Identification of structural heart disease in asymptomatic individuals could allow early disease-modifying treatment. Echocardiography is frequently used to evaluate low-risk individuals, and there is an increasing interest in cardiovascular screening because of public awareness of unexplained cardiac deaths among adults and athletes.¹⁻³ Because of the low prevalence of structural heart disease among the general population, echocardiography has traditionally not been considered justified in low-risk individuals, although it is recommended in screening asymptomatic individuals with a family history of sudden death or hereditary diseases affecting the heart or the great vessels.⁴⁻⁶ In the present study, we examined whether echocardiographic screening for structural heart disease in the general population improves long-term survival or reduces the risk of cardiovascular disease.

**Methods**

**Study Population**
The Tromsø Study is a population-based, prospective cohort study conducted in the municipality of Tromsø, Norway. It was initiated in 1974, with a focus on cardiovascular disease. The study design includes repeated population health surveys, to which selected birth cohorts and random samples of other cohorts were invited. The study population comprises a homogeneous population of white race/ethnicity. All inhabitants 25 years or older were invited to the fourth survey (1994-1995). Of the eligible persons, 27,159 (77.0%) attended the first visit. All individuals aged 55 to 74 years and random 5% to 10% samples of the other age groups (aged 25-54 and 75-85 years) were invited to a second visit for more extensive examina-
Echocardiographic Examinations

Two expert cardiologists and a research fellow (H.S.) examined participants in the screening group using a cardiac ultrasound system (CFM 750; VirgoMed Sound A/S). A combined 3.25-MHz mechanical and 2.5-MHz Doppler probe was applied. Standard apical and parasternal long-axis and short-axis views were used. Left ventricular dimensions were measured from 2-dimensional guided M-mode recordings using a software package (EchoPAC, GE Healthcare).

Valvular disease was evaluated by 2-dimensional color Doppler imaging for mitral and aortic insufficiency (color M-mode for aortic insufficiency, pulsed Doppler for mitral stenosis, and continuous Doppler for aortic stenosis). Other cardiac pathologic conditions, including wall motion abnormalities, were noted. Participants were examined at rest in the supine position. They were informed about the results of the echocardiographic examination. In addition to the 1994-1995 echocardiographic screening, 1950 participants were reexamined in 2001 and 1456 participants in 2007 as part of the fifth and sixth surveys, respectively, of the Tromsø Study.

Follow-up Examination

The predefined echocardiographic criteria for referral to clinical follow-up examination were the following: wall thickness exceeding 1.4 cm, aortic root diameter exceeding 4.5 cm, mitral stenosis (all identified participants), aortic stenosis (peak gradient >30 mm Hg), hereditary abnormalities (all suspected cases), mitral insufficiency (regurgitant jet area >4 cm²), left ventricle diastolic diameter exceeding 6.5 cm, heart failure (left ventricle ejection fraction <50%), atrial fibrillation (if not receiving anticoagulant therapy), anatomical abnormalities (if clinical relevance was suspected), and aortic insufficiency (jet >30% of left ventricle outflow tract diameter or, if not measurable, jet reaching the bottom of the ventricle).

Of 362 participants who met the referral criteria, 17 were not referred for follow-up examination (5 had recently undergone extensive examinations for cardiac disease, 8 had grade 2 asymptomatic aortic or mitral insufficiency without any other pathologic conditions, and 4 were reexamined by an expert cardiologist at screening, who decided that no further follow-up examination was needed), and 55 did not attend the follow-up examination (46 missed the appointment for various reasons, and 9 died before reexamination, of which 2 were due to cardiovascular disease). The remaining 290 participants were followed up at the Division of Cardiology, University Hospital of North Norway, and were examined at least once. The follow-up examination included complete medical history, clinical examination, transthoracic echocardiography, resting and exercise electrocardiography, and if (clinically indicated) transesophageal echocardiography or invasive studies. Participants with verified cardiac or valvular pathologic conditions underwent standard treatment and subsequent clinical follow-up examination.

