CHS/ARIC Manuscript Proposal # 654

Ancillary Study Manuscript
CHS Ancillary Study C5, ARIC Ancillary Study, Epidemiology of Venous Thrombosis and Pulmonary Embolism in the ARIC and CHS Cohorts

1.   **Title:**

   Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology (LITE)

2.   **Short Title:**

   Venous thromboembolism: ARIC / CHS

3.   **Timeline:**

   Analysis: Spring 1999; Draft MS: Summer 1999; Submission: Fall 1999

4.   **Proposed Authors:**

   Mary Cushman
   University of Vermont
   55A South Park Dr
   Colchester, VT 05446
   ph: 802-656-8959; fax:802-656-8965; email: mcushman@salus.uvm.edu

   Wayne D. Rosamond, Susan Heckbert, Scott S. Emerson, Richard White, Aaron R. Folsom.

5.   **Key Words:** deep vein thrombosis / pulmonary embolism / epidemiology

6.   **Background**

   Venous thromboembolism (VTE), consisting of deep vein thrombosis and pulmonary embolus, is thought to be the third most common life-threatening cardiovascular disease in the United

States (1). Various studies have attempted to describe the incidence rates of diagnosed VTE (2-7) but most have been subject to forms of ascertainment bias. The main source of this is reliance only on discharge codes, rather than review of medical records. There are little population-based data that describe the acute precipitants and associated conditions at the time of diagnosis of these disorders.

The purpose of this paper will be to, (1) describe the methods used for case ascertainment and validation in the LITE study; (2) report predictive values of ICD-9-CM codes used to identify potential cases, (3) report incidence rates of DVT and PE in LITE, (4) describe the objective tests used to diagnose VTE in these cohorts.

7.   **Methods**

Subjects
This is a cohort study combining the CHS and ARIC cohorts. Cases of possible VTE were identified primarily by hospital discharge codes (ICD-9-CM, 415.1x, 451.1x, 451.2, 451.8x 451.9, 453.0, 453.1, 453.2, 453.8, 453.9, 996.7, 996.7X, 997.2, 999.2, 38.7) reported for participants in both studies. In CHS there were three strategies used to ascertain events missed by discharge codes:

First, hospitalization discharge summaries were reviewed for all participants who self-reported VTE during follow up and who also reported warfarin use at any time during follow up (CHS routinely collects all discharge summaries for participants admitted to a hospital). Second, records were reviewed for deaths reportedly due to VTE, that were missed by discharge codes. Third, a sample of records of participants who self-reported VTE but did not report warfarin use were reviewed.

In ARIC, two strategies were used (hospital discharge summaries not available for review as in CHS):
First, participants attending the 4th visit were asked if a doctor had ever told them they had a blood clot in a leg or in their lungs. Any of these self-reported events, if they occurred after baseline and were not identified by the discharge codes above, were further investigated by review of annual reports of hospitalizations. Second, records were reviewed for deaths reportedly due to VTE, that were missed by discharge codes.

Medical records were abstracted by trained abstractors at each field center to obtain physician and consultant reports, radiological studies, and records of hospitalizations within three months of the index hospitalization.

Information retrieved by research personnel from the hospital records was adjudicated separately by two physicians (MC, ARF) using pre-defined definitions for endpoints. Classification of DVT was as absent, definite or probable based on radiologic findings. Classification of PE was as absent or definite based on the PIOPED criteria or angiogram results. Adjudication results were reviewed and differences between the two physicians were resolved by discussion and further review of records, when necessary. For all potential cases, information recorded during adjudication included results of radiology reports of testing for VTE and any autopsy confirmation of VTE presence or absence. For confirmed VTE events the following information was recorded: physician statements regarding past medical history of DVT or PE (categorized as less than or greater than 90 days prior to the event), use of warfarin or heparin at the time of admission, known cancer diagnosis within 1 year before or after the event, past history of quiescent cancer; and a stated history of hospital admission, myocardial infarction, congestive heart failure, renal failure, major trauma, major surgery, marked immobility, autoimmune disease, or chemotherapy administration all within 90 days prior to admission for VTE. If there was a major surgery or major trauma, the type was recorded. Recorded family history of VTE or identified thrombophilic disorder was ascertained. Data were recorded on forms and key-entered at each study=s statistical coordinating center.

At the time of adjudication each event was classified as idiopathic or secondary thrombosis, with all events occurring within 90 days of major trauma, surgery, marked immobility, or associated with active cancer or chemotherapy, being classified as secondary. Classification as first or recurrent VTE, and as acute or chronic VTE was made. For this purpose, prior VTE was considered present based on the medical record information or results of prior adjudications for the same patient. Chronic VTE was diagnosed based on radiological characteristics and comparison to old radiological studies. Further review of the discharge codes databases for each study was used to identify cancer diagnoses occurring within one year before or after VTE diagnosis, for each validated case. Results of adjudication were validated in part by blinded re-review of a sample of abstracted charts.

