

Screening for early detection of cardiovascular disease in asymptomatic individuals

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Objective Primary prevention of cardiovascular disease has been aimed at risk factor identification and treatment without efforts to document early cardiovascular disease. The objective of the current study is to screen individuals with vascular and cardiac tests aimed at identifying early abnormalities likely to progress and to measure risk contributors susceptible to therapy.

Methods A center was established for comprehensive screening of an asymptomatic population with 10 tests designed to detect early vascular and cardiac abnormalities and blood tests to identify potential targets for risk contributor intervention. The first 396 individuals screened in the center have been analyzed.

Results Using a scoring system from 0 (no disease) to 20 (advanced disease), 49% of the population exhibited scores of ≥ 5 and 39% exhibited scores of ≥ 6 . These scores appear indicative of early disease mandating initiation of or change in medical therapy, which was recommended to the individuals screened and to their primary care physicians.

Conclusion The screening tests utilized are effective in uncovering unsuspected early cardiovascular disease in which targeted treatment could be effective in reducing the incidence of cardiovascular events in susceptible individuals. Documentation of the sensitivity and specificity of this approach requires longitudinal study. (*Am Heart J* 2003;146: 679–85.)

See related Editorial on page 572.

Most preventive efforts nationally have been devoted to risk factor modification in the asymptomatic population (primary prevention)^{1,2} or intervention in individuals who have sustained cardiovascular morbid events (secondary prevention).^{3–6} Pharmacopreventive therapy in those who have had an atherosclerotic cardiovascular event is remarkably effective in preventing subsequent events and prolonging life.^{3–6} Nonetheless, chronic disability in many such patients results in reduced quality of life, increased health care costs, and the economic burden of unemployment.

Risk factor modification in asymptomatic individuals is aimed at slowing the progression of atherosclerotic disease that is at the root of most cardiovascular morbid events. These risk markers, such as elevated levels of blood pressure, cholesterol, blood sugar, homocys-

teine and c-reactive protein, are statistically related to the risk of an event,^{7–10} but they may be viewed as risk contributors, not as direct markers for the atherosclerotic disease. Many individuals who harbor these markers are free of disease and many individuals with atherosclerotic disease manifest none of the risk markers.

Atherosclerosis is a progressive process that appears to be initiated by endothelial dysfunction and cellular infiltration in the wall.¹¹ Plaque formation in conduit arteries and thrombotic episodes that may initiate acute events are likely late manifestations of this arterial wall disease. Thus the presence of endothelial dysfunction and/or structural or functional changes in the arterial wall should identify individuals at biological risk for an atherosclerotic event. Furthermore, the absence of such vascular abnormalities should identify individuals not at risk for events and therefore not in need of preventive therapy. Focus on the vascular dysfunction rather than on so called risk factors has the potential to improve the precision of therapeutic intervention to prevent events in asymptomatic individuals.¹² This hypothesis needs confirmation in longitudinal studies.

Cardiac disease, which may lead to heart failure, is commonly asymptomatic. Although atherosclerosis is a common cause of such disease, left ventricular dysfunction frequently is idiopathic. Both imaging meth-

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ods and biochemical methods have been advocated to detect the asymptomatic phase of the disease, particularly because of the evidence that early intervention can delay or prevent the symptoms from developing.^{13,14}

In order to identify asymptomatic individuals with early vascular or cardiac disease in need of intervention and to establish a database to evaluate the sensitivity and specificity of screening efforts, the Rasmussen Center for Cardiovascular Disease Prevention was opened at the University of Minnesota in January 2001. A comprehensive array of noninvasive testing was developed using techniques that have either been established or advocated for early detection. These tests represent a reasonable approach to screening for pre-clinical vascular and cardiac disease, but they may be modified as new data become available. In addition, we undertook measurement of modifiable risk contributors that could serve to steer interventions in those with markers for disease.

The purpose of this preliminary communication is to describe the diagnostic array being utilized in the Center and to review the early experience. A comprehensive database is being established that will allow long-term tracking of individuals and correlation of screening results with outcomes.

Methods

The history, physical examination, and laboratory testing in the center are carried out by a nurse practitioner and a medical technologist. The total duration of the center visit is confined to 2 hours: 1 hour dedicated to extensive history, cardiovascular examination and lifestyle discussion and 1 hour to the testing procedures. Physician oversight includes chart and data review, report generation and, only when indicated, direct patient contact.

Screening consists of 3 phases: (1) risk category assignment; (2) early disease assessment; and (3) modifiable disease contributor assessment.