Outcomes

The primary outcome measure was death from all causes. Secondary outcome measures were sudden death, death from heart disease, and fatal and nonfatal myocardial infarction and stroke.
Information on death was collected from the Norwegian Causes of Death Registry. The underlying causes of death were coded according to the International Classification of Diseases, Ninth Revision (ICD-9) or the International Statistical Classification of Diseases, 10th Revision (ICD-10). We defined death from heart disease as death with an underlying cause of death reported as heart disease (ICD-9 codes 390-398, 402, or 404-429 or ICD-10 codes I00-I09, I11, I13, I20-I25, or I30-I52). We defined sudden death as death with the only underlying cause reported as instantaneous death or cardiac arrest (ICD-9 code 798.1 or ICD-10 codes R96.0 and I46).

An independent end point committee (M.-L.L., E.B.M., I.N., and T.W.) adjudicated cases of fatal and nonfatal myocardial infarction and stroke based on data from hospital and outpatient records, autopsy records, and death certificates. The primary and secondary outcomes were treated as dichotomous variables.

Individuals who had died or emigrated were identified through the Population Register of Norway. Follow-up time was assigned from the date of examination, and participants were followed up until the occurrence of death, emigration from Norway, or the end of the follow-up period at 15 years after the date of examination, whichever occurred first. For the analyses of incident myocardial infarction or stroke, individuals were followed up until the occurrence of the secondary outcome measure of death, emigration from the municipality of Tromsø, or the end of the follow-up period at 15 years after the date of examination, whichever occurred first.

### Table 1. Baseline Characteristics of the Screening Group and the Control Group in the Tromsø Study, 1994 to 1995

<table>
<thead>
<tr>
<th>Variable</th>
<th>Screening Group (n = 3272)</th>
<th>Control Group (n = 3589)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>60.0 (10.3)</td>
<td>60.5 (9.9)</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>1873 (57.2)</td>
<td>1608 (44.8)</td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>145 (22)</td>
<td>145 (23)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83 (13)</td>
<td>83 (13)</td>
</tr>
<tr>
<td>Presence of hypertension, No. (%)</td>
<td>1924 (58.8)</td>
<td>2158 (60.1)</td>
</tr>
<tr>
<td>Current cigarette smoker, No. (%)</td>
<td>1032 (31.5)</td>
<td>1142 (31.8)</td>
</tr>
<tr>
<td>Serum lipid levels, mean (SD), mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>263 (50)</td>
<td>259 (50)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>58 (15)</td>
<td>58 (15)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>150 (97)</td>
<td>150 (97)</td>
</tr>
<tr>
<td>Presence of diabetes mellitus, No. (%)</td>
<td>127 (3.9)</td>
<td>155 (4.3)</td>
</tr>
<tr>
<td>Self-reported history of coronary heart disease, No. (%)</td>
<td>406 (12.4)</td>
<td>437 (12.2)</td>
</tr>
<tr>
<td>Family history of early myocardial infarction, No. (%)</td>
<td>803 (24.5)</td>
<td>896 (25.0)</td>
</tr>
<tr>
<td>Use of antihypertensive medication, No. (%)</td>
<td>484 (14.8)</td>
<td>441 (12.3)</td>
</tr>
<tr>
<td>Use of cholesterol-lowering medication, No. (%)</td>
<td>71 (2.2)</td>
<td>71 (2.0)</td>
</tr>
</tbody>
</table>

Table 1. Baseline Characteristics of the Screening Group and the Control Group in the Tromsø Study, 1994 to 1995

### Statistical Analysis

We examined the data according to a predefined plan. Baseline characteristics for the echocardiographic screening and control groups were reported with means (SDs) for continuous variables and with numbers (percentages) for binary variables. We used Cox proportional hazards regression models to estimate hazard ratios (95% CIs) for comparison of event rates between the study groups. Our study was not initially planned as a randomized experiment, and data on which examination line each individual had been allocated to (the randomization status) were no longer available. Therefore, we analyzed the data using the as-treated approach. Hazard ratios were calculated unadjusted and adjusted for baseline characteristics. We used the Kaplan-Meier method for time-to-event analyses and compared survival curves for screening and control groups using the log-rank test. Departure from the Cox proportional hazards regression assumption was examined by evaluation of Schoenfeld residuals and by inspection of log-log survival plots. Analyses were performed unadjusted and adjusted for potential confounding factors (age, sex, smoking habits, triglycerides level, the presence of diabetes mellitus, systolic and diastolic blood pressures, self-reported history of coronary heart disease, total and high-density lipoprotein cholesterol levels, and the use of antihypertensive and cholesterol-lowering medications). We calculated absolute risk reductions and numbers needed to screen.

