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THE ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) STUDY: DESIGN AND OBJECTIVES

THE ARIC INVESTIGATORS[1]

The ARIC Investigators (School of Public Health, U. of North Carolina, Suite 203, NCNB Plaza, 137 E. Franklin St., Chapel Hill, NC 27514). The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol* 1989;129:687-702.

Atherosclerosis Risk in Communities (ARIC) is a new prospective study to investigate the etiology of atherosclerosis and its clinical sequelae and variation in cardiovascular risk factors, medical care, and disease by race, sex, place, and time. In each of four US communities—Forsyth County, North Carolina, Jackson, Mississippi, suburbs of Minneapolis, Minnesota, and Washington County, Maryland—4,000 adults aged 45–64 years will be examined twice, three years apart. ARIC has coordinating, ultrasound, pulmonary, and electrocardiographic centers and three central laboratories. Three cohorts represent the ethnic mix of their communities; the Jackson cohort, its black population. Examinations include ultrasound scanning of carotid and popliteal arteries; lipids, lipoproteins, and apolipoproteins assayed in the Lipid Laboratory; and coagulation, inhibition, and platelet and fibrinolytic activity assayed in the Hemostasis Laboratory. Surveillance for coronary heart disease will involve review of hospitalizations and deaths among community residents aged 35–74 years. ARIC aims to study atherosclerosis by direct observation of the disease and by use of modern biochemistry.

arteriosclerosis; cardiovascular diseases; coronary disease; hemostasis; lipoproteins

Atherosclerosis Risk in Communities (ARIC) is a prospective investigation of the etiology and natural history of atherosclerosis and the etiology of clinical atherosclerotic disease in four US communities. The study also measures variation in cardiovas-

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; CCSP, Community Cardiovascular Surveillance Program; HDL, high density lipoprotein; LDL, low density lipoprotein.

[1] The ARIC Steering Committee: Department of Epidemiology, The Johns Hopkins University, Baltimore, MD—*Moyses Szklo, Chairperson*; Bowman Gray School of Medicine, Winston-Salem, NC—Ralph Barnes; Division of Epidemiology, University of Minnesota, Minneapolis, MN—Aaron Folsom; Department of Epidemiology, University of North Carolina, Chapel Hill, NC—Gerardo Heiss; Department of Medicine, University of Mississippi Medical Center, Jackson, MS—Richard Hutchinson; Department of Internal Medicine, Baylor College of Medicine, Houston, TX—Wolfgang Patsch; Epidemiology and Biometry Program, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD—A. Richey Sharrett; Department of Biostatistics, University of North Carolina, Chapel Hill, NC—O. Dale Williams; Division of Hematology-Oncology, University of Texas Medical School at Houston, Houston, TX—Kenneth Wu.

Participating institutions and principal staff: *Field centers*—Forsyth County, NC: University of North Carolina, Chapel Hill—Drs. Gerardo Heiss, James F. Toole, Herman A. Tyroler, L. E. Chambless and Fredric J. Romm, Ann Rhyne DiSanto, Karen Barr, Betty Barnhardt, Jane Bergsten, Judy Conrad, Reba Elliott, *Dannalee Furr, Barbara Hafer, Amy Haire, Valerie* Jackson, Jane Jensen, Phyllis Johnson, Jean Marlow, Bonnie Monger, Diane Mooney, Delilah Posey, Dawn Scott, Charles Sofley, Cathy Tatum, Ann Toledo, Alice White, Carmen Woody; Jackson, MS: University of Mississippi—Drs. Richard Hutchinson, Robert Watson, Robert Smith, David Conwill, Seshadri Raju and William Cushman, Jane Johnson, Drs. Alfredo Figueroa and Allen Thompson, Barbara Davis, Bobbie Alliston, Dr. Herbert Langford, Brenda Asken, Royanne Asken, Faye Blackburn, Clara Bowman, Sandra Bowton, Lisa Feild, Rose Franklin, Dorothy Hathorn, Roberta Howell, Martha Nelson, Virginia Overman, Stephanie Oxner, Doris Pitts, Gloria Shelton, Brenda Watson, Mattye Watson; Minneapolis, MN: Univer-

cular risk factors, medical care, and disease by race, sex, place, and time. It has cohort and community surveillance components.

In the cohort component, a sample of 16,000 persons aged 45–64 years is being selected, comprising 4,000 persons representative of each of the four communities. Cohort members will participate in two examinations three years apart and follow-up interviews annually. Atherosclerosis is evaluated in carotid and popliteal arteries by B-mode ultrasound, and risk factors are assessed by interview, examination, measurement of blood lipids and hemostatic factors, and other methods. Cohort members are followed for clinical atherosclerotic events, primarily coronary heart disease and stroke.

In the community surveillance component, the occurrence of events defined as hospitalized myocardial infarction and coronary heart disease death is ascertained for all residents of the four communities aged 35–74 years. Events are investigated by review of hospital records and by query of physicians and family members and are given standardized diagnoses.

The first of two cycles of currently funded cohort examinations began in November 1986. The first cycle will be completed by the end of 1989, at which time the second three-year cycle will begin. Community surveillance ascertains events occurring after January 1, 1987, and will continue for six years.

The cardiovascular research community has long recognized the continuing need for prospective studies to identify factors that place people at risk for atherosclerotic diseases. The recent development of reliable ultrasound arterial examination (1) enhances the expected benefit of such studies. Ultrasound imaging permits ARIC to investigate the relation of risk factors to the underlying arterial disease in healthy people. Initiation of a prospective study at this time is further enhanced by recent improvements in laboratory methods that permit investigation of new biochemical risk factors.

