Prognostic Value of Stress Echocardiography in Patients With Low-Intermediate or High Short-Term (10 Years) Versus Low (<39%) or High (≥39%) Lifetime Predicted Risk of Cardiovascular Disease According to the American College of Cardiology/American Heart Association 2013 Cardiovascular Risk Calculator

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This study evaluates the prognostic value of stress echocardiography (Secho) in short-term (10 years) and lifetime atherosclerotic cardiovascular disease risk–defined groups according to the American College of Cardiology/American Heart Association 2013 cardiovascular risk calculator. The ideal risk assessment and management of patients with low-to-intermediate or high short-term versus low (<39%) or high (≥39%) lifetime CV risk is unclear. The purpose of this study was to evaluate the prognostic value of Secho in short-term and lifetime CV risk–defined groups. We evaluated 4,566 patients (60 ± 13 years; 46% men) who underwent Secho (41% treadmill and 59% dobutamine) with low-intermediate short-term (<20%) risk divided into low (<39%, n = 368) or high (≥39%, n = 661) lifetime CV risk and third group with high short-term risk (≥20%, n = 3,537). Follow-up (3.2 ± 1.5 years) for nonfatal myocardial infarction (n = 102) and cardiac death (n = 140) were obtained. By univariate analysis, age (p <0.001) and ≥3 new ischemic wall motion abnormalities (WMAs, p <0.001) were significant predictors of cardiac events. Cumulative survival in patients was significantly worse in patients with ≥3 WMA versus <3 WMA in low-intermediate short-term and low (3.3% vs 0.3% per year, p <0.001) or high (2.0% vs 0% per year, p <0.001) lifetime risk and also in those with high short-term CV risk group (3.5% vs 1.0% per year, p <0.001). Multivariate Cox proportional hazards analysis identified ≥3 new ischemic WMAs as the strongest predictor of cardiac events (hazard ratio 3.0, 95% confidence interval 2.3 to 3.9, p <0.001). In conclusion, Secho results (absence or presence of ≥3 new ischemic segments) can further refine risk assessment in patients with low-intermediate or high short-term versus low or high lifetime cardiovascular risk. Event rate with normal Secho is low (≤1% per year) but higher in patients with high short-term CV risk by the American College of Cardiology/American Heart Association 2013 cardiovascular risk calculator. **(Am J Cardiol 2015;116:725–729)**

Stress echocardiographic results can effectively risk-stratify patients with known or suspected coronary artery disease (CAD) into low, intermediate, and high-risk groups.[1] A normal stress echocardiographic study confers a benign short-term prognosis.[1–6] The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines on the assessment of cardiovascular risk released a new gender-specific algorithm CV risk estimator to enable health care providers and patients to estimate short-term (10 years) and lifetime risk for atherosclerotic CV disease.[7,8] The present study evaluates the prognostic value of stress echocardiography (Secho) to further substratify risk in patients previously evaluated by CV risk estimator into 3 short-term (10 years) and lifetime risk groups.

Methods

We identified 4,566 patients who were referred for exercise or pharmacologic Secho from March 21, 2000, to December 31, 2012 (Mount Sinai St. Luke's and Mount Sinai Roosevelt Hospitals, New York, New York). Follow-up (100%) for cardiac events ≥1 year was obtained in all patients.

As suggested by the 2013 ACC/AHA 2013 cardiovascular risk calculator, we entered age, gender, race, serum levels of total and high-density lipoprotein cholesterol, smoking, blood pressure, and treatment for hypertension to estimate the short-term and lifetime risk of atherosclerotic disease. Low-intermediate short-term risk was defined as an estimated 10-year risk <20% of fatal or nonfatal coronary heart disease.

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Table 1
Clinical characteristics stratified according to American College of Cardiology / American Heart Association 2013 cardiovascular risk calculator short-term and lifetime predicted cardiovascular risk groups