We performed exploratory analyses of the risk of death from all causes in the following 6 predefined subgroups: participants with hypertension, participants with diabetes mellitus, a family history of early myocardial infarction (defined as myocardial infarction in a first-degree relative <60 years of age), and participants with low, moderate, and high cardiovascular risk profiles (defined as <5%, 5%-14%, and ≥15%, respectively, 10-year risk of fatal cardiovascular disease). The subgroups were not mutually exclusive and accordingly were analyzed separately. The subgroups were analyzed individually and were adjusted for multiple comparisons using the Bonferroni method.

We analyzed the data with statistical software (STATA, version 12; StataCorp LP). All analyses used a 5% 2-sided level of significance.

### Results

Baseline characteristics of the screening and control groups are given in Table 1. In the screening group, 290 participants (8.9%) underwent follow-up examinations because of abnormal findings on the initial echocardiogram. Cardiac or valvular pathologic conditions were verified in 249 participants (7.6%) who underwent standard treatment and subsequent clinical follow-up examination (Table 2).
During 15 follow-up years, 880 persons (26.9%) in the screening group and 989 persons (27.6%) in the control group died (Figure). No statistically significant differences between the screening and control groups were observed in the primary or secondary outcome measures (Table 3). Adjustment for potential confounding factors did not change the effect estimates or significance of the results (data not shown).

Hazard ratios for death from all causes in the predefined subgroups are given in Table 4. Adjustment for potential confounding factors did not change the effect estimates or significance of the results (data not shown). Screening reduced the risk of death from all causes in participants with a family history of early myocardial infarction but not in the other subgroups. For participants with a family history of early myocardial infarction who were allocated to the screening group, the absolute risk reduction in mortality after 15 years was 4.7%. This translates into a number needed to screen of 21 to prevent 1 death. The finding was not significant after adjustment for multiple comparisons. In this subgroup, the proportion of screened participants with pathologic findings on the initial echocardiography was 11.3%.

Discussion

This study of echocardiographic screening of the general population found similar risk of death from cardiovascular disease and death from all causes in the screening group and in the control group. The cardiac and all-cause mortality was similar to that in the general Norwegian population.14 The study included 6861 middle-aged participants from the population-based Tromsø Study, randomly allocated to echocardiography or control groups and followed up for 15 years.

Our findings provide evidence that echocardiographic screening for structural and valvular heart disease in the general population provides no benefit for mortality or for the risk of myocardial infarction and stroke. Among the screening group, the prevalence of structural heart and valvular disease was 7.6%, and the most common finding was valvular disease. However, diagnosing asymptomatic disease is useful only if it can lead to clinical action that slows or stops progression of disease. Although sclerosis of the aortic and mitral valves has been associated with a substantial increased risk of cardiovascular disease,15-17 we did not find that early diagnosis of valvular disease in the general population translated into reduced risk of death or cardiovascular events. This supports existing guidelines that echocardiography is not recommended for cardiovascular risk assessment in asymptomatic adults.1-6

The importance of our findings is that they add empirical evidence to a recommendation based on an expert consensus opinion. Although our results were negative, we believe that they are of clinical importance because they may contribute to reducing the overuse of echocardiography. The number of echocardiograms is increasing annually, and studies of practice patterns show that echocardiography is frequently used to evaluate asymptomatic and low-risk individuals. Furthermore, pocket mobile echocardiography may in the future become part of routine examinations at the bedside and in general practice.18,19 This could substantially increase the future annual number of echocardiograms among low-risk individuals.

Our subgroup analyses found no benefit of echocardiographic screening for all-cause mortality for participants with hypertension, diabetes mellitus, or a high 10-year risk of fatal cardiovascular disease. The findings do not support general echocardiographic screening for structural and valvular heart disease in these patients.

