

Age and Cardiovascular Disease

Prediction of Risk for First Age-Related Cardiovascular Events in an Elderly Population: The Incremental Value of Echocardiography

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OBJECTIVES	We sought to determine if echocardiography enhances prediction of first age-related cardiovascular events.
BACKGROUND	Whether echocardiographic assessment improves risk stratification for first cardiovascular events is not well known.
METHODS	This retrospective cohort study included randomly selected residents of Olmsted County, Minnesota, age ≥ 65 years, who had ≥ 1 transthoracic echocardiograms at the Mayo Clinic between 1990 and 1998, in sinus rhythm, without valvular or congenital heart disease, and followed through medical records for first myocardial infarction (MI), coronary revascularization, atrial fibrillation (AF), congestive heart failure (CHF), transient ischemic attack (TIA), stroke, or cardiovascular death. Patients were excluded if they had any of these events before the baseline echocardiogram.
RESULTS	Of 1,160 patients (age 75 ± 7 years; 746 women) followed for a mean of 3.8 ± 2.7 years, 333 (29%) first events occurred (70 AF, 67 coronary revascularization procedures, 65 CHF, 48 MI, 38 stroke, 25 TIA, and 20 cardiovascular deaths). In a multivariate model, age ($p < 0.001$), male gender ($p < 0.001$), diabetes mellitus ($p = 0.005$), systemic hypertension ($p < 0.001$), left atrial volume/body surface area ≥ 32 ml/m ² ($p = 0.003$), left ventricular (LV) mass/height ≥ 120 g/m ($p = 0.014$), LV systolic dysfunction ($p < 0.001$), and LV diastolic dysfunction ($p = 0.029$) were independent predictors. A risk-scoring algorithm was developed and validated for the prediction of first events. The five-year event-free survival was 90%, 74%, and 50% for low-, medium-, and high-risk groups, respectively.
CONCLUSIONS	Echocardiography enhanced prediction of first cardiovascular events in this referral-based elderly cohort. Its role in risk stratification for primary prevention of these events in the community warrants further investigations. (J Am Coll Cardiol 2003;42:1199-205) © 2003 by the American College of Cardiology Foundation

Congestive heart failure (CHF) and atrial fibrillation (AF) have reached epidemic proportions in the U.S. (1,2). Coronary heart disease remains the number one cause of death in the country, while stroke is the leading cause of disability for both men and women (3). The magnitude of these

See page 1206

age-related conditions is expected to increase because of the burgeoning older population. Significant progress has been made in the evaluation and treatment of certain clinical risk factors for primary and secondary prevention of cardiovascular diseases. The value of echocardiographic assessment of subclinical abnormalities for stratification of risk for age-related cardiovascular outcomes is not well known.

Our aim in this study was to determine, within an elderly cohort, which subclinical abnormalities detected by noninvasive echocardiography are predictive of first age-related cardiovascular events including CHF, AF, myocardial infarction (MI), coronary revascularization, stroke, transient ischemic attack (TIA), and cardiovascular death. We hypothesized that certain abnormalities, which may not be clinically overt, portend greater risk for future cardiovascular events, independent of and incremental to conventional clinical cardiovascular risk factors.

METHODS

Study design and population. A retrospective cohort design was used. After obtaining approval from the Mayo Foundation Institutional Review Board, a list of potential subjects was identified from a computerized search of the echocardiography database. Search criteria were residence in Olmsted County, Minnesota, and record of ≥ 1 transthoracic echocardiograms performed at Mayo Clinic or Olmsted Medical Center or their affiliated hospitals between January 1, 1990, and December 31, 1998. Olmsted County

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Abbreviations and Acronyms

AF	= atrial fibrillation
CHF	= congestive heart failure
CI	= confidence interval
HR	= hazard ratio
LA	= left atrial
LV	= left ventricle
MI	= myocardial infarction
SD	= standard deviation
TIA	= transient ischemic attack

is relatively isolated geographically, with healthcare provided by a few well-defined health providers, the largest of which is Mayo Clinic, which provides all echocardiographic services. In a prior study, it was demonstrated that 96% of Olmsted County residents age 65 to 74 years had ≥ 1 encounters with the Mayo medical system within a three-year period (4).