This paper presents an overview of ARIC and its objectives. Novel and key design features are explained and justified briefly. Detail on specific methods is available in the ARIC manuals of operation (2) and will be supplemented in subsequent reports.

sity of Minnesota—Drs. Aaron Folsom, Linda Goldman, Stanley Edlavitch and Ken Cram, Dorothy Buckingham, Gina Tritle, John O'Brien, Katherine Provinzino, Leone Reed, Gail Murton, Azmi Nabulsi, Elizabeth Justiniano, Laura Bartel, Anne Murrill, Marilyn Bowers, Barb Kuehl, Hilare Hamele, Virginia Wyum, Linda Sherman, Donna Ottenstroer; Washington County, MD: The Johns Hopkins University—Drs. Moyses Skzlo, George Comstock, Linda Fried and Roger Sanders, Joel Hill, Dr. Robert Rock, Joyce Chabot, Carol Christman, Dorrie Costa, Sunny Harrell, Vicki Hastings, Will Kelly, Beverly Kittel, Trudy Littenburg, Thomas Markam, Joan Nelling, Brenda Price, Ann Seibert, Carvel Wright; *Coordinating Center*: University of North Carolina, Chapel Hill—Drs. O. Dale Williams, David Christiansen, Lloyd E. Chambless, Jean Burge, Lars Ekelund, James Hosking, William Kalsbeek, and Allen Rosman, Jeffrey Abolafia, Dr. Edward Bachmann, I-Yiin Chang, Richard Cohn, Donna Coyne, Connie Hansen, Doris Jones, Joanne Kucharski, Michael Litzsinger, Robert McMahon, Catherine Paton, Allan Rosen, Debra Rubin, Julie Smith-Fortune, Robert Thompson, Laurence Wallman, Deborah Weiner, Marston Youngblood; *Ultrasound Reading Center*: Bowman Gray School of Medicine—Drs. Ralph Barnes, M. Gene Bond, George Howard and Ward A. Riley, Jr., Delilah Cook, Robert Ellison, Gina Enevold, Gregory Evans, Cheryl Fishel, Gina Gladstone, Maureen Goldstein, Barbara Owens, Suzanne Pillsbury, Anne Safrit, Omega Smith, Betsy Vestal, Sharon Wilmoth, Billie Young; *Central Hemostasis Laboratory*: University of Texas, Houston—Drs. Kenneth Wu, Arthur Bracey and Keith Hoots, Audrey Papp; *Central Lipid Laboratory*: Baylor College of Medicine—Drs. Wolfgang Patsch, Spencer Brown, Joel Morrisett and Louis Smith, Charlie Rhodes, Lynette Rogers, Sarah Helbing; *Central Chemistry Laboratory*: University of Minnesota—Dr. John Eckfeldt, Mavis Hawkinson; *ECG centers*: University of Minnesota—Dr. Richard Crow, Margaret O'Donnell; Dalhousie University—Dr. Pentti Rautaharju, Brian Hoyt; *Pulmonary Function Center*: The Johns Hopkins University—Dr. Melvyn Tockman, Pat Wilkinson, Michele Donithan, Anne Chase; *National Heart, Lung, and Blood Institute*: Drs. A. Richey Sharrett, Project Officer, Paul Sorlie, Andrew Dannenberg and Millicent Higgins, Betty Nordan.

Reprint requests to Dr. O. Dale Williams, ARIC Coordinating Center, School of Public Health, University of North Carolina, Suite 203, NCNB Plaza, 137 E. Franklin St., Chapel Hill, NC 27514.

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STUDY COMMUNITIES

The ARIC study communities are Forsyth County, North Carolina (including the city of Winston-Salem), the city of Jackson, Mississippi, the northwestern suburbs of Minneapolis, Minnesota, and Washington County, Maryland (including the city of Hagerstown). For Jackson, unlike the other three communities, only blacks are included in the cohort, although community surveillance covers all races in all communities. The ARIC communities provide an opportunity for testing the consistency of study results across four geographic locations with a range of mortality rates, in urban, suburban, and rural settings, and among men, women, blacks, and whites. Criteria for community selection included geographic and ethnic balance, census-defined borders, and evidence of a potentially cooperative population. Tables 1 and 2 provide demographic characteristics and mortality rates for the communities.

COHORT DESIGN

The cohort component of the study involves sampling, home interview, recruitment, clinic examinations, annual telephone follow-up, and identification, investigation, and diagnosis of clinical events.

Sampling and recruitment

Each community cohort is selected by probability sampling. In Forsyth County, households are identified by area sampling. In the other communities, selection involves sampling age-eligible persons from listings and then identifying their households. The following lists are used: in Jackson, a list of persons with driver's licenses or state identification cards; in Minneapolis, persons eligible for jury duty (with driver's licenses, voter registration cards, or identification cards); and in Washington County, persons with driver's licenses or listed in a 1975 private county health census. In all communities, all age-eligible per-

TABLE 1

*The ARIC study communities: demographic characteristics, 1980**

Study community	Population		% black	% urban	% with ≥12 years of education	Median annual income (dollars)
	Ages 35–74 years	Total				
Forsyth County, North Carolina	95,863	243,683	24	75	63	16,600
Jackson, Mississippi	68,303	202,895	48	100	71	14,800
Minneapolis suburbs, Minnesota	69,338	192,004	1	100	85	24,165
Washington County, Maryland	45,539	113,068	4	57	60	16,623
Total	279,043	751,650				

* Source, US census of the population 1980 (3).

TABLE 2

Age-adjusted mortality rates for men and women aged 35–74 years in the ARIC study communities, 1980*

Study community	All-cause mortality		Heart disease mortality†	
	Men	Women	Men	Women
Forsyth County, North Carolina	16.3	8.7	6.7	2.7
Jackson, Mississippi (blacks only)	20.8	10.0	6.6	2.9
Minneapolis suburbs, Minnesota	9.4	6.3	4.2	1.3
Washington County, Maryland	16.1	8.2	7.8	2.8
US total	14.4	8.0	5.7	2.6

* Indirect age adjustment; annual rate per 1,000 population.