Current guidelines provide no recommendations on screening for asymptomatic coronary heart disease in individuals with a family history of myocardial infarction.20-22 Our finding that echocardiographic screening was associated with
The primary endpoint of the present study was all-cause mortality. Although echocardiographic screening is unlikely to influence noncardiovascular mortality, we believe that all-cause mortality is of more interest than disease-specific mortality in screening trials because it puts the magnitude of any benefit from screening into perspective for prospective decision making.24

Referral to echocardiography from general practice is usually guided by clinical examination, including heart auscultation. We did not examine the usefulness of echocardiography in patients with different cardiac murmurs because the physical examination of our participants did not include heart auscultation. However, the benefit of echocardiography in examining asymptomatic individuals with cardiac murmurs is probably small because the prevalence of cardiac murmurs is high among older persons and most individuals with cardiac murmurs have normal findings on echocardiography.25

Although echocardiography is noninvasive and does not involve irradiation, unwarranted screening is not without caveats. Further cardiac workup because of incidental findings on the echocardiogram may result in anxiety, psychological harm, and unwarranted complications, with little clinical benefit.

Strengths of the present study include a population-based design, random allocation to echocardiographic screening or a control group, and rigorous case validation. A possible limitation is that the data were analyzed using the as-treated approach instead of the intent-to-screen approach. Although all individuals were formally randomized to echocardiographic screening or a control group, we were unable to use the intent-to-screen approach because the data on which examination line each individual was allocated to (randomization status) was not stored because the study was not initially planned as a randomized experiment. The benefit of the intent-to-screen approach instead of the as-treated approach is that it eliminates potential bias associated with non-random loss or crossover of participants. However, we doubt that the as-treated approach influenced the results of the present study. The information on mortality was obtained through linkage with the Norwegian Causes of Death Registry, and only 51 participants (<1%) who had emigrated from Norway were lost to follow-up data in the mortality analyses. About 5% of the individuals allocated to screening did not undergo echocardiography because of equipment malfunction or unavailability of the examiners. These participants were included as control subjects. Because the order of examination was random, the crossover from the screening group to the control group was also random. Other limitations are lack of data on possible prognostic factors such as pro–brain natriuretic peptide and functional class and on the number of participants who saw a cardiologist outside of the study. However, this is un-

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Participants</th>
<th>Death From All Causes, No./Total No. (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of hypertension</td>
<td>408</td>
<td>638/1924 (33.2)</td>
<td>739/2158 (34.2)</td>
<td>0.96 (0.86-1.06)</td>
</tr>
<tr>
<td>Presence of diabetes mellitus</td>
<td>282</td>
<td>75/127 (59.1)</td>
<td>96/155 (61.9)</td>
<td>0.92 (0.68-1.24)</td>
</tr>
<tr>
<td>Family history of early myocardial infarctionb</td>
<td>1699</td>
<td>189/803 (23.5)</td>
<td>252/896 (28.1)</td>
<td>0.81 (0.67-0.98)</td>
</tr>
<tr>
<td>10-Year risk of fatal cardiovascular diseasec</td>
<td>1007</td>
<td>289/485 (59.6)</td>
<td>326/522 (62.5)</td>
<td>0.94 (0.80-1.10)</td>
</tr>
<tr>
<td>Moderate, 5%-14%</td>
<td>2475</td>
<td>415/1165 (35.6)</td>
<td>451/1310 (34.4)</td>
<td>1.04 (0.91-1.18)</td>
</tr>
<tr>
<td>Low, &lt;5%</td>
<td>3337</td>
<td>174/1611 (10.8)</td>
<td>210/1726 (12.2)</td>
<td>0.88 (0.72-1.08)</td>
</tr>
</tbody>
</table>

a Bonferroni method.

b Defined as myocardial infarction in a first-degree relative younger than 60 years.

c Assessed with the Systematic Coronary Risk Evaluation estimates for low-risk countries based on age, sex, systolic blood pressure, total cholesterol level, and smoking habits.7
likely to introduce bias unless it differs between the study groups. Furthermore, study participants were examined for other cardiovascular risk factors, including ultrasonographic examination for carotid artery stenosis and abdominal aortic aneurysm. Although this too is unlikely to have introduced bias to the present study, it may have attenuated the results. Last, 15.2% of participants with abnormal findings on echocardiography did not attend the follow-up examination. This loss to follow-up data may also have attenuated the results.