The population from which the study sample was drawn included all Olmsted County residents of age ≥ 65 years, who were referred for a transthoracic echocardiogram between 1990 and 1998 and had provided permission to use their records for research purposes. The earliest examination within the study period was designated as the baseline study. The list of patients was cross-referenced with the computerized Mayo Clinic registration file, medical index (containing diagnostic codes), surgical database, and electrocardiographic database. These administrative databases allowed screening of patients with conditions that were exclusion criteria. A total of 3,520 patients remained eligible after cross-referencing the administrative databases, and a random sample of 2,240 (64%) was drawn by SAS random number selection program. Retrospective comprehensive review of the Mayo Clinic medical records of these 2,240 patients was undertaken. During this review, a further 1,080 patients were excluded, 942 of these owing to baseline presence of more than mild valvular disease by echocardiographic criteria, and 138 because of presence of exclusion criteria not detected by the administrative databases. The remaining 1,160 patients constituted the study population.

Clinical and echocardiographic data. The medical records of each of the 1,160 eligible patients were comprehensively reviewed for the clinical data. The indication for echocardiography was directly retrieved from a specific field from the Echocardiography Laboratory database called "indication or referral diagnosis," which had to be entered at the time of booking for echocardiography study. The definitions of coronary artery disease, peripheral artery disease, carotid artery disease, smoking status, hyperlipidemia, systemic hypertension, diabetes mellitus, and family history of coronary artery disease were as per standard clinical diagnoses, and had previously been described in detail (5).

Criteria defining the outcomes of interest were specified a priori. The patients with any of these outcomes on or before the date of baseline echocardiogram were excluded

from the study. The type and date of detection of each outcome were abstracted. Congestive heart failure was defined according to Framingham criteria, requiring the presence of two major, or one major and two minor Framingham criteria (6). A history of MI was considered present if ≥ 2 of the three diagnostic criteria were fulfilled: compatible clinical presentation, diagnostic cardiac enzyme levels, and electrocardiographic changes consistent with MI. Coronary revascularization referred to coronary artery bypass grafting or percutaneous coronary intervention. Atrial fibrillation was defined as the presence of clinically documented and electrocardiographically confirmed irregular rhythm with disorganized atrial activity and without discrete P-waves. Stroke in this study included development of any type of stroke, as defined by clinical documentation of the diagnosis with confirmatory findings on imaging studies. A TIA was defined by the clinical documentation of the diagnosis, in the absence of other conditions that could be responsible for the neurological symptoms.

Left atrial (LA) volume was measured offline using the biplane area-length method (7) and was indexed to body surface area (indexed LA volume). The cardiologists measuring LA volume were blinded to patients' clinical data and outcome status. All other echocardiographic data were retrieved electronically from the computerized echocardiographic database.

The transmitral Doppler flow profile is integral to the assessment of diastolic function (8). Abnormal relaxation is the mildest form of diastolic dysfunction. In our study, the presence of mitral E/A < 0.75 or deceleration time > 240 ms was considered evidence of abnormal relaxation. In patients with pseudonormal LV filling, or moderate diastolic dysfunction, transmitral flow characteristics are similar to those observed in normal diastolic function, although the left atrium is typically enlarged from elevated LV filling pressures. In this study, both pseudonormal and normal LV filling were defined by the presence of mitral E/A of 0.75 to 1.5 and deceleration time of 151 to 240 ms, but distinguished by whether LA volume was ≥ 28 ml/m² (pseudonormal) or < 28 ml/m² (normal) (9). The severe form of diastolic dysfunction is characterized by the presence of restrictive diastolic filling with markedly elevated filling pressures (8). In this study, the presence of mitral E/A > 1.5 or deceleration time ≤ 150 ms was considered evidence of restrictive diastolic filling. Unlike other transmitral flow parameters, isovolumic relaxation time was not routinely measured during the study period and was therefore not used for analyses.