† *International Classification of Diseases*, Ninth Revision, codes 390–398, 402, and 404–429.

sons usually residing in the identified household are selected as potential cohort members. For each community, sampling is performed monthly to provide replicate subsamples, so that monthly data can be used in study monitoring. The sampling method differences among communities, which resulted from differences in sampling frame availability, may cause small differences in cohort representativeness, but they should have no important effect on risk factor associations.

A home interview administered to each potential cohort member includes items on cardiovascular risk factors, socioeconomic factors, and family medical history. This is followed by an invitation to the clinic examination. Participants are asked to fast for 12 hours prior to the examination and to bring all prescription and nonprescription drugs used in the two weeks prior to the examination.

Clinic examination

The baseline examination ascertains cardiovascular conditions and measures risk factors. The key factors measured are those thought to be atherogenic, in accord with the view that atherogenesis involves primarily lipid infiltration and thrombosis (4). Other measures are included to help interpret results for the primary factors. For example, medication use, an important potential confounder in risk factor-disease associations, is recorded in detail.

Informed consent is obtained when a participant arrives at the clinic. The examination consists of the elements shown in table 3. Sitting blood pressure, anthropometry, and the venipuncture are performed while the participant is fasting, and then a caffeine-free snack is provided. The order of the remaining exam elements is flexible.

Ultrasound

The 45-minute ultrasound examination consists of imaging carotid arteries bilaterally and a popliteal artery in one leg and measuring distensibility of the left common carotid artery. Ultrasound imaging is a sensitive method for detecting significant arterial stenoses in symptomatic patients (1). The ARIC methods, however, based on measurements described by Pignoli et al. (5), focus on arterial wall thickening, which precedes significant stenosis. These methods and their precision are described in detail elsewhere (6, 7). Carotid and popliteal arteries are sites of predilection for

TABLE 3

Elements of the ARIC cohort baseline examination

Sitting blood pressure	Three measurements with random zero sphygmomanometer.
Anthropometry	Weight, standing and sitting height, triceps and subscapular skinfolds, waist, hip, arm, and calf girths, and wrist breadth.
Venipuncture	Fasting blood samples for lipids, hemostasis, hematology, and chemistry.
Electrocardiogram	Digitally recorded 12-lead electrocardiogram and two-minute rhythm strip.
Ultrasound, postural change	B-mode scan for wall and lumen measurements in both carotid arteries and one popliteal artery. Supine brachial and ankle blood pressures, and heart rate and blood pressures as participant rises.
Interview	Medical history, including the Rose Questionnaire, physical activity, transient ischemic attack and respiratory symptoms, reproductive history, and medication use; and food frequency.
Pulmonary function	Digitally recorded forced vital capacity and timed expiratory volumes.
Physical exam	Brief examination, including heart, lungs, extremities, neurologic examination, and breast examination.
Medical data review	Verify selected positive findings, report selected results to participants, refer for diagnosis or treatment.
Reporting of results (deferred)	Mail results from routine medical tests to participants and their physicians.

early atherosclerosis (4, 8) and are sufficiently superficial for accurate ultrasound evaluation. Arterial distensibility, measured as the ratio of the change in lumen diameter to the change in blood pressure during a cardiac cycle, may be an indicator of even earlier atherosclerotic changes (9). A duplex scanner (Biosound 2,000 II sa, Biosound Incorporated, Indianapolis, IN) is used, its doppler mode aiding in locating arterial segments for imaging. The participant is prone for examination of the popliteal artery and supine for examination of the carotid arteries. The distal centimeter of the common carotid artery is viewed from three angles: near-lateral (selected to optimize arterial interface images), anterior, and posterior. The carotid bifurcation and proximal centimeter of the internal carotid artery are viewed from a near-lateral angle.

The ultrasound examination is recorded on ¾-inch (1.91-cm) videotape and interpreted at the ARIC Ultrasound Reading Center. For a 1-cm length of each arterial segment, the Reading Center measures average and maximal thickness for the near wall and the far wall and average and minimal lumen diameter. Thickness of a wall is measured from the blood-intimal to the medial-adventitial interface. The presence of discrete arterial lesions is noted.

Blood analyses

Blood is drawn for assays by the ARIC Central Lipid, Hemostasis, and Chemistry laboratories and by local hematology laboratories (table 4). Some measurements are performed on blood from all participants; others are performed only on frozen blood from a sample of cases and matched controls. Cases are defined at baseline examination as participants with ultrasound evidence of atherosclerosis. Subsequent to the examination, cases are identified as those participants with new cardiovascular events. Atherosclerotic and clinical event cases will be analyzed in separate case-control studies.

A minimally traumatic venipuncture is required (monitored by time required to fill the first tube). Sample processing requires special preservatives, filtration, and low temperature centrifugation and shipping. Blood is stored in the central laboratories at −70 C, with extra aliquots designated for additional measurements not listed in table 4.

Lipid measurements include both traditional and less established risk factors: low density lipoprotein (LDL) cholesterol, apolipoprotein B, high density lipoprotein (HDL) cholesterol, HDL subfractions, and apolipoprotein A-I. Lipoprotein(a) is included to test whether it is a strong independent risk factor (10). Subclasses of lipoproteins and apolipoproteins are measured in case-control studies: LDL subclasses, because small, dense LDL identified in polyacrylamide gel may be particularly associated with coronary heart disease (11, 12), and apolipoprotein E phenotypes, because of their complex associations with lipoprotein cholesterol concentrations (13). Heterogeneity will be studied using monoclonal antibodies for apolipoprotein B epitopes and Southern blotting for identification of restriction fragment length polymorphs.

Each of the major processes involved in arterial thrombosis is represented by factors measured in ARIC (figure 1). Only three have been shown in prospective studies to predict cardiovascular events: fibrinogen (14–16), factor VII (15), and factor VIII (17). Other hemostatic factors were selected either from knowledge of their roles in hemostasis or because of evidence from case-control studies. The latter provide an uncertain type of evidence since hemostatic factors are modified by the presence of disease.