Variable	Low-intermediate short-term		High short-term	P value
	I.-Low Lifetime (n = 368)	II-High lifetime (n = 661)	III.-High lifetime (n = 3537)	
Age (years)	49 ± 11	47 ± 10	64 ± 12	<0.001
Men	59 (16%)	239 (36%)	1797 (51%)	<0.001
Systemic hypertension	108 (29%)	335 (51%)	2571 (73%)	<0.001
Hyperlipidemia	33 (9%)	133 (20%)	1785 (51%)	<0.001
Smoker	64 (17%)	109 (17%)	1290 (37%)	<0.001
Number of cardiac risk factors	0.7 ± 0.7	1.5 ± 0.9	2.2 ± 1.1	<0.001
Previous percutaneous coronary intervention	0	0	423 (12%)	<0.001
Previous coronary bypass	0	0	336 (10%)	<0.001
Abnormal rest electrocardiogram	109 (30%)	188 (28%)	1608 (46%)	<0.001
Exercise stress echocardiogram	241 (66%)	403 (61%)	1248 (35%)	<0.001
≥ 3 ischemic segments	29 (7.9%)	48 (7.3%)	750 (21%)	<0.001
Peak wall motion score index	1.1 ± 0.4	1.1 ± 0.4	1.3 ± 0.6	<0.001
Ejection fraction (%)	57 ± 8	57 ± 8	53 ± 12	<0.001
Cardiac events	8 (2.2%)	8 (1.2%)	226 (6.4%)	<0.001

Table 2
Clinical characteristics in patients with cardiac events and no events

Variable	No events (n = 4324)	Cardiac events (n = 242)	p Value
Age (years)	60 ± 13	67 ± 12	<0.001
Men	1965 (45%)	130 (54%)	0.01
Systemic hypertension	2824 (65%)	190 (79%)	<0.001
Diabetes mellitus	1285 (30%)	105 (43%)	<0.001
Hyperlipidemia	1839 (43%)	112 (46%)	0.25
Smoker	1375 (32%)	88 (36%)	0.14
Number of cardiac risk factors	1.9 ± 1.2	2.3 ± 1.1	<0.001
Previous myocardial infarction	594 (14%)	85 (35%)	<0.001
Previous percutaneous coronary intervention	395 (9%)	28 (12%)	0.20
Previous coronary bypass	305 (7%)	31 (13%)	0.001
Abnormal rest electrocardiogram	1746 (40%)	159 (66%)	<0.001
% maximum age-predicted heart rate	91 ± 12	86 ± 13	<0.001
Exercise stress echocardiogram	1852 (43%)	40 (17%)	<0.001
≥ 3 ischemic segments	720 (17%)	107 (44%)	<0.001
Peak wall motion score index	1.2 ± 0.5	1.8 ± 0.9	<0.001
Ejection fraction (%)	55 ± 10	44 ± 18	<0.001

Patients with low-intermediate short-term CV risk (<20%) were divided into low (<39%; group I, n = 368) or high (≥39%; group II, n = 661) lifetime risk. A third group with high short-term risk (group III, n = 3,537) was defined as an estimated 10-year risk ≥20%. All patients with diabetes or established CAD (history of myocardial infarction [MI], percutaneous coronary intervention, or coronary bypass) were included in high short-term risk group III.

Maximal symptom-limited treadmill exercise testing was performed using the standard Bruce protocol. Patients exercised to general fatigue, with premature termination for severe angina, ventricular tachycardia, hemodynamically significant arrhythmias, or hemodynamic instability. Post-exercise echocardiographic images were acquired within 30 to 60 seconds after termination of treadmill exercise.

Dobutamine was administered intravenously beginning at a dose of 5 to 10 μg/kg/min and increased by 10 μg/kg/min every 3 minutes up to a maximum of 40 μg/kg/min or until a study end point was achieved. The end points for termination of the dobutamine infusion included development of new segmental WMAs, attainment of >85% of age-predicted maximum heart rate, or the development of significant adverse effects related to the dobutamine infusion. Atropine was administered intravenously in 0.25 to 0.5 mg increments up to a maximum dose of 2.0 mg if a study end point was not achieved.

During both types of stress, transthoracic echocardiographic images were obtained using standard views with commercially available ultrasound equipment (Acuson Sequoia, Mountain View, California, and Hewlett Packard Sonos 5500, Andover, Massachusetts). Echocardiographic images were acquired at baseline, with each increment of dobutamine infusion (if pharmacologic stress) and during the recovery phase.

The left ventricle was divided into 16 segments as recommended by the American Society of Echocardiography,[9] and a score was assigned to each segment at baseline, with each stage of stress (dobutamine only) and during recovery. Each segment was scored as follows: 1 = normal, 2 = mild-to-moderate hypokinesis (reduced wall thickening and excursion), 3 = severe hypokinesis (markedly reduced wall thickening and excursion), 4 = akinesis (no wall thickening and excursion), and 5 = dyskinesis (paradoxical wall motion away from the center of the LV during systole).[10] All echocardiograms were interpreted by experienced echocardiographers who were blinded to patient's treatment and outcome. Contrast (Definity; Lantheus Medical Imaging, N. Billerica, MA) was used in ~13% of stress echocardiographic studies for endocardial border delineation both at rest and stress.