Outcome ascertainment. The outcomes of interest for this study were first documented MI, coronary revascularization, CHF, AF, stroke, TIA, and cardiovascular death. The ascertainment of any of these outcomes was accomplished through comprehensive review of the medical records and cross-referencing the multiple administrative databases available (medical, surgical, electrocardiography, and echocardiography) to detect any inconsistencies. The same

Table 1. Baseline Clinical, Electrocardiographic, and Echocardiographic Characteristics of Study Population Stratified by Event Status

Characteristic (Number With Data)	Had Events (333)	No Events (827)	p
Age, mean ± SD, yr (1,160)	77 ± 7	74 ± 6	< 0.001*
Men, % (1,160)	38	35	0.269
Pulse rate, mean ± SD, beats/min (1,117)	67 ± 19	64 ± 18	0.044
Systolic blood pressure, mean ± SD, mm Hg (948)	146 ± 23	142 ± 23	0.011
Pulse pressure, mean ± SD, mm Hg (948)	67 ± 19	64 ± 18	0.044
History of hypertension, % (1,160)	63	48	< 0.001
History of vascular disease, % (960)	26	13	< 0.001
History of diabetes mellitus, % (1,160)	11	7	0.026
LVH on ECG, % (1,160)	6	3	0.043
M-mode LA dimension, mean ± SD, mm (1,014)	41 ± 7	40 ± 6	0.001*
LA volume, mean ± SD, ml (1,018)	64 ± 22	56 ± 21	< 0.001*
Indexed LA volume, mean ± SD, ml/m ² (1,018)	36 ± 12	31 ± 12	< 0.001
LV diastolic septal wall thickness, mean ± SD, mm (765)	12 ± 3	11 ± 2	< 0.001*
LV diastolic posterior wall thickness, mean ± SD, mm (792)	11 ± 2	10 ± 2	< 0.001*
LV mass/height, mean ± SD, g/m (733)	131 ± 44	109 ± 26	< 0.001*
LV ejection fraction, mean ± SD, % (866)	61 ± 11	63 ± 9	0.018*

*Rank-sum test was used. Other variables that did not differ significantly between the two groups: weight, height, body surface area, body mass index, diastolic blood pressure, hyperlipidemia, smoking (current or past), family history of coronary artery disease, chronic obstructive pulmonary disease, LV end-systolic and end-diastolic dimensions, pulmonary venous systolic and diastolic forward flow velocities, pulmonary venous atrial reversal velocity, mitral peak E and peak A velocities, mitral early deceleration time, and tricuspid regurgitation velocity.

ECG = electrocardiography; LA = left atrial; LV = left ventricular; LVH = left ventricular hypertrophy.

definitions and criteria for adjudication of events were used for all patients throughout the study period.

Statistical methods. Differences in baseline characteristics between patients who did and did not develop outcome events of interest after baseline echocardiography were assessed using chi-square analyses for categorical variables (Table 1). For continuous variables, two-sample t tests were used for variables that had a normal distribution, and Wilcoxon rank-sum tests for those with a non-normal distribution. Descriptive statistics for both groups were tabulated as means and standard deviations (SD) or frequency percentages.

To evaluate the incremental prognostic value of echocardiographic variables, the global log likelihood ratio chi-square statistics for models developed using: 1) clinical risk factors alone; 2) echocardiographic variables alone; and 3) combined clinical and echocardiographic variables were determined by Cox proportional hazards regression. In all cases, statistical significance was defined as two-tailed p < 0.05.