The three factors supported by prospective studies are coagulation factors representing the intrinsic (factor VIII) and extrinsic (factor VII) pathways and the final substrate in the process (fibrinogen). von Willebrand factor, also studied in ARIC,

TABLE 4

Blood measurements and methods in the ARIC cohorts: 16,000 residents aged 45–64 years in four US communities

Laboratory	Measurement	Method
Lipid		
All participants		
	Total cholesterol	Enzymatic
	Total triglycerides	Enzymatic
	HDL* cholesterol	Dextran, magnesium precipitation
	HDL_3 cholesterol	Dextran, magnesium precipitation
	HDL_2 cholesterol	Calculated by subtraction
	LDL* cholesterol	Calculated, Friedewald formula
	Apolipoprotein A-I	Radioimmunoassay
	Apolipoprotein B	Radioimmunoassay
	Lipoprotein(a)	Enzyme-linked immunosorbent assay
Cases and controls		
	Apolipoprotein B epitopes	Monoclonal antibodies
	Apolipoprotein E phenotypes	Isoelectric focusing
	Restriction fragment length polymorphism of apolipoprotein genes	Southern blotting
	LDL subfractions	Polyacrylamide gradient gel electrophoresis
Hemostasis		
All participants		
	Coagulation factors	
	Fibrinogen	Coagulation test
	Factor VII	Coagulation test
	Factor VIII	Coagulation test
	von Willebrand factor antigen	Enzyme-linked immunosorbent assay
	Coagulation inhibitors	
	Antithrombin III	Thrombin inactivation
	Protein C	Enzyme-linked immunosorbent assay
	General screen	
	Activated partial thromboplastin time	Coagulation test
Cases and controls		
	Coagulation activation	
	Fibrinopeptide A	Radioimmunoassay
	Platelet activation	
	Beta-thromboglobulin	Radioimmunoassay
	Platelet factor 4	Radioimmunoassay
	Serum thromboxane B2	Radioimmunoassay
	Fibrinolytic activity	
	Tissue plasminogen activator antigen	Enzyme-linked immunosorbent assay
Chemistry		
All participants		
	Glucose	Hexokinase/glucose-6-phosphate dehydrogenase
	Insulin	Radioimmunoassay
	Sodium, potassium	Ion selective electrode
	Calcium	Ø-Cresolphthalein complexone
	Magnesium	Calmagite
	Phosphorus	Phosphomolybdate
	Creatinine	Jaffe test
	Urea nitrogen	Urease
	Uric acid	Uricase
	Albumin	Bromocresol green
	Protein	Biuret
Local hematology		
All participants		
	Hemoglobin	Cyanomethemoglobin
	Hematocrit	Calculated
	RBC,* WBC,* and platelet count	Automated counter

* HDL, high density lipoprotein; LDL, low density lipoprotein; RBC, red blood cell; WBC, white blood cell.

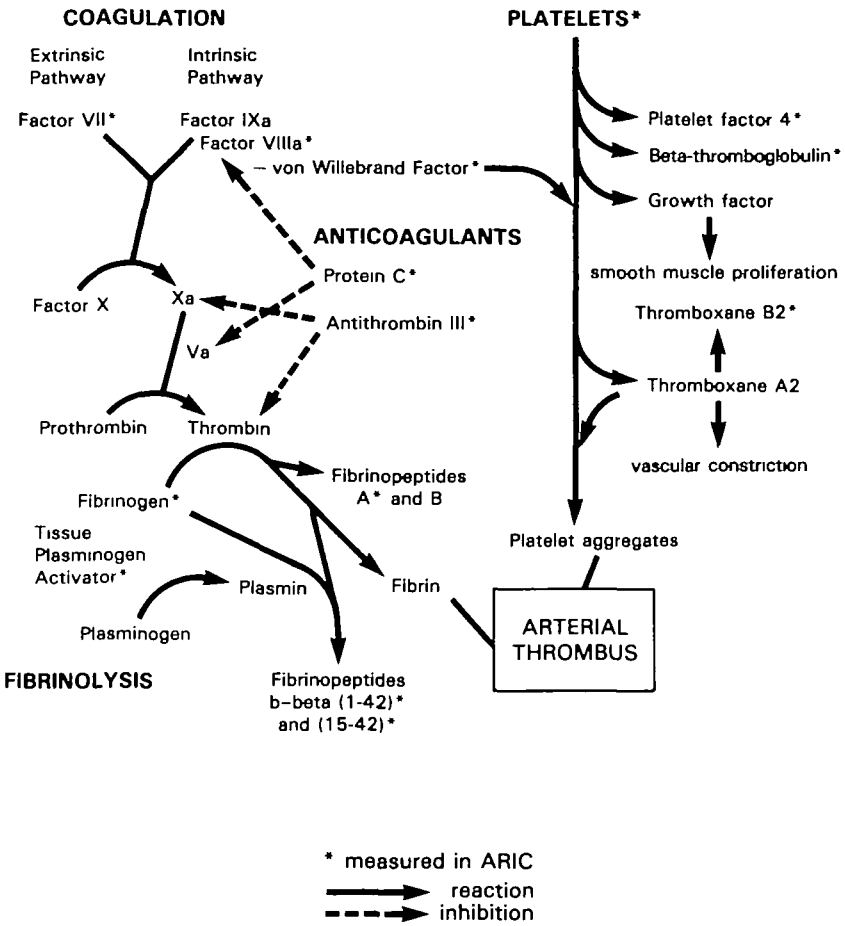

FIGURE 1. Components of arterial thrombosis measured in the Atherosclerosis Risk in Communities (ARIC) Study.

regulates the initiating event, platelet adhesion to the vessel wall.

Coagulation inhibitors and components of the fibrinolytic system are measured because they are the principal deterrents to arterial thrombosis (18). Antithrombin III, which neutralizes thrombin, is the major inhibitor (19), and protein C inactivates factors V and VIII (18). Tissue plasminogen activator activates the fibrinolytic system by converting plasminogen to plasmin (20). The balance of coagulant, anticoagulant, and fibrinolytic activity results in either fibrin formation or lysis. ARIC assesses fibrin formation or lysis by measuring fibrinopeptide A (a by-product of fibrin formation) and the fibrinopeptide B-beta fragments (a result of fibrin lysis).