Risk category assignment

The extensiveness of the screening evaluation and its cost is based on risk category assignment. Certain tests are highly unlikely to be abnormal in low-risk individuals and their performance then cannot be justified on cost-benefit analysis. Individuals are therefore placed in low- or high-risk categories on the basis of information obtained on initial interview. The following are criteria for high-risk assignment.

1. Age. Men >45 years of age and women >55 years of age.
2. Family history. Individuals with 1 primary relative (parent or sibling) or 2 secondary relatives (grandparent, cousin, etc) with cardiovascular disease or diabetes before the age of 65 in women and before 55 in men.
3. Personal history. Individuals who present with a history of an abnormal risk factor (blood pressure, cholesterol, blood sugar) or a previous presumed cardiovascular event.
4. Smokers.

5. Abnormal test results. In addition, individuals assigned to the low-risk category are reassigned to high-risk if any of their initial screening tests are determined to be abnormal.

Early disease assessment

The screening tests employed are designed to separately assess early markers for arterial and left ventricular disease.

Arterial disease. Because endothelial dysfunction may be the earliest manifestation of arterial disease likely to progress to symptomatic atherosclerosis,¹¹ the goal has been to assess early markers for endothelial and vascular dysfunction in an attempt to identify disease that has not become symptomatic. The following tests are employed.

1. Arterial elasticity. Pulse contour analysis allows separate assessment of the elasticity of the large conduit arteries and the small arteries that serve as sites of reflected waves in the circulation. A pulse wave analysis methodology developed at the University of Minnesota and now Food and Drug Administration approved and commercially marketed (Hypertension Diagnostics, Inc, Eagan, Minn) is utilized. It consists of applying a piezoelectric transducer to a radial artery with on-line computer analysis of the pulse wave with a rapid printout of a cardiovascular profile that includes large artery elasticity (C_1) and small artery elasticity (C_2). Previous studies have validated the methodology, demonstrated the decline in C_1 and C_2 with aging, demonstrated abnormally low C_2 levels in patients with cardiovascular disease, and shown a correlation between risk factors for cardiovascular disease and a low C_2 .¹⁵
2. Blood pressure at rest and during exercise. Resting sitting blood pressure is recorded by standard sphygmomanometry. The patient then stands on a treadmill and exercises for 3 minutes at a 5 met (metabolic equivalents) workload. The exercise-induced change in blood pressure is recorded. A brisk rise has previously been shown to correlate with reduced arterial elasticity or compliance.¹⁶
3. Optic fundus photos. A digital camera (Canon, Greenville, SC) is used to image the optic fundus without the need for mydriasis. Fundus photos are analyzed for the A:V ratio and the presence of A:V crossing changes.
4. Microalbuminuria. A spot urine sample is analyzed for the albumin excretion per mg creatinine, a marker for small artery disease in the kidney.¹⁷
5. Ankle/brachial index (high-risk only). Systolic blood pressure is measured in the arm and leg by Doppler detection. A ratio of leg/arm systolic pressure below 0.90 is taken as evidence for lower extremity occlusive disease.¹⁸

Cardiac disease. Left ventricular disease precedes the onset of symptoms of cardiac dysfunction. Identification of early cardiac disease could allow intervention that may be effective in slowing progression.¹¹

1. Electrocardiogram (high-risk only).
2. Left ventricular ultrasound. A hand-held portable echocardiographic unit (Sonosite, Bothell, Wash) is used to screen the left ventricle (LV) for transverse diameter, wall thickness, and calculated LV mass.
3. Plasma B-type peptide (BNP) concentration. BNP levels are a sensitive guide to left ventricular dysfunction.¹⁹ BNP is assayed using an on-line platform that utilizes a drop of venous

Table I. Range of values of arterial elasticity measurement

Age category	Sex	C ₁ (large artery)(mL/mm Hg × 10)			C ₂ (small artery)(mL/mm Hg × 100)		
		Normal	Borderline	Abnormal	Normal	Borderline	Abnormal
≤45 y	Male	≥15	12–14.9	<12	≥7	6–6.9	<6
	Female	≥12	10–11.9	<10	≥5	4–4.9	<4
46–64 y	Male	≥12	10–11.9	<10	≥6	5–5.9	<5
	Female	≥10	9–9.9	<9	≥4	3.5–3.9	<3.5
≥65 y	Male	≥10	9–9.9	<9	≥5	4–4.9	<4
	Female	≥9	8–8.9	<8	≥3	2.5–2.9	<2.5