Development of model and risk-scoring algorithm. Using Cox proportional hazards analyses, age- and gender-adjusted models, as well as models with multiple adjustments, were developed to estimate the associations between clinical and echocardiographic variables, and time to first cardiovascular event. From these models, hazard ratios (HR), 95% confidence intervals (CI), and the associated p values were generated. Ordinal versions of each of the echocardiographic variables of the multivariate model, with two to four levels, were created, and represented by threshold indicator variables. When a certain echocardiographic measurement was missing in a patient, an additional level

(missing) for that variable was assigned. With the exception of age, the clinical variables were dichotomous.

Next, a backward stepwise Cox regression procedure was used, starting with the four clinical variables and 14 echocardiographic indicator variables. In addition to requiring that each variable remain significant at p < 0.05 level, it was also mandated that the degree of risk change unidirectionally with each step-up in level for all echocardiographic variables. The missing category for each echocardiographic variable was simply combined with whichever of the corresponding ordinal levels it most closely resembled in relative risk.

Finally, a risk score was developed by assigning small integer values to each category (clinical or echocardiographic), which were approximately proportional to the model-based log hazard differences between the categories. The log (hazard) associated with a 10-year age increase was similarly converted to an integer value. It was anticipated that the resulting score would account appropriately for the missing values, and therefore would be generalizable to other situations with different patterns of missingness. Cumulative event-free survival, stratified by three risk groups (low-, medium-, and high-risk scores), was estimated by Kaplan-Meier analysis.

Validation of model and score. The multivariate model for prediction and risk scoring algorithm were displayed in Tables 2 and 3. We investigated the robustness of the model using two approaches. First, a bootstrap (10) resampling study (n = 500) was done relative to the backward stepwise procedure to determine the likelihood that all of the clinical and echocardiographic variables in our final models would appear also in the final model of these bootstrap samples. It

Table 2. Multivariate Model for Prediction of First Age-Related Events

Variables	Parameter Estimate	HR (95% CI)	p
Age, yrs	0.06	1.06 (1.04–1.08)	< 0.001
Male gender	0.41	1.50 (1.19–1.88)	< 0.001
Diabetes mellitus	0.50	1.64 (1.16–2.32)	0.005
Systemic hypertension	0.50	1.64 (1.30–2.06)	< 0.001
Indexed LA volume ≥ 32 ml/m ²	0.35	1.42 (1.13–1.78)	0.003
LV mass/height ≥ 120 g/m	0.45	1.57 (1.10–2.26)	0.014
LV ejection fraction < 50%	0.80	2.22 (1.44–3.42)	< 0.001
Presence of any diastolic dysfunction	0.49	1.64 (1.10–2.55)	0.029

*p > 0.05 for the following variables: systolic blood pressure, diastolic blood pressure, pulse pressure, pulse rate, hyperlipidemia, carotid artery disease, smoking (current or past), chronic obstructive pulmonary disease.
CI = confidence interval; HR = hazard ratio; LA = left atrial; LV = left ventricular.

was not required that the same set of threshold variables for each echocardiographic variable be selected, but merely that the variable was represented by at least one of the threshold variables.

The second method of validation was to apply the model to a separate population of a prospective study (referred from here on as the prospective validation cohort). In this prospective cohort, all 410 patients were referred to the echocardiography laboratory subsequent to 1998, and were recruited and followed prospectively. A total of 62 outcome events occurred during a two-year follow-up in this prospective cohort. This prospective study had no residency requirement and included many non-Olmsted County residents. The final model (ordinal variable version) was re-estimated on this prospective validation cohort, and the model chi-square statistics (normalized to the number of events) compared. In addition, risk scores were calculated for the 410 patients in the prospective validation cohort, and used to stratify the patients in the same way as in study cohort. The corresponding Kaplan-Meier event-free survival curves were generated and compared with those of the

study cohort. The empiric risk estimates at year 1 and year 2 were compared between the study population and the prospective validation cohort (Table 4).