Platelet functions assessed in ARIC participants may play key roles in atherogenesis. Platelet activation, a key event in arterial thrombosis, is evaluated from two release products, platelet factor 4 and beta-thromboglobulin. Both are measured, because their relative concentrations may distinguish in vitro from in vivo platelet activation (21). They also provide an index to the release of platelet-derived growth factor, which may promote the smooth muscle proliferation in atheromata (22). A thromboxane metabolite (thromboxane B2) measured in the serum of ARIC participants evaluates platelet capacity for thromboxane release. Thromboxane, a potent platelet aggregator and vasoconstrictor, may stimulate atherogenesis and may be

particularly important in the development of unstable angina (23). The set of hemostasis measurements used in ARIC is similar to that used in a European study of the prognosis of angina pectoris (24).

Spirometry is included in ARIC because, even after adjustment for smoking (25), impaired ventilation is associated with cardiovascular mortality. Measurements are made with a volume-displacement spirometer supported by computer. Quality assurance is provided by ARIC's Pulmonary Function Center, and the procedure follows American Thoracic Society guidelines (26).

Participant review session

After the examination, a physician or physician assistant reviews results with the participant, verifying abnormal findings and initiating any appropriate referrals for diagnosis or treatment. Referrals follow guidelines of the National Cholesterol Education Program and the National High Blood Pressure Education Program and are tracked in ARIC follow-up.

Cohort follow-up

After each examination, a telephone questionnaire is administered annually, including the Rose Questionnaire and items on general health, hospitalization, and the occurrence of transient ischemic attack or stroke. Medical events are identified in cohort members by means of the annual questionnaire, the three-year examinations, and the community-wide surveillance procedures. Events of interest include hospitalized and nonhospitalized myocardial infarction, coronary heart disease death, angina pectoris, stroke, and intermittent claudication.

All discharge diagnoses for all cohort hospitalizations are recorded. If the diagnosis included any cardiovascular code, the discharge summary is reviewed. The full hospital record is abstracted if the diagnosis included any of the more specific codes used in community surveillance, if the diagnosis was stroke, or if the discharge summary mentioned myocardial infarction or stroke (Appendix 1). Hospital abstraction to determine whether the event met ARIC's myocardial infarction criteria follows procedures described in the section on community surveillance, except that electrocardiograms are interpreted at the University of Minnesota ECG Center using the full Minnesota code (27). Strokes are investigated using a separate abstracting form. Cohort hospitalizations that qualify as surveillance events are abstracted twice independently; reproducibility is evaluated, and substantive discrepancies are reconciled.

Underlying and contributory causes are recorded for all deaths in cohort members. Deaths with specified diagnoses (Appendix 1) are investigated to determine whether they meet coronary heart disease death criteria, using family and physician contacts, as described below for surveillance. Cohort deaths qualifying as surveillance events are investigated only once. The name of any decedent identified in surveillance is checked against the list of cohort members before a family member or physician is contacted. If the decedent was a cohort member, the family or physician contact is made citing the permission and using the names and addresses given by the cohort member.

COMMUNITY SURVEILLANCE DESIGN

Community surveillance planning began in response to the recommendations of the 1978 National Heart, Lung, and Blood Institute Workshop on the Decline in Coronary Heart Disease Mortality, and it was extended in ARIC to evaluate coronary heart disease incidence differences by race and by geographic location. A surveillance protocol was developed and tested in the 1980–1984 National Heart, Lung, and Blood Institute Community Cardiovascular Surveillance Program (CCSP) (28), and with appropriate modifications, this protocol forms the basis for the current surveillance design.

Community surveillance estimates event

rates for hospitalized myocardial infarction and coronary heart disease death for all ARIC community residents aged 35–74 years. Hospitalized myocardial infarctions are ascertained from discharge listings from all hospitals in or serving the communities; coronary heart disease deaths are ascertained from death certificates. Hospital records are abstracted for all eligible events discharged as acute myocardial infarction and for a sample of discharges with related diagnoses. Sampling of death certificates is based on the underlying cause of death. (Diagnostic codes and sampling fractions are shown in Appendix 1). The sampling plan was devised using CCSP data to minimize the variance of event rate estimates without unnecessary investigation of events unlikely to meet diagnostic criteria.

Hospital records are abstracted, and the following items are recorded: demographics, chest pain, medical history (heart diseases, hypertension, and stroke), hospital procedures and medications, and complications (shock, congestive heart failure, or death). Cardiac enzyme levels are recorded as often as nine times: three times for the day after arrival at hospital (or an in-hospital event) and two times for each of the next three days. Up to three electrocardiograms are reviewed and coded: the first after arrival, the last before discharge, and one taken on day 3 or 4 after admission. Only Q waves are coded, using the Minnesota code. We expect Q-wave coding to miss 20–30 per cent of acute hospitalized myocardial infarctions on the basis of CCSP data and published reports (29, 30), but it was adopted to improve standardization and diagnostic specificity (diagnosing only transmural infarctions and nontransmural infarctions with supportive pain or enzyme evidence). Supporting this design feature is the fact that ST- and T-wave coding by nurse abstractors was not reproducible and did not agree well with coding by the University of Minnesota Coding Center in CCSP, and myocardial infarctions diagnosed without Q waves were usually not diagnosed as acute myocardial infarction by attending physicians.

Deaths are investigated to determine whether the cause was coronary heart disease. If the death occurred in hospital, the hospital record is used. If the decedent had no vital signs on arrival or died outside the hospital, family interviews, physician questionnaires, and coroner records are used. Maryland law forbids contacting families and physicians using information on death certificates, so investigations there are limited to coroner records. The restriction does not apply to cohort deaths, because prior approval is obtained for these contacts. Family members are asked about the decedent's medical history (hospitalizations, physician visits, coronary symptoms, diseases and treatments, and stroke), the circumstances surrounding the death (symptoms and their duration), and the use of emergency medical services. ARIC's physician and coroner forms cover medical history (with more detail on specific diagnoses and medications) and circumstances surrounding the death.