Table II. Range of values of markers for cardiovascular disease

Test	Normal	Borderline	Abnormal
Arterial elasticity*			
Resting blood pressure (mm Hg)	SBP <130 and DBP <85	SBP 130–139 or DBP 85–89	SBP ≥140 or DBP ≥90
Exercise blood pressure (mm Hg)	SBP rise <30 and SBP ≤169	SBP rise 30–39 or SBP 170–179	SBP rise ≥40 or SBP ≥180
Optic fundus	A:V ratio >3:5	A:V ratio ≤3:5 or Mild A:V crossing changes	A:V ratio ≤1:2 or A:V nicking
Microalbuminuria (mg/mmol)	≤0.6	0.61–0.99	≥1.00
Ankle brachial index	>0.90	–	<0.90
Electrocardiogram	No abnormalities	Nonspecific abnormality	Diagnostic abnormality
LV ultrasound	LVIDD/BSA (cm/m ²) 2.70 (M); 2.60 (F) and LVM/BSA (gm/m ²) <120 (M); <110(F)	LVIDD/BSA (cm/m ²) 2.70–2.89 (M); 2.60–2.79 (F) or LVM/BSA (gm/m ²) 120–129 (M); 110–119 (F)	LVIDD/BSA (cm/m ²) ≥2.9 (M); ≥2.8 (F) or LVM/BSA (gm/m ²) ≥130 (M); ≥120 (F)
BNP (pg/dL)	≤50	51–99	≥100

M, Male; F, female.
*See Table I.

blood placed on a slide device for immediate analysis (Bio-site, San Diego, Calif).

Scoring system

Each of the tests employed can be categorized as normal, borderline, or abnormal. The ranges assigned to each test are shown in Tables I and II. An arbitrary decision was made to assign each abnormal test a score of 2 and each borderline test a score of 1. The 7 vascular and 3 cardiac tests can yield an overall score of 0 to 20. Although each test may not have the same clinical value in detecting cardiovascular disease, there was no rational basis for an alternate scoring system. This score therefore provides a continuum from no evidence for disease to strong evidence for disease. The hypothesis is that the disease score will be a sensitive guide to the risk for a cardiovascular event.

Modifiable disease contributors

When early disease is present, identification and aggressive treatment of modifiable factors that contribute to disease progression is mandatory. Such aggressive intervention may also be appropriate in unusually high-risk individuals (eg, patients with diabetes), even if early disease cannot be identified.

When disease is not present, modest life-style interventions to lower the risk of future disease development may still be prudent.

1. Blood pressure. Taken seated at rest.
2. Fasting lipid levels. Patients are instructed to come to the center fasting and blood is drawn for analysis of cholesterol, low-density lipoproteins, high-density lipoproteins, and triglycerides.
3. Fasting blood sugar.
4. C-reactive protein. This inflammatory marker is associated with the risk of atherosclerotic events. Anti-inflammatory therapy may suppress the levels.
5. PAI-1. This platelet-aggregating factor may increase the risk of thrombotic events and may be suppressed by therapy.
6. Homocysteine. Elevated levels have been identified as a risk factor for atherosclerosis and may be suppressed by folic acid.

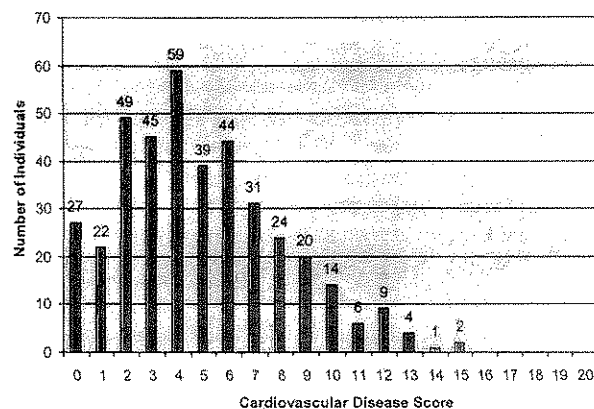
The results of some of these tests are divided into optimal, borderline, and abnormal, with abnormal results clear targets for therapy and borderline tests optional targets, depending on the evidence for cardiovascular disease (Table III).

Table III. Laboratory test disease contributors

Laboratory test		Reference range			Units
		Optimal	Borderline	Abnormal	
HDL cholesterol	(HDL-C)	≥45 Men, ≥55 women	40–45 Men, 50–55 women	≤40 Men, ≤50 women	mg/dL
LDL cholesterol	(LDL-C)	≤100	101–129	≥130	mg/dL
Triglycerides	(TG)	≤150	151–199	≥200	mg/dL
Glucose	(GLUC)	≤110	111–125	≥126	mg/dL
C-reactive protein	(HsCRP)	≤0.300		>0.300	mg/dL
Plasminogen activator inhibitor-1	(PAI-1)	≤43		>43	ng/dL
Homocysteine	(HCY)	≤10	10.1–12	>12	μmo/L

Table IV. Subjects by age and sex

Age category	Sex	
	Male	Female
<40 y	39	24
40–54 y	125	57
55–64 y	59	39
≥65 y	32	21

Figure 1

Cardiovascular disease scores in 396 individuals screened at the Rasmussen Center for Cardiovascular Disease Prevention.