Among the first X potential cases identified only by vascular complications codes (eg. 996.7x, 997.2, 999.2, without a coexisting DVT or PE code), adjudication revealed X objectively validated VTE cases. Most of these potential cases were participants with peripheral vascular disease. Subsequently, the record abstractors did not forward records on these codes as long as there was, (1) no venogram, venous ultrasound, impedance plethysmography, ventilation perfusion scan, or pulmonary angiogram performed, and (2) absence of recorded venous thrombosis or pulmonary embolism on the discharge diagnoses list. If the abstractor was uncertain, the records were forwarded for review.

Data to be Used

We will use baseline data from the ARIC and CHS datasets. The variables to be used include

field center, age, sex, race, and medication use (anticoagulants, hormone therapy). Baseline disease status variables may be used (arterial diagnoses, diabetes, hypertension, history of cancer). Follow up ARIC and CHS variables pertaining to cancer diagnoses will be used. A separate dataset we have created containing variables generated from LITE case adjudication will be used.

Analysis

Cases identified through a set time point representing closure of the discharge codes databases for each study (CHS, ARIC) will be included. Tabulation of the number of records reviewed for each ICD-9CM code used in screening for VTE will be presented. Results of additional screening of the cohort for events (self-reports and VTE deaths not coded by discharge codes) will be presented. Positive predictive value of a discharge code for DVT or PE (451, 415) will be calculated, as well as predictive value of other groups of diagnosis and procedure codes (453, 996.7 + 997.2 + 999.2; 38.7), and for non-coded self reports and deaths. Overall, sex, race, cohort (CHS or ARIC), and age specific incidence rates will be calculated for first diagnosis of DVT, PE and either diagnosis. Characteristics of these cases (sex, race, field center distribution, mean age, location of clot, method of diagnosis, categorization as primary versus secondary, and cancer versus non-cancer associated) will be described. Incidence rates of recurrent thrombosis after validated first thrombosis and/or pre-baseline self-reported thrombosis will be computed. To analyze patterns of recurrence, Chi-squared analysis will be used to determine whether DVT or PE is more frequent after a first event that is a DVT, and whether DVT or PE is more frequent after a first event that is a PE.

8.   Expected Results

We expect that positive predictive values for specific codes will be highest among potential cases ascertained by discharge codes for DVT and PE (400 codes). Validation rates will be low among potential cases ascertained by only vascular complication codes or self-reports. Venous duplex ultrasound and ventilation perfusion scanning will be the most commonly used tests for making a diagnosis. Incidence rates will be slightly lower than those reported in prior studies which relied only on discharge codes (without records review) for ascertainment. Incidence rates may also be lower due to >healthy cohort= effects. The incidence of DVT will be higher than PE. There will be a rise in incidence rate with age and higher incidence rates in Caucasians and men.

9.   Conclusions

This will be the first prospective US study to report incidence rates of validated venous

thrombosis in a cohort study representing wide age, race, and geographical ranges of the general population. Results will better clarify the scope of the public health impact of venous thrombosis. Results will provide information that might be helpful to other researchers designing studies which require validation of VTE cases. Results will provide background information for citation in future LITE papers.

References

1. Goldhaber S. Epidemiology of pulmonary embolism and deep vein thrombosis. In: Bloom A, Forbes C, Thomas D, Tuddenham E, eds. *Haemostasis and Thrombosis.* New York: Churchill Livingstone; 1994:1327-1333
2. Silverstein M, Heit J, Mohr D, Petterson T, O'Fallon W, Melton III L. Trends in the incidence of deep vein thrombosis and pulmonary embolism. *Arch Intern Med.* 1988; 158:585-593.
3. Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. *J Intern Med.* 1992; 232:155-160.
4. Kniffen W, Baron J, Barrett J, BIrkmeyer J, Anderson F. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. *Arch Intern Med.* 1994; 154:861-866.
5. Hansson P, Welin L, Tibblin G, Eriksson H. Deep vein thrombosis and pulmonary embolism in the general population: the Study of Men Born in 1913. *Arch Intern Med.* 1997; 157:1665-1670.
6. White R, Zhou H, Romano P. Incidence of idiopathic deep venous thrombosis and secondary thromboembolism among ethnic groups in California. *Ann Intern Med.* 1998; 128:737-740.
7. White R, Romano P, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med.* 1998; 158:1525-1531.