Diagnoses

ARIC diagnostic criteria for hospitalized myocardial infarction and coronary heart disease death (provided in Appendix 2) are adapted from those of the American Heart Association Council on Epidemiology (31).

Cohort and surveillance diagnostic criteria are identical for coronary heart disease death, but they differ for hospitalized myocardial infarction, since only Q waves are coded for surveillance events, whereas for cohort events ST- and T-wave abnormalities are also coded. For this reason, and because investigations are more thorough for cohort events, the nomenclature differs: The surveillance equivalent of a "definite" cohort event is a "confirmed" event. Since surveillance diagnoses require the same or less information than cohort diagnoses, cohort events can be reclassified into the diagnoses used for community surveillance,

for comparison of cohort and surveillance procedures.

A number of diagnoses are made only in cohort members: nonhospitalized myocardial infarction (based on comparison of successive clinic electrocardiograms), prevalent myocardial infarction (based on history or a diagnostic electrocardiogram at baseline), angina pectoris and intermittent claudication (based on the Rose Questionnaire), stroke (based on criteria from the Asymptomatic Carotid Atherosclerosis Study), and others.

Diagnoses are assigned by computer whenever data are unequivocal, as is usually the case for hospitalized events. Exceptions involve chest pain or elevated enzymes recorded as due to noncardiac causes. For such cases, a panel of ARIC physicians, the Morbidity and Mortality Classification Committee, reviews the abstracted record. The committee is usually needed to diagnose coronary heart disease death, particularly to judge whether the death may have a sufficient non-coronary heart disease explanation. Narrative information recorded from family members pertaining to events surrounding the death is important in making this judgement. The Morbidity and Mortality Classification Committee is also involved in quality control. All computer diagnoses for cohort events are reviewed by members of the committee, with differences adjudicated by the full committee. Special attention is given to ARIC diagnoses that disagree with diagnoses given in the community. In selected instances of this type, an ARIC physician or supervisor rereviews the hospital record.

Data collection

ARIC uses an innovative computer-assisted data collection system in which clinic staff directly record into microcomputers much of the data obtained from cohort interviews and exams (32). Immediate entry of data into the computer-assisted system eliminates a transcription step and allows detection of suspicious values while the participant is still available to provide confirmation or correction. Study data are mailed on diskettes from clinics to the Coordinating Center weekly to update the main study data base and for additional editing. Routine data reports for study-wide monitoring are generated using current data. The system is based on commercially available software customized by the Coordinating Center.

Rigorous quality control measures have been implemented to assure that data are collected uniformly at each center and over time. Staff are trained and certified in data collection procedures as detailed in the ARIC manuals of operation (2). Staff performance is monitored, and recertification and retraining are implemented as needed. Supervisory staff observe data collection directly and review tape-recorded participant interviews. Selected measures (anthropometry and ultrasound) are repeated during the examination by the same or different technicians. Duplicate blood samples are drawn and shipped to each laboratory at a later date with separate identification numbers. Duplicate electrocardiograms are transmitted blindly to the ECG Center. Other data quality analyses include assessment of blood pressure data for digit preference, spirometry for maximum participant effort, and venipuncture for blood flow rate. Data monitoring provides the mechanism with which to identify and address problems within a field center or laboratory, between centers, or over time.

Study questions

The diversity of measurements included in ARIC permits it to address many important questions. Illustrative examples, grouped by ARIC's three primary objectives, are presented here.

Investigate the etiology and natural history of atherosclerosis

ARIC ultrasound images of carotid and popliteal arteries have a resolution of approximately 0.1 mm, permitting identifica-

tion of signs of early arterial disease. Combinations of ultrasound measurements from all arteries examined will be used to index the extent of a participant's atherosclerotic involvement in analyses of the associations between atherosclerosis and its putative causes. Arterial wall dimensions will be used in one set of analyses, arterial distensibility measures in another set.

ARIC will test hypotheses relating a number of factors to these indices of atherosclerosis. We expect atherosclerosis to be associated with the following lipid parameters:

Elevated fasting blood concentrations of
- Total cholesterol, LDL cholesterol, and apolipoprotein B, the association being stronger for apolipoprotein B;
- Lipoprotein(a), independent of other lipid factors; and
- Triglycerides, the association being stronger when LDL is low.

Reduced fasting blood concentrations of
- HDL cholesterol, associated at all levels of LDL cholesterol, and apolipoprotein A-I; and
- HDL_2 cholesterol, more strongly associated than HDL cholesterol.

A predominance of small LDL.

Distinct apolipoprotein B epitopes, apolipoprotein E phenotypes, and DNA restriction fragment length polymorphisms of apolipoprotein genes.

We expect hemostatic factors to be atherogenic if they promote platelet and fibrin deposition. Deposition may be due to enhanced coagulant or platelet activity or to reduced anticoagulant or fibrinolytic activity. Hence, we believe that indices of atherosclerosis will be associated with one or more of the following:

Elevated concentrations of
- Coagulation factors, particularly factor VII and fibrinogen;
- Measures of platelet activation—beta-thromboglobulin, platelet factor 4, and serum thromboxane B2; and
- Indicators of active fibrin formation (fibrinopeptide A).

Reduced concentrations of
- Coagulation inhibitors, antithrombin III, and protein C; and
- The fibrinolytic activator, tissue plasminogen activator.

ARIC will also evaluate associations of indices of atherosclerosis with factors that are less directly related to the lipid and thrombosis theories—for example, other established risk factors for clinical coronary heart disease (hypertension and cigarette smoking), fasting insulin and glucose levels, routine hematologic measures (white blood cell, red blood cell, and platelet counts and hematocrit), and lifestyle factors (diet and physical activity).

