,[1] heart failure,[2] and mortality.[3] In the Studies of Left Ventricular Dysfunction (SOLVD), lower hematocrit was an independent risk factor for mortality among individuals with left ventricular dysfunction.[4] In that analysis, patients with lower hematocrit and lower kidney function were at an even higher risk of mortality than would be expected from the combined effects of each risk factor. There are fewer studies on the association between anemia and cardiovascular disease (CVD) among individuals in the general population.

In an analysis of 549 CVD events in the ARIC public use data, Sarnak et al found that anemia, defined as hemoglobin <12 g/dL in men and <11 g/dL in women, was associated with a 57% higher risk of cardiovascular disease.[5] In a separate analysis of the public use data, Manjunath et al reported that each 10 mL/min/1.73m^2 lower estimated GFR was associated with an adjusted relative hazard of 1.05 for total atherosclerotic CVD and 1.07 for de novo atherosclerotic CVD.[6] The interaction between anemia and kidney dysfunction was not addressed in either study.

We propose to extend the previous analyses of the prospective relationships of anemia and kidney function with subsequent cardiovascular disease. The most recent ARIC data release has nearly three times as many events as were included in the previous study of the association between anemia and CVD. This additional power will allow us to examine the

associations in more detail. For example, the interaction between lower kidney function and anemia may be more harmful than would be predicted from the independent effects of either abnormality. We will address this by assessing the association between anemia and CVD in subgroups of the ARIC Cohort stratified by level of kidney function. We also will examine other subgroups stratified by gender, age, race, hypertension, diabetes, smoking, previous CVD, and menopausal status in women. Manjunath et al reported that the association of kidney function with atherosclerotic CVD appeared to be stronger among African Americans than whites (p=0.08).[6] The increased power available in the updated dataset will allow us to investigate whether there is an interaction with race, and whether this interaction is due to the lower levels of hemoglobin found in African Americans at every level of kidney function.[7] The increased number of deaths in the ARIC Cohort also will allow us to examine all-cause and cardiovascular mortality, in addition to all cardiovascular events. This may be an important analysis, as anemia may be more strongly related to mortality among individuals with cardiovascular disease than the development of de novo CVD.

Serum creatinine, as measured at Visit 1 using a modified kinetic Jaffe reaction, will be used in conjunction with demographic information to estimate GFR as a measure of kidney function.[5] Serum creatinine concentration will be corrected for inter-laboratory differences and calibrated with Cleveland Clinic measurement standards by subtraction of 0.24 mg/dl from the reported values. Anemia at Visit 1 will be defined as hemoglobin < 13 g/dL in men and <12 g/dL in women. Other cutpoints and categories of hemoglobin levels will also be used. Anemia and level of kidney function will be used to predict CVD events and all-cause and CVD mortality, independent of potential confounders, including age, race, sex, blood pressure, diabetes, history of coronary heart disease, body mass index, smoking status, lipid levels and levels of markers of inflammation (albumin, von Willebrand factor, fibrinogen). Additional analyses, stratified on these covariates, will also be performed.

5. Main hypothesis/study questions:

Does anemia at baseline independently predict CVD events, all-cause mortality and CVD mortality?

Does kidney dysfunction at baseline independently predict CVD events, all-cause mortality and CVD mortality?

Does the presence of both anemia and kidney dysfunction at baseline interact to predict higher rates of CVD events, all-cause mortality and CVD mortality than would be expected from their independent associations? We hypothesize that anemia will be most influential in the presence of kidney dysfunction when other risk factors are elevated.

Do these associations differ by race and/or sex?

6. Data: The following variables will be needed for these analyses: age, sex, race, center, serum creatinine, hemoglobin, and CVD events. Covariates of interest include age, race, sex, blood pressure, diabetes, history of coronary heart disease, body mass index, smoking status, lipid levels and levels of markers of inflammation (albumin, von Willebrand factor, fibrinogen).

7. Will the data be used for non-CVD analysis in this manuscript? No; the outcomes of interest are CVD events and all-cause and CVD mortality.

8. Will the DNA data be used in this manuscript? No

9. Review of existing ARIC Study manuscript proposals: No overlapping proposals were found. Related analyses were done using the public use data with fewer events.

Reference List

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2. Harnett JD, Foley RN, Kent GM, Barre PE, Murray D, Parfrey PS: Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. Kidney Int. 47:884-890, 1995

3. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE: The impact of anemia on cardiomyopathy, morbidity, and and mortality in end-stage renal disease. Am.J.Kidney Dis 28:53-61, 1996

4. Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, Sarnak MJ: Reduced kidney function and anemia as risk factors for mortality inpatients with left ventricular dysfunction. J.Am.Coll.Cardiol. 38:955-962, 2001

5. Sarnak MJ, Tighiouart H, Manjunath G, MacLeod B, Griffith J, Salem D, Levey AS: Anemia as a risk factor for cardiovascular disease in The Atherosclerosis Risk in Communities (ARIC) study. J.Am.Coll.Cardiol. 40:27-33, 2002

6. Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL, Coresh J, Levey AS, Sarnak MJ: Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. Journal of the American College of Cardiology 41:47-55, 2003

7. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J: Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). Arch.Intern.Med. 162:1401-1408, 2002