A normal response to stress was defined as normal wall motion at rest with increase in wall thickening and excursion during stress. An abnormal (ischemic) response to stress was defined as (1) an LV wall segment that did not increase in thickening and excursion during stress (lack of a

Table 3
Univariate and multivariate predictors of cardiac events

	Univariate	P value	Multivariate	P value
Age (years)	1.0 (1.0 - 1.1)	<0.001	1.0 (1.0 - 1.1)	<0.001
Diabetes mellitus	1.8 (1.4 − 2.3)	<0.001	1.3 (1.0 − 1.7)	0.07
Previous myocardial infarction	3.4 (2.6 − 4.4)	<0.001	1.4 (1.0 − 1.9)	0.04
≥ 3 ischemic segments	4.2 (3.3 − 5.4)	<0.001	3.0 (2.3 − 3.9)	<0.001

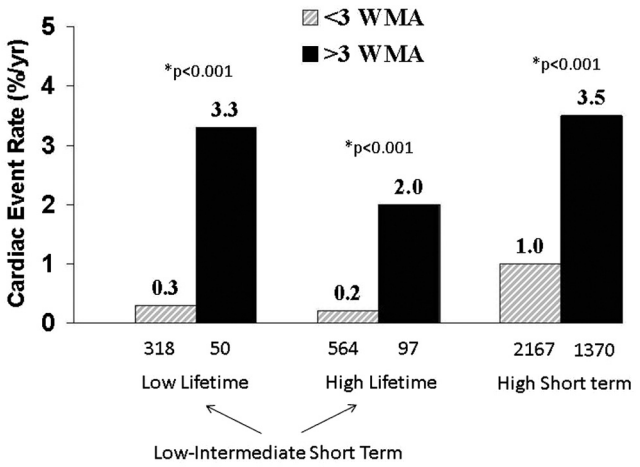

Figure 1. Short-term and lifetime risk of CV disease and stress echocardiographic results (<3 or ≥3 new ischemic segments) versus cardiac event rate. The number of patients within each subgroup is shown below each column.

hyperdynamic wall motion response) or (2) a deterioration in LV wall segment thickening and excursion during stress (increase in wall motion score of ≥1 grade) and (3) a biphasic response with dobutamine stress. Peak wall motion score index after stress was derived from the cumulative sum score of 16 LV wall segments divided by the number of visualized segments. Resting left ventricular ejection fraction used in the study analysis was visual estimated[11] by experienced echocardiographers who were blinded to patient's treatment and outcome. Interobserver and intraobserver variabilities of Secho wall motion and ejection fraction estimation were both <5%.

Follow-up was obtained in all patients by means of physician-directed telephone interviews using a standardized questionnaire. The hard end points of the study were nonfatal MI or cardiac death. Nonfatal MI was documented when diagnostic changes in cardiac enzymes (troponin) were accompanied by appropriate clinical symptoms, electrocardiographic findings, or both. Cardiac death was confirmed by review of hospital medical records, death certificate, and autopsy records when available.

All analysis was carried out using SPSS for Windows, version 13.0 (SPSS, Inc., Chicago, Illinois). Continuous variables are expressed as mean ± SD. Patient groups were compared using Student's *t* tests and single-factor analysis of variance. Differences in categorical variables among groups were assessed using the chi-square analysis.

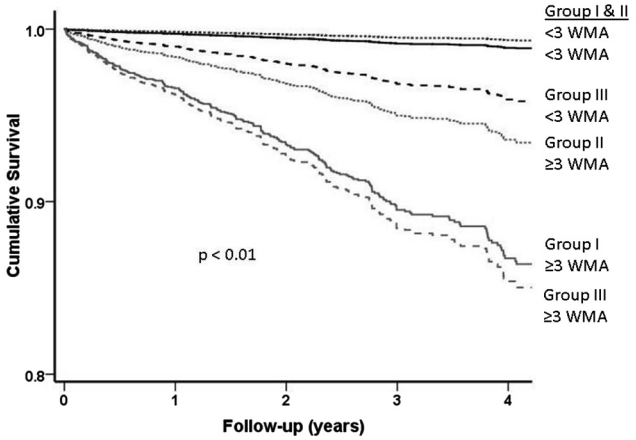

Figure 2. Cumulative survival as a function of CV-defined group and stress echocardiographic results using cardiac events as an end point. Group I = *solid line*; group II = *short, dashed line*; group III = *long, dashed line*.