RESULTS

Baseline characteristics of the study population. A total of 1,160 residents (746 women; 414 men) of Olmsted County, Minnesota, mean age 75 ± 7 years (range 65 to 100 years) fulfilled all study criteria and constituted the study population. The principal indications for echocardiographic assessment were dyspnea (32%), chest discomfort (20%), palpitations, lightheadedness, presyncope or syncope (18%), cardiac function assessment (20%), murmurs (8%), and other reasons (2%). Further review of the records of the group of patients with a referral indication of “cardiac function assessment” showed that 38% had dyspnea as a predominant symptom, 32% had chest discomfort, 20% had fatigue, and 10% had various combinations of these symptoms. Over a mean follow-up period of 3.8 ± 2.7 years, 333 (29%) patients had a total of 536 events of interest. A total of 307 patients died during the follow-up period. First events (n = 333) included 70 AF, 67 coronary revascularization procedures, 65 CHF, 48 MI, 38 stroke, 25 TIA, and 20 cardiovascular deaths. A number of baseline characteristics differed between the patients who had ≥ 1 outcome event versus those who did not have an event during follow-up (Table 1). The majority of the patients (1,113 patients; 96%) had normal LV systolic function with ejection fraction $\geq 50\%$. Left ventricular diastolic function was classified as normal in 150 patients, mildly abnormal (ab-

Table 3. Risk-Scoring Algorithm for the Prediction of First Age-Related Cardiovascular Events

Variable	Risk Score
Clinical	
Age 65–69.9 yrs	0
Age 70–74.9 yrs	+1
Age 75–79.9 yrs	+2
Age 80–84.9 yrs	+3
Age ≥ 85 yrs	+4
Male gender	+1
Diabetes mellitus	+1
Systemic hypertension	+1
Echocardiographic	
LV ejection fraction $\geq 50\%$ or missing	0
LV ejection fraction < 50%	+2
Normal diastolic function	0
Any diastolic dysfunction or missing	+1
Indexed LA volume < 32 ml/m ² or missing	0
Indexed LA volume ≥ 32 ml/m ²	+1
LV mass/height < 120 g/m or missing	0
LV mass/height ≥ 120 g/m	+1

LA = left atrial; LV = left ventricular.

Table 4. Kaplan-Meier Event Rates for the Study Population and Prospective Validation Cohort

Risk Groups	Study Population	Validation Cohort
At year 1		
Low	3	2
Medium	8	7
High	17	13
At year 2		
Low	5	2
Medium	12	10
High	25	23

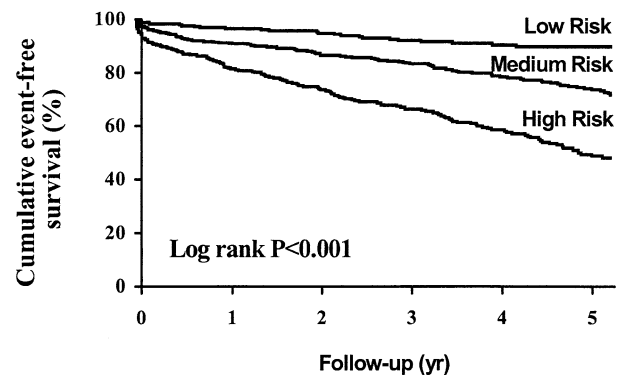
normal relaxation) in 473 patients, moderately abnormal (pseudonormal) in 192 patients, and severely abnormal (restrictive) in 32 patients.