Other analyses will focus specifically on carotid or popliteal disease. Although coronary heart disease, stroke, and intermittent claudication are all predicted by blood pressure, total cholesterol, and cigarette smoking (33), there are striking differences in the population distribution of these diseases (34) and of the underlying coronary, carotid, and lower extremity artery diseases. For example, carotid disease has a similar prevalence in men and women (35), whereas disease in femoral and popliteal arteries, like coronary heart disease, predominates in males (33, 36–38). Blood pressure, smoking, and glucose metabolism are expected to have somewhat different relations to atherosclerosis in different arterial beds.

Investigate the etiology of clinical atherosclerotic diseases

Both risk factors and indicators of preclinical disease will be studied in relation to subsequent coronary heart disease, stroke, and intermittent claudication. The risk factors measured in ARIC permit testing of new hypotheses. Indications of preclinical disease will include not only the ultrasound measurements but also an ankle-arm index of peripheral vascular dis-

ease, subtle changes in the digitized electrocardiogram, and transient ischemic attack symptoms.

Measure variation in cardiovascular risk factors, medical care, and disease by race, sex, place, and time

The ARIC communities differ in their reported cardiovascular mortality rates (table 2) and are expected to differ in incidence and mortality rates ascertained in community surveillance. Atherosclerosis prevalence rates in each cohort may also differ. Although formal hypothesis testing is not possible with a sample size of four, the ecologic comparison of community rates with the factors that may influence these rates (factors such as those measured in the cohorts, for example) will be of interest. Surveillance may also detect a time trend in coronary heart disease incidence in the four communities (although the study does not have the power to test the significance of trends in separate communities), and this can be compared with the national mortality trend.

Effects of the study design

ARIC's ability to meet its objectives is enhanced by several design features. Evidence of the consistency and generalizability of ARIC's results will be available within the study. Consistency is evaluated by studying associations in four geographic locations among men, women, blacks, and whites. Generalizability is examined by nesting cohorts into communities covered by broad surveillance, which permits interpretation of study results in terms of the representativeness of the cohort participants and their coronary heart disease events in their communities and the characteristics of those communities.

Surveillance rates are monitored and, in part, validated by the cohorts, both by replication of event identification, investigation, and diagnosis activity and by the greater effort for accuracy that is afforded each potential cohort event. Cohorts also provide information on risk factors, preclinical disease, and medical care which will be used to interpret the rates of clinical disease found in surveillance.

The ARIC cohort study is prospective, the design of choice for identifying precursors of disease. Prospective design is important for studying any potential risk factor that may be influenced by disease or by the changes in medications, diet, or habits resulting from disease. All major coronary risk factors, such as lipids, blood pressure, and smoking, are influenced by the presence of disease to some extent, but for hemostatic factors the prospective design is crucial.

ARIC observes directly the early signs of atherosclerosis. Thus, it assesses the association of factors with atherosclerosis in particular. The inquiry seeks evidence regarding specific pathogenic theories. By contrast, the etiology of an end-stage disease, such as myocardial infarction, is more complex. ARIC attempts to unravel some complexity by investigating risk factor associations with both atherosclerosis and its clinical sequelae. For example, if any risk factors predict coronary heart disease better after we have controlled for atherosclerosis, they may be identified as triggering elements or specific myocardial factors.

At Framingham Study rates (39), we would expect 15,086 cohort participants to be free of coronary heart disease at baseline and 471 of them to experience coronary heart disease events (myocardial infarction, coronary heart disease death, or angina) by the time of the second examination; but the national downward trend in mortality, if it is paralleled by a change in incidence in the ARIC communities, would suggest a downward adjustment to approximately 300 events. However, a substantial proportion of examinees will have wall thickenings in one or more arteries; others will have reduced arterial distensibility. Thus, for analyses of risk factor associations with indices of early atherosclerosis, the number of "cases" is much larger.

The statistical power in ARIC cohorts permits:

Subgroup analyses. Is fibrinogen associated with atherosclerosis in participants

who do or do not smoke cigarettes? When LDL is low, does low HDL remain important?; do elevated triglycerides become more important?

Comparisons of the strength of correlated variables. Which has the stronger association with atherosclerosis—central obesity or peripheral obesity?; LDL cholesterol or apolipoprotein B?

Comparison of risk factor effects. Are factors associated with carotid atherosclerosis different from those associated with popliteal disease? Are there coronary heart disease risk factors that are not associated with atherosclerosis?

The design features listed above (prospective design, direct observation of the underlying disease, and sufficient statistical power) would not advance understanding of the etiology of disease unless appropriate risk factors were selected. ARIC benefits from the remarkable progress in modern biochemistry, measuring for the first time in such a study substances whose metabolic roles are understood and believed to be related to atherogenic processes. For many of these factors, practical, accurate assays have only recently become available. By storing multiple aliquots of frozen blood in several laboratories, ARIC will continue to utilize new biochemical technology.

The role of epidemiologic research in the investigation of etiologic hypotheses is one of active interchange with other disciplines. Sometimes a basic discovery comes first in epidemiology. The importance of specific lipoprotein fractions, for example, was found first in population studies, and this led to specific investigations of cholesterol transport. If ARIC confirms the importance of coagulation factors in cardiovascular disease, this would suggest new research directions in hematology. The multidisciplinary team of ARIC investigators hopes to promote such scientific interchange.

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APPENDIX 1

EVENT IDENTIFICATION

Hospital records are abstracted and deaths are investigated according to discharge diagnosis or cause of death codes using sampling percentages shown below.