Univariate Cox proportional hazards analysis was performed to determine the relation between clinical and echocardiographic variables and cardiac events. Univariate predictors of cardiac events were considered in multivariate logistic regression analysis. Kaplan-Meier cumulative survival analysis with stratification by normal or abnormal stress echocardiographic test results was performed. The comparison of survival between groups was made using the Mantel-Cox test (log-rank test). Statistical significance was defined as $p < 0.05$.

A forward conditional (Wald) Cox proportional hazards model with all assumptions tested was used to determine the incremental prognostic value of stress echocardiographic variables over the ACC/AHA 2013 cardiovascular risk calculator, decreased left ventricular ejection fraction, pharmacologic stress test, and ≥3 new ischemic segments. The incremental prognostic value of the added variables was determined by comparison of the global chi-square calculated at each step. The stepwise selection or removal of variables for inclusion was based on clinical judgment and univariate statistical significance.

Results

In the study cohort of 4,566 patients, 1,892 (41%) underwent treadmill exercise and 2,674 (59%) underwent pharmacologic stress. The study indications were 56% chest pain (27% with typical angina), 25% CAD risk assessment, 6% dyspnea, 5% preoperative, and 8% other. The patient characteristics and stress echocardiographic results in defined CV risk groups are characterized in Table 1. In the high short-term risk group III, there were 34% with diabetes, 19% with previous MI, 12% with previous PCI, and 10% with previous bypass surgery.

Patients were followed for up to 5 years (mean 3.2 ± 1.5 years), and all patients were followed for ≥1 year. The mean age of the overall cohort was 60 ± 13 years and consisted of 2,095 men (46%).

Among the study cohort of 4,566 patients, there were a total of 242 cardiac events during the follow-up. These included 102 nonfatal MI and 140 cardiac deaths. There

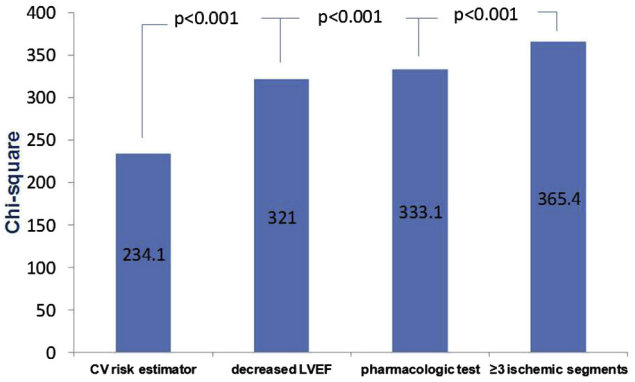

Figure 3. Independent and incremental prognostic power of new ACC/AHA 2013 cardiovascular risk calculator, low ejection fraction, pharmacologic stress test, and ≥3 new ischemic WMAs.

were 202 of 2,674 cardiac events (7.6%) in patients who underwent pharmacologic stress test and 40 of 1,892 cardiac events (2.1%) in patients who underwent treadmill stress echocardiogram (2.5% vs 0.75% per year, p <0.0001; Table 2). All variables listed in Table 1 were considered in the univariate analysis. Significant univariate predictors of cardiac events are listed in Table 3. Clinical and echocardiographic variables significant on univariate analysis were considered in multivariate analysis.

Figure 1 shows the cardiac event rate in patients according to CV risk–defined groups in patients with <3 or ≥3 new ischemic wall motion abnormalities (WMAs). Patients in group III (high short-term and lifetime CV risk) had the highest cardiac event rate. Patients with ≥3 new ischemic WMAs in each CV risk–defined group had a significantly higher cardiac event rate. The lower cardiac event rate of patients in group II with ischemia compared with those in group 1 with ischemia is not significant; this was because of small number of patients in each subgroup. Figure 2 shows cumulative survival curves in patients according to the CV risk–defined groups as a function of Secho results. Cumulative survival was worst in group 3 (high short-term CV risk).

The chi-square statistic is an index of the predictive power of variables from 4 grouping of variables (Figure 3). The addition of decreased ejection fraction to CV risk estimator improved the chi-square value from 234 to 321 (p <0.001). The subsequent addition of pharmacologic stress testing (e.g., dobutamine studies) further improved the chi-square value to 333 (p <0.001). The highest chi-square value of 365 (p <0.0001) included addition of variable ≥3 new ischemic WMAs on Secho to existing variables of CV risk estimator, decreased ejection fraction, and pharmacologic stress testing.

Discussion

Our study resulted in important findings. Stress echocardiography provides additional risk stratification and prognostic value in patients grouped according to the new ACC/AHA 2013 cardiovascular risk calculator. The presence of <3 or ≥3 new ischemic WMAs by Secho effectively substratified patients in existing short-term and lifetime CV risk–defined groups. Multivariate Cox proportional hazard analysis identified ≥3 new ischemic WMAs as the most significant predictor of adverse cardiac events.