Results

The Rasmussen Center for Cardiovascular Disease Prevention was opened in October 2000. Through the end of 2000, free certificates were distributed to individuals for screening visits that allowed us to establish and test our internal screening techniques. Beginning in January 2001, marketing efforts were initiated. Media coverage was sought and letters encouraging indi-

viduals to come for screening were mailed to families identified to be in the higher economic groups. Letters to physicians encouraging the referral of their patients also were generated, and large corporations in the Twin Cities were approached about executive and employee screening. All of these efforts have contributed to early volume in the center.

Although our initial approach was to charge the patient for our bundled fee for service (approximately \$600 for a first and subsequent visit), it soon became apparent that insurance reimbursement was an important issue for our prospective patients. Approaches were made to the major health care insurers in the Twin Cities and they have agreed to reimburse for appropriate CPT codes. The magnitude of this reimbursement is currently being tracked and varies from payer to payer.

The demographics of the first 396 individuals whose results have been entered into the database are shown in Table IV. Although it was our initial concept that we would be screening healthy individuals to identify early, subclinical cardiovascular disease, it soon became apparent that individuals with overt disease, such as untreated hypertension and symptomatic coronary disease, were also referring themselves to the center. Therapy was recommended or initiated in these individuals based on traditional guidelines.

Our testing procedures also identified more subtle preclinical vascular and cardiac disease that mandated initiation or change in medical therapy. Early disease scores in these 396 subjects are depicted in Figure 1. Borderline or abnormal blood pressure and borderline or abnormal small arterial elasticity were the most common abnormalities. Note, however, that the blood pressure levels classified as borderline are within the traditionally defined normal levels and that an elevated systolic (>140 mm Hg) or diastolic (>90 mm Hg) qualifies as abnormal. Furthermore, the scoring system utilized provides a maximum of 4 points for these 2 abnormalities, yet 49% of the individuals (194/396) exhibited scores of ≥5, and 39% (155/396) had scores

of ≥ 6 . The most common additional abnormalities were the rise in blood pressure with exercise (often in individuals with normal resting pressure) and microalbuminuria. Only 7% of the population were free of any abnormalities by virtue of scores of 0.

Because age and sex are important determinants of risk, we also examined disease scores separately in men and women in different age groups (Table V). As expected, the frequency of significant early disease, defined arbitrarily as a score of ≥ 5 , was strikingly age-dependent in both men and women, with disease less common in younger women than men but more common in older women than men.

Abnormalities in the laboratory tests for disease contributors provide therapeutic opportunities, especially for those with detectable early disease. Recommendations for intervention are provided in a complete report sent both to the patient and the identified primary care physician. Subjects are invited to return for follow-up evaluation at intervals dependent on the severity of disease identified. It must be recognized that this early experience in the Rasmussen Center is not necessarily representative of the general population. It is likely that individuals with strong family histories of cardiovascular disease and appropriate health concerns were more likely to refer themselves to the Rasmussen Center in the early months of its existence. A better cross-section may be available if executive and employee groups from large corporations are referred directly for screening.

Discussion

The traditional approach to reduction of risk for cardiovascular disease events has been 2-fold: (1) screen the healthy population for "risk factors" and intervene with nonpharmacologic or pharmacologic approaches in those whose measurements are above a level defined as "normal"; and (2) intervene aggressively in those individuals who have suffered from a cardiovascular event with therapy aimed at "secondary prevention."

Documented cardiovascular events provide evidence for advanced atherosclerotic disease. Secondary preventive therapy initiated in such patients slows progression of the disease and reduces the risk for subsequent events. Because atherosclerosis presents with a long asymptomatic phase, therapy initiated before an event should be effective in reducing the risk for a first event. However, the primary preventive approach in screening for risk factors captures many individuals who have no vascular precursors of atherosclerosis and excludes many individuals destined to develop progressive atherosclerosis. Focusing on the vasculature should therefore improve the specificity and sensitivity to detect those individuals in need of therapy

Table V. Cardiovascular disease detected (scores ≥ 5) by age and sex

Age	Sex	Scores of ≥ 5
<40 y	Male	11/39 (28%)
<40 y	Female	1/24 (4%)
40-54 y	Male	55/125 (44%)
40-54 y	Female	20/57 (35%)
55-64 y	Male	33/59 (56%)
55-64 y	Female	26/39 (67%)
≥ 65	Male	27/32 (84%)
≥ 65	Female	21/21 (100%)

to prevent progression of the vascular disease. In such individuals, guidelines now recommend aggressive treatment of risk factors to levels well below the traditional standards for risk factor interventions.