ICD-9, CM* code(s)	Disease(s)	Sampling percentage	
		Cohort	Surveillance
	Hospitalizations		
410	Acute myocardial infarction	100	100
411	Other acute and subacute forms of ischemic heart disease	100	50
412–414	Old myocardial infarction, angina pectoris, other forms of chronic ischemic heart disease	100	25
402	Hypertensive heart disease	100	10
427–428	Cardiac dysrhythmias, heart failure	100	10
518.4	Acute edema of the lung, unspecified	100	10
430–438	Cerebrovascular disease	100	0

* ICD-9, CM, *International Classification of Diseases, Ninth Revision, Clinical Modification.*

APPENDIX 1—*continued*

ICD-9, CM* code(s)	Disease(s)	Sampling percentage	
		Cohort	Surveillance
	Deaths		
410–414	Ischemic heart disease	100	100
429.2	Cardiovascular disease, unspecified	100	100
250	Diabetes mellitus	100	25
401–402	Essential hypertension, hypertensive heart disease	100	25
427–429	Cardiac dysrhythmias, heart failure, ill-defined descriptions and complications of heart disease	100	25
440	Atherosclerosis	100	25
518.4	Acute edema of the lung, unspecified	100	10
798–799	Sudden death, cause unknown; other ill-defined and unknown causes	100	25
430–437	Cerebrovascular disease	100	0

* ICD-9, CM, *International Classification of Diseases, Ninth Revision, Clinical Modification.*

For cohort hospitalizations, in addition, all discharge codes for all hospitalizations are recorded. The discharge summary is reviewed for any hospitalization with the following codes:

ICD-9, CM* code(s)	Disease(s)
250	Diabetes mellitus
390–459	Diseases of the circulatory system
35–39	Cardiac surgery
88.5	Angiocardiography
745–747	Congenital anomalies of the heart
794.3	Nonspecific abnormal results of cardiovascular function studies
798–799	Sudden death, cause unknown; other ill-defined and unknown causes of morbidity and mortality

* ICD-9, CM, *International Classification of Diseases, Ninth Revision, Clinical Modification.*

If the discharge summary mentions myocardial infarction or stroke or any synonym of these conditions, the full hospital record is abstracted, even if it is not required on the basis of the discharge code.

APPENDIX 2

DIAGNOSTIC CRITERIA FOR CORONARY HEART DISEASE EVENTS

Fatal coronary heart disease

Cohort diagnosis of "definite fatal coronary heart disease" and surveillance diagnosis of "confirmed fatal coronary heart disease" require both of the following:

1. No known nonatherosclerotic or noncardiac atherosclerotic process or event that was probably lethal.
2. The presence of one or both of the following:
   a. A history of chest pain within 72 hours of death.
   b. A history of ever having had chronic ischemic heart disease, such as definite or possible myocardial infarction, coronary insufficiency, or angina pectoris, in the absence of valvular disease or nonischemic cardiomyopathy.

Hospitalized myocardial infarction

Cohort criteria for "definite hospitalized myocardial infarction" are not identical to community surveillance criteria for "confirmed hospitalized myocardial infarction."

A cohort event is diagnosed as "definite hospitalized myocardial infarction" if it meets one or more of the following criteria:

1. Evolving diagnostic electrocardiographic pattern.
2. Diagnostic electrocardiographic pattern and abnormal enzymes.
3. Cardiac pain and abnormal enzymes and:
   a. Evolving ST-T pattern or
   b. Equivocal electrocardiographic pattern.

Hospitalized cohort events that fail to meet the above criteria are classified as "probable," "suspect," or "no myocardial infarction" on the basis of the criteria shown in Appendix table 1.

Community surveillance hospitalized events are diagnosed without full Minnesota coding of electrocardiograms. A "confirmed hospitalized myocardial infarction," therefore, meets one or more of the following criteria:

1. Evolving diagnostic Q wave.
2. Diagnostic Q wave and abnormal enzymes.
3. Cardiac pain and abnormal enzymes.

Electrocardiographic classifications "evolving," "diagnostic," "equivocal," etc. are based on Minnesota codes. For the cohort only, "evolving" requires an additional step: side-by-side comparison of paired tracings and measurement of specific differences. Definitions of electrocardiographic classifications, of "cardiac pain," and of "abnormal," "equivocal," and "normal" enzymes are provided in ARIC manuals 2 and 3 (2). Enzymes considered include lactate dehydrogenase, lactate dehydrogenase subfractions, and creatine phosphokinase and its myocardial fraction.

APPENDIX TABLE 1

Summary of ARIC cohort diagnostic criteria for hospitalized myocardial infarction

ECG* findings	Enzymes	Diagnosis
Cardiac pain present		
Evolving diagnostic ECG pattern	Abnormal	Definite MI*
	Equivocal	Definite MI
	Incomplete	Definite MI
	Normal	Definite MI
Diagnostic ECG pattern	Abnormal	Definite MI
	Equivocal	Probable MI
	Incomplete	Suspect MI
	Normal	No MI
Evolving ST-T pattern	Abnormal	Definite MI
	Equivocal	Probable MI
	Incomplete	Suspect MI
	Normal	No MI
Equivocal ECG pattern	Abnormal	Definite MI
	Equivocal	Suspect MI
	Incomplete	No MI
	Normal	No MI
Absent, uncodable, or other	Abnormal	Probable MI
	Equivocal	Suspect MI
	Incomplete	No MI
	Normal	No MI
Cardiac pain absent		
Evolving diagnostic ECG pattern	Abnormal	Definite MI
	Equivocal	Definite MI
	Incomplete	Definite MI
	Normal	Definite MI
Diagnostic ECG pattern	Abnormal	Definite MI
	Equivocal	Suspect MI
	Incomplete	No MI
	Normal	No MI
Evolving ST-T pattern	Abnormal	Probable MI
	Equivocal	Suspect MI
	Incomplete	No MI
	Normal	No MI
Equivocal ECG pattern	Abnormal	Suspect MI
	Equivocal	Suspect MI
	Incomplete	No MI
	Normal	No MI
Absent, uncodable, or other	Abnormal	Suspect MI
	Equivocal	No MI
	Incomplete	No MI
	Normal	No MI

* ECG, electrocardiographic; MI, myocardial infarction.