The Adult Treatment Panel III stated that the intensity of prevention efforts should match the absolute risk of the patient, specifically using an estimate of 10-year risk (based on the Framingham Risk Score).[12,13] If calculated to be <10%, lifestyle modification alone is recommended; if >20% or the presence of diabetes, lifestyle modification should be used along with pharmacologic therapy of aspirin and statin for primary prevention. The question arises what to do when the calculated risk is from 10% to 20% or among patients with low short-term risk but high lifetime CV risk. Typically, further testing may be necessary to help determine whether there is a need for pharmacotherapy with aspirin and statin.

Patients and physicians may commonly overestimate or underestimate risk.[13,14] There are a number of risk scores to help assess patients.[7,12] There is disagreement as to whether end points of risk algorithms should be limited to hard events (cardiac death and nonfatal MI) or should also include softer events of unstable angina or revascularization that is weakened by geographic variations in use. Additionally, the Framingham Risk Score may underestimate risk by classifying younger men and a large proportion of women as low risk, despite substantial risk factor burden.

The management of patients with low short-term or high CV risk may be more straightforward. The difficulty is about how to refine the prediction of risk in subjects with intermediate short-term or those with low short-term but high lifetime CV risk. The prognostic value of Secho has been previously reported.[1–6] Normal Secho in patients without diabetes is associated with a benign prognosis for up to 18 months.[15] The annualized event rate of <1.0% per year is similar to that of a normal age-matched population and also that of patients with normal coronary angiographic results.[1]

Stress echocardiographic imaging to identify a substantial threshold of ischemia is one of the approaches meant to help identify subclinical atherosclerosis as an anatomical marker of otherwise unrecognized CV risk. In the present study, patients with ≥3 new ischemic WMAs, indicating most likely multivessel disease in each of the 3 ACC/AHA CV risk–defined groups, had a significantly high event rate. Conversely, patients with <3 new ischemic WMAs (mostly single-vessel disease) were identified by Secho to have a low event rate of ≤1%.

The combination of Secho and ACC/AHA 2013 cardiovascular risk calculator may supplement global risk assessment and enhance more appropriate prescribing of aspirin and statin for patients with higher CV risk. The presence of ischemia by Secho is associated with a poorer prognosis. Several studies have demonstrated that even in asymptomatic patients with no known history of CAD, ischemia detected during ambulatory electrocardiographic monitoring or stress testing identifies a higher risk cohort at increased risk of cardiac events and cardiac death.[16]

Patients with markedly abnormal Secho (peak wall motion score index >1.7) or those with transient ischemic cavity dilation are most often patients with multivessel CAD and are at highest risk for cardiac events.[1,17,18] Routine

clinical practice supports the premise that high-risk patients should be referred for coronary angiography and consideration of revascularization as the best strategy to modify and reduce cardiac risk.[19] This strategy of revascularization in patients with markedly abnormal Secho may improve patient outcome by preventing cardiac events.[20]

Although stress imaging clearly adds information of risk stratification and prognosis, prospective data on improvement in clinical outcomes are lacking. The International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial[21] will likely provide valuable insight into the optimal management strategy for patients with stable but obstructive CAD and build on results from the COURAGE trial substudy.[22] ISCHEMIA is a large multicenter trial that will enroll >8,000 patients with at least moderate ischemia on noninvasive testing (≥10% myocardium on nuclear myocardial perfusion or ≥3 of 16 segments with stress-induced severe hypokinesis or akinesis on Secho or cardiac magnetic resonance imaging). Patients will be randomized before cardiac catheterization to a strategy of early revascularization in addition to optimal medical therapy versus conservative approach of optimal medical therapy alone.

Disclosures

The authors have no conflicts of interest to disclose.

1. Yao S, Qureshi E, Sherrid MV, Chaudhry FA. Practical applications in stress echocardiography: risk stratification and prognosis in patients with known or suspected ischemic heart disease. *J Am Coll Cardiol* 2003;42:1084−1090.
2. Marwick TH, Mehta R, Arheart K, Lauer MS. Use of exercise echocardiography for prognostic evaluation of patients with known or suspected coronary artery disease. *J Am Coll Cardiol* 1997;30:83−90.
3. Chuah SC, Pellikka PA, Roger VL, McCully RB, Seward JB. Role of dobutamine stress echocardiography in predicting outcome in 860 patients with known or suspected coronary artery disease. *Circulation* 1998;97:