Prediction of first age-related cardiovascular events. AGE AND GENDER-ADJUSTED MODELS FOR PREDICTION OF FIRST EVENTS. When adjusted for both age and gender, the significant clinical and echocardiographic predictors included age (per year) (HR 1.06; 95% CI 1.05 to 1.08; $p < 0.001$); male gender (HR 1.20; 95% CI 0.96 to 1.50; $p = 0.105$); body mass index (per 5 kg/m²) (HR 1.02; 95% CI 1.01 to 1.05; $p = 0.037$); systemic hypertension (HR 1.75; 95% CI 1.40 to 2.19; $p < 0.001$); coronary artery disease (HR 1.85; 95% CI, 1.08 to 3.17; $p = 0.025$); diabetes mellitus (HR 1.84; 95% CI 1.31 to 2.60; $p = 0.001$), and the following echocardiographic variables: indexed LA volume (per 10 ml/m²) (HR 1.29; 95% CI 1.19 to 1.40; $p < 0.001$); LV end-systolic dimension (per 5 mm) (HR 1.23; 95% CI 1.10 to 1.36; $p < 0.001$); LV ejection fraction (per 10%) (HR 0.77; 95% CI 0.68 to 0.86; $p < 0.001$); LV mass/height (per 10 g/m) (HR 1.01; 95% CI 1.01 to 1.02; $p < 0.001$); and presence of diastolic dysfunction (HR 1.36; 95% CI 1.16 to 1.60; $p < 0.001$).

MULTIVARIATE MODEL FOR PREDICTION OF FIRST EVENTS. A multivariate model was developed for the prediction of first events. This contained four clinical and four echocardiographic variables, all statistically independent of each other: age, gender, diabetes mellitus, systemic hypertension, LV systolic function, LV diastolic function, LV mass, and LA volume (Table 2). The global log likelihood ratio chi-square statistics for the models containing: 1) the four clinical risk factors only; 2) the four echocardiographic variables only; and 3) combined four clinical and four echocardiographic variables were 99, 54, and 143 (vs. 99 or 54, $p < 0.001$), respectively. We also tested for any independent predictive value of symptoms (chest pain, dyspnea, lightheadedness, palpitations, presyncope, syncope), and found that presenting symptoms that led to echocardiography referral were not independently predictive of first events in univariate or multivariate model. Also, adding symptoms to the multivariate model with the eight independent clinical and echocardiographic variables (Table 2) did not diminish the predictive value of any of the parameters in the model.

RISK-SCORING ALGORITHM FOR PREDICTION OF FIRST EVENTS. A risk score was generated for each patient based on the multivariate model of four clinical and four echocardiographic variables, using the method outlined in the Methods section. The minimum score was 0 and the maximum score was 12 (Table 3). The Kaplan-Meier five-year event-free survival stratified by low (≤ 2), medium (3 to 4), and high (≥ 5) risk scores were 90%, 74%, and 50% (Fig. 1).

The risk score was validated both within the study population, as well as in a prospective validation cohort of 410 patients (see Methods). Within the study population



Risk Groups	No. at risk					
Low	271	251	227	187	153	121
Medium	487	410	358	295	226	174
High	399	300	243	176	127	77

Figure 1. Kaplan-Meier estimates of cumulative event-free survival for the study population.

from which 500 random samples were drawn by the bootstrapping technique, only 2% did not include at least seven of the eight predictor variables of the multivariate model. This means that the multivariate model was highly stable when subjected to random sampling within the study population. Notably, indexed LA volume was the only echocardiographic variable that appeared in 100% of the samples in this random sampling. The risk score in this study population was associated with a HR of 1.44 (95% CI 1.35 to 1.53; $p < 0.001$), so that every increment of one point was associated with a hazard increase of 44%.

We also validated the model and risk score with a completely separate population of 410 patients, who were referred to the echocardiography laboratory and followed prospectively in a different study. Over a two-year follow-up, a total of 62 outcome events developed. In this prospective population, the model fitting was highly acceptable (global model chi-square of 38 for 62 events, versus global model chi-square of 143 for 333 events in the study population). The risk score calculated for the prospective validation cohort was associated with a HR of 1.40 (95% CI 1.25 to 1.58; $p < 0.001$). Thus, the hazard associated with the risk score in the study population (HR 1.44) and that with the validation cohort (HR 1.40) compared closely. Further, the Kaplan-Meier event-free survival curves for the prospective validation cohort and the study population compared closely, when stratified by the low-, medium-, and high-risk scores, as did the estimated cumulative event rates at one and two years (Fig. 2, Table 4).

