ARIC Manuscript Proposal #1838

PC Reviewed: 8/23/11  Status: A  Priority: 2
SC Reviewed:_______  Status:_______  Priority:__________

1  a. Full Title: White blood cell differential and ischemic stroke subtype incidence in the ARIC study
   b. Abbreviated Title: WBC differential and risk of ischemic stroke subtypes

2 Writing Group:
   Writing group members:
   Hiroshi Yatsuya, Tetsuya Ohira, Aaron Folsom, others welcome
   I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. HY

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3 Timeline: Analysis will begin immediately, once the proposal is accepted, using surveillance data files through 2008 or the latest available. A draft will be prepared within four months and will be submitted to the Publications committee by 6 months.
4 Rationale:
A moderate elevation of the white blood cell (WBC) count is considered to be a non-specific marker of systemic subclinical inflammation. Although the roles and functions of each WBC subtype in vivo have been investigated, the clinical significance of their blood level is not well understood. Epidemiologically, WBC count has been associated with an increased incidence of coronary heart disease (CHD), ischemic stroke especially of lacunar and cardioembolic subtypes, total cardiovascular disease (CVD), heart failure, and sudden death, but not with intraparenchymal hemorrhage (IPH) in prospective analyses of the ARIC Study. WBC count was also associated with incidences of peripheral artery disease in diabetic subjects and chronic kidney disease, focal narrowing of retinal artery, and weight gain in the ARIC. Furthermore, it was cross-sectionally associated with carotid artery lesions and blood level of thrombomodulin. Yet, a few studies have looked at WBC differential, which consists of granulocytes (neutrophils, eosinophils, and basophils), monocytes and lymphocytes. In one ARIC analysis with a mean follow-up of 8 years, both granulocytes and monocytes counts were positively associated with incidences of CHD and ischemic stroke, while lymphocytes were not associated with any types of CVD. Another ARIC study showed that increased neutrophils and decreased lymphocytes were significantly correlated with the development of hypertension, especially in African-Americans. However, no previous studies (not limited to ARIC) have prospectively examined whether WBC differentials have different associations with incidences of different subtypes of ischemic stroke. Since monocytes play an important role in the process of atherosclerosis, the monocyte count could be associated only with non-lacunar thrombotic (i.e., large artery) subtype of ischemic stroke. Therefore, we will examine WBC differential counts with incidence of ischemic stroke subtypes, which might help better understanding of pathophysiology of ischemic stroke subtypes.

5 Main Hypothesis/Study Questions:

a. WBC and neutrophil count are significantly positively associated with each ischemic stroke subtype independent of socio-demographic and lifestyle variables including smoking status (Model 2). However, the association would be attenuated after accounting for other biochemical variables (Model 3).

b. Monocyte count is positively associated only with non-lacunar thrombotic stroke.

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:** A prospective cohort study

**Inclusion/Exclusion:**
Inclusion: all black and white, ARIC visit 1 participants with no missing WBC and differential data (excludes Washington County, which did not do differentials), without a self-reported history of stroke at visit 1.

**Dependent variables:** incident stroke, incident ischemic stroke subtypes (lacunar, nonlacunar and cardioembolic) measured through 2008 or the latest available. Details on ascertainment and classification of stroke are described elsewhere. Briefly, a stroke was classified as “lacunar” on the basis of the recorded neuroimaging results when two criteria were met: (1) typical location of the infarct (basal ganglia, brain stem, thalamus, internal capsule, or cerebral white matter) and (2) infarct size of ≤ 2 cm or unstated size. Definite or probable “cardioembolic” stroke required the same criteria as ischemic infarction, plus either (1) autopsy evidence of an infarcted area in the brain and a source of possible cerebral emboli in a vessel or the presence of an embolus in the brain or (2) medical record evidence of a possible source of embolus such as moderate or greater valvular heart disease, atrial fibrillation, cardiac or arterial procedure, or intracardiac thrombus. Definite or probable ischemic strokes that were not deemed lacunar or embolic were labeled “nonlacunar.” CT or MRI was available for 90% of the ischemic stroke cases.

**Independent variable:** WBC counts, WBC differential count

**Covariates:** age, sex, race (Model 1), smoking status, pack-years, usual alcohol consumption, physical activity, education level (Model 2), systolic blood pressure, use of antihypertensive medication, prevalent diabetes, and serum HDL cholesterol (Model 3).

**Modeling:**
1. Hazard ratios for each ischemic stroke subtype by the WBC/WBC differential counts quartiles will be assessed by Cox proportional hazards model.

**Analysis plan:**
Assumption of hazards proportionality will be assessed by examining the parallelness of the ln (-ln) survival curves for WBC/WBC differential counts quartiles. A formal test will be carried out by including an interaction term between the quartile and time (continuous or dichotomous at median (10-year)) in the Cox model.

**Stratified analyses:**
If interactions are significant with WBC or differentials, analyses will be performed by stratified by (1) current smoking (2) race and (3) diabetes.
7 Will the data be used for non-CVD analysis in this manuscript?
   ______ Yes   ______ No

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

   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"?

   c. If yes, is the author aware that the participants with RES_DNA ="not for profit"
      restriction must be excluded if the data used by a for profit group?

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.
   ______ 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# 709. White blood cell (WBC) count and incidence of coronary heart disease
             (CHD) and stroke, and mortality from cardiovascular disease in
             African-American men and women: the ARIC Study
             WBC count was positively associated with incidence of CHD, ischemic stroke and the
             composite CVD. Both granulocytes and monocytes counts were also positively
             associated with those outcomes.1 (Lee CD, Am J Epidemiol, 2001)

   MS#1090. Risk Factors for Ischemic Stroke Subtypes. The Atherosclerosis Risk in
             Communities (ARIC) Study
             Arteriovenous nicking and any retinopathy were associated with increased incidence
             of ischemic stroke independent of age, sex, race, mean arterial blood pressure over
             three ARIC examinations, hypertensive medication, diabetes status, smoking status
             and total and HDL cholesterol, triglyceride, and fasting glucose.4 (Ohira T, Stroke,
             2006).

11 Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary
   study data?
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