In conclusion, this randomized study found that echocardiographic screening for structural and valvular heart disease in the general population provided no benefit for mortality. Furthermore, no benefit was observed for the risk of myocardial infarction or stroke.

REFERENCES
10. Schirmer H, Løchen, Mathiesen, Njølstad, Eivind Berge, MD, PhD, provided comments on the manuscript. Løchen, Mathiesen, Njølstad, Arne Skagseth, MD, and Per Lunde, MD, contributed to the acquisition of data. Eivind Berge, MD, PhD, provided comments on the manuscript.
Echoing the Appropriate Use Criteria
The Role of Echocardiography for Cardiovascular Risk Assessment of the Asymptomatic Individual

Erin D. Michos, MD, MHS; Theodore P. Abraham, MD

Cardiovascular disease (CVD) is the leading cause of death in developed countries, and many who die suddenly of CVD have no previous symptoms. Therefore, there is great interest in identifying at-risk individuals so that appropriate preventive measures can be implemented. All asymptomatic adults should undergo global risk assessment. For carefully selected individuals deemed at intermediate risk, noninvasive imaging methods for measuring coronary artery calcium level or carotid intima-media thickness are additional tools for risk stratification, with class IIa indications (benefits exceed risks) in the 2010 American College of Cardiology Foundation/American Heart Association guidelines. Although predictive risk assessment with echocardiography can predict cardiovascular and all-cause mortality independent of blood pressure and other risk factors, the American College of Cardiology Foundation/American Heart Association guidelines give resting echocardiography screening a class IIb indication (benefit somewhat better than risk) for the detection of LV hypertrophy and LV dysfunction for asymptomatic adults with hypertrophy but a class III (no benefit) for those without hypertension. To date, no studies have examined whether a patient’s knowledge of his or her echocardiogram results, including LV hypertrophy, improves adherence to preventive measures and lifestyle recommendations.

Among Medicare-recipient patients, there has been increased use of noninvasive and invasive cardiac services from 1993 to 2011, not explained by changes in CVD prevalence. Cardiovascular disease mortality has also declined between 1997 and 2007 by 26%, although the burden of CVD remains high. In response to the growing use of echocardiography (about an 8% annual increase), the American Society of Echocardiography in 2011 updated their appropriate use criteria (AUC) consensus statement. Since then, AUC have been a focus for accreditation societies and payers alike to improve quality and curtail medical expenses. The AUC for echocardiography are mostly based on expert consensus and observational data because randomized clinical trial data testing the usefulness of echocardiography-guided management were unavailable for most indications.

Hypertrophic cardiomyopathy is present in 1 in 500 of the general population and is the most frequent cause of sudden cardiac death in young people (including trained athletes). After the introduction of a preparticipation athletic screening program in Italy (first with physical examination and an electrocardiogram, and then echocardiography if needed), a declining incidence of sudden cardiac death in athletes was noted. However, the AUC by the American Society of Echocardiography do not endorse routine echocardiography screening for athletes participating in competitive sports who have normal results on a cardiovascular examination. The role for cardiovascular screening of presumably healthy athletes remains controversial given generally low rates of sudden cardiac death in this population.

In this issue of JAMA Internal Medicine, Lindekleiv et al present results from the Tromsø cohort, a population-based study conducted in Norway. During their fourth survey, participants were randomly allocated to 1 of 2 types of examination. This design essentially randomized unselected, generally middle-aged, individuals to a strategy of echocardiography screening vs no echocardiography. This was not designed as a clinical trial, nor was the usefulness of echocardiography screening for mortality their a priori hypothesis. Of 3272 participants allocated to echocardiography, 362 had findings that met the referral criteria for cardiology, and 290 (8.9%) were newly evaluated as a result of screening. Significant incidental findings noted included myxoma, LV dysfunction, wall motion abnormality, and valvular disease. Despite cardiology referral for these diagnoses, mortality during 15 follow-up years was unchanged between the screened and nonscreened groups. There was no reduction in incident myocardial infarction or stroke, but other morbidity outcomes, such as freedom from cardiac surgery (perhaps for valvular disease), were not examined.

During the Tromsø Study fourth examination, 6727 individuals underwent carotid screening. It is unclear how many of these individuals also had echocardiography. If these individuals were in the no echocardiogram treatment arm, the authors may be comparing echocardiography with other types