DISCUSSION

Prediction of age-related cardiovascular events in the elderly: beyond clinical risk factor assessment. This study provides evidence that assessment of certain subclinical parameters by noninvasive echocardiography improves risk stratification for the development of first age-related cardiovascular events in the elderly. The events considered in

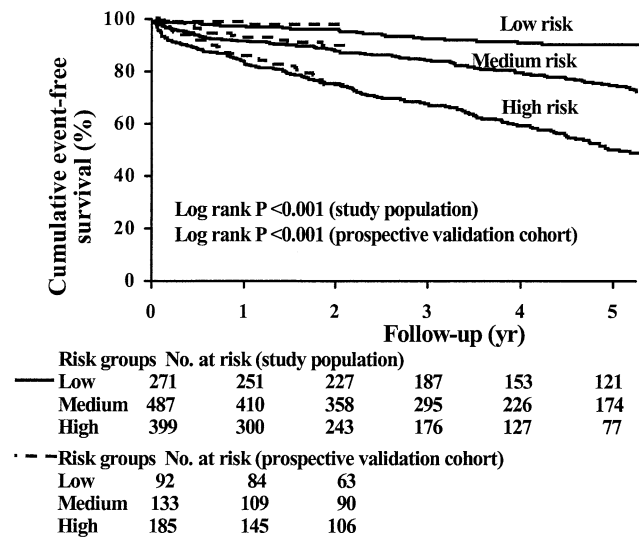


Figure 2. Comparison of Kaplan-Meier estimates of cumulative event-free survival between the study population and the prospective validation cohort, stratified by risk groups.

this study are common age-related conditions. Nearly one-third of the entire cohort who were free from any events of interest at baseline developed at least one event during a mean follow-up time of only 3.8 years.

Advancing age, male gender, systemic hypertension, and diabetes mellitus are well-established cardiovascular risk factors, and were independent predictors of first events in this study, even after echocardiographic parameters were added to the model. From the risk modification standpoint, chronologic age and male gender are immutable. In contrast, systemic hypertension is highly treatable, yet has remained grossly undertreated in the community (11,12). Diabetes mellitus is a potent cardiovascular risk factor, and is now considered equivalent to established coronary heart disease in terms of its status as a risk factor (13). Early diagnosis and control of this metabolic disease has major implications on cardiovascular outcomes. Although there are abundant data on the impact of detection and treatment of these clinical risk factors on cardiovascular outcomes, there is a paucity of data with regard to assessment and treatment of echocardiographic risk markers.

The echocardiographic predictors of first events identified in this study can be readily obtained with any echocardiography system, including the more advanced hand-held devices. Based on the multivariate model in this study (Table 2), simple identification of whether an elderly individual has: 1) abnormal systolic function (LV ejection fraction <50%); 2) evidence of any diastolic dysfunction; 3) LA volume/body surface area ≥ 32 ml/m² (≥ 2 SD from the normal mean value); and 4) LV mass/height of ≥ 120 g/m contributes to the prediction of first events. Although LV systolic function (14,15), diastolic function (5,16), and mass (17) have been shown to be important prognostic indicators for various cardiovascular outcomes, few studies have demonstrated LA volume to be independent of all these echo-

cardiographic risk markers, and of clinical risk factors, for the prediction of the first cardiovascular events in the elderly. Notably, LA volume was the only echocardiographic predictor that was represented in the model for each of the 500 samples randomly drawn from the study population in the risk score validation procedure, attesting to its robustness as a predictor for first events.

Symptoms that led to echocardiographic referral, such as chest pain, dyspnea, palpitations, lightheadedness, presyncope, or syncope, were not independently predictive of first events. This could be related to the relatively nonspecific nature of these symptoms, which are often subjective and not readily quantifiable. In contrast, echocardiography provides a more objective, quantifiable, and reproducible assessment.