Cardiac screening is aimed at a different chain of events. Asymptomatic left ventricular dysfunction may exist long before the clinical syndrome of heart failure appears. In population-based surveys, 3% to 5% of the adult population exhibits evidence for ventricular dysfunction likely to progress.^{20,21} Therapy introduced during this phase can delay or prevent the occurrence of symptomatic heart failure with its poor prognosis.¹³

Despite the rationale for early detection and the availability of newer screening tools to detect vascular and cardiac disease, little effort has been expended nationally to evaluate the sensitivity and specificity of comprehensive screening programs. The Rasmussen Center for Cardiovascular Disease Prevention may be the first community-oriented facility to undertake this effort. In its first 2 years of operation, the magnitude of the unmet need in the community has begun to become apparent. Among the first 396 individuals screened, nearly 50% exhibited early cardiovascular disease scores deemed to require intervention, usually with pharmacologic therapy. Drugs most commonly recommended included statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and other antihypertensive drugs. Prescription of such chronic pharmacopreventive therapy in asymptomatic individuals may seem aggressive, but it appears potentially more rational than the current approach of antihypertensive and cholesterol-reducing therapy in asymptomatic individuals who may have no direct evidence for vascular or cardiac disease. The impact of age and sex on the prevalence of early cardiovascular disease raises issues of cost-effectiveness and screening criteria that must be addressed, preferably after longitudinal data provide documentation of sensitivity and specificity for cardiovascular events.

Because most of these screened individuals were in a high socioeconomic group with health insurance and access to primary care physicians, it is clear that our

health care system is not providing adequate management to identify and treat high-risk individuals. Furthermore, because these individuals did not exhibit organ system symptoms that might have precipitated referral to a cardiovascular specialist, the burden of diagnosis and treatment must fall on the primary care physician.

The philosophy behind the Rasmussen Center is that a specialized, nurse-practitioner managed screening program using state-of-the-art methodology not generally available in the primary care setting could empower primary care physicians with data and recommendations that can be incorporated into their care of those individuals screened. The modest cost of the screening visit should be returned many times over by the prevention or delay in development of costly cardiovascular events.

The procedures utilized to screen for early vascular and cardiac disease in the center were selected on the basis of current published experience with many of the tests and physiologic concepts that led to the development of others. The philosophy of the center is that early disease rather than abnormal risk factors should be the focus of therapeutic intervention. Indeed, the distinction between normal and abnormal values for risk factor assessment loses its meaning when early disease is present. In that setting, treatment of even so called normal levels of blood pressure and cholesterol are currently recommended. In the absence of evidence for vascular or cardiac disease it is likely—although not yet proven—that events will not occur prematurely. Because management strategies in the present era can at best delay but cannot prevent future events, and because individuals without early disease may eventually develop disease and events in their later years, the economic burden of health care for cardiovascular events may merely be shifted to an older age. Thus, critical to the overall goal of reducing health care costs might be a societal decision regarding the upper age at which aggressive and expensive medical care would be provided.

The array of tests currently used in the Rasmussen Center may change as experience grows and data accumulate. Based on our early experience, we have already elected to eliminate the ankle/brachial index assessment because of its insensitivity in this asymptomatic population. We will, instead, be performing carotid ultrasound assessment of intimal-medial thickness. The strength is that an array of tests should provide better discrimination than a single test. The scoring system described in this report represents an effort to quantitate the evidence for early vascular or cardiac disease. It is our hypothesis that the higher the score the greater likelihood a cardiovascular event will occur. Placebo-controlled drug trials are planned to docu-

ment effects on the disease score and to serve as a pilot for outcome studies.

Therapy recommended currently on the basis of the screening procedures may tend to obscure a relationship between disease score and subsequent cardiovascular events. However, an important potential benefit of the screening procedure is the identification of individuals with low scores who we would predict are not at risk for events. Documentation of such a low risk would validate the usefulness of the array of tests utilized. Identification of individuals without early disease who do not require intervention may be as important for quality of life as is the aggressive intervention in the population with early disease.

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