Risk-scoring algorithm for prediction of first events in the elderly. A risk-scoring algorithm was developed in this study, based on the multivariate model for the prediction of first events, which was validated both within the study population and in a separate cohort containing 410 patients followed prospectively for two years. The Framingham investigators have been instrumental in the development of algorithms for risk stratification and event prediction. The Framingham data used to generate equations for estimating risk of manifest cardiovascular disease were derived from a middle-aged population of white men and women (18), and not from an elderly population as in this study. The Framingham investigators had also described a general stroke risk profile (19,20), as had the investigators of Israeli Ischemic Heart Disease project (21) and the Cardiovascular Health Study (22). Subclinical risk factors, such as those measured by echocardiography in our study, have not been included in these risk-scoring algorithms. Further, most risk-scoring methods to date were developed to predict a specific condition. Therefore, different risk prediction rules have to be applied to estimate the risks for different outcomes of interest. The clinical application of multiple metrics for quantifying the risks for different events can be intimidating. In the case of primary prevention of a first cardiovascular event, it is desirable to having a simple unifying algorithm that enables point-of-care risk stratification for common age-related conditions that share similar risk factors, such as AF, stroke, MI, CHF, revascularization, and cardiovascular death.

The feasibility of utilizing echocardiography to screen the elderly population for subclinical predictors and applying a simple scoring algorithm for risk stratification requires prospective investigation. The impact of detection and treatment of these abnormalities on cardiovascular outcomes and the cost-effectiveness of such a program will need to be determined. With the availability of highly sophisticated hand-held echocardiographic devices that now allow measurement of these subclinical parameters readily in an office setting, the future possibility of applying noninvasive echocardiographic technology effectively at the point of care for

risk stratification in primary prevention is appealing and warrants further investigation.

Study limitations. This is a retrospective referral-based cohort study, and subject to biases inherent to the design. The majority of this elderly cohort was of Caucasian descent, and the generalizability of the findings to other racial/ethnic groups and to non-referral-based populations could not be determined. Outcome ascertainment, based on chart review, might have underestimated the number of events. However, given the relative geographic isolation of Olmsted County, and the near exclusive utilization of Mayo Clinic as the health provider by the residents of this county (4), it is relatively unlikely that the underestimation would be significant.

Because of the era in which the echocardiograms were performed, pulmonary venous flow velocities and tissue Doppler mitral annular velocities were not available in a significant number of the patients. The categorization of diastolic function status was based on simple mitral inflow characteristics and LA volume, and therefore, misclassification of diastolic function status was possible.

The echocardiographic variables in the multivariate model for the prediction of first events were purposely defined categorically to preserve simplicity. It is possible that the ability to predict first age-related cardiovascular events may be further enhanced if the echocardiographic variables were evaluated as continuous variables. Such a model, however, would be more cumbersome to use clinically.

In this study, we also did not develop a unique prediction model specific for each outcome event. Our intent was to develop a unifying prediction metric, or risk-scoring method, for estimating the overall risk for first cardiovascular events of interest that share similar risk factors. This risk stratification approach does sacrifice event-specific prediction, but is eminently more practical and feasible. Although the risk-scoring algorithm was validated within the study population, and also in a separate referral-based population prospectively followed for outcome events, further validation procedures using community-based non-referral-based populations would be important.

Conclusions. The noninvasive echocardiographic identification of subclinical risk markers, such as LV systolic or diastolic dysfunction, enlarged left atrium, and increased LV mass, enhanced risk stratification for the development of first age-related cardiovascular events in our referral-based elderly cohort, incremental to clinical risk profiling alone. Prospective studies to confirm these findings in other populations, including community free-living individuals, and to determine the cost-effectiveness of primary prevention programs that incorporate echocardiographic evaluation in risk stratification for first events in the elderly may have important public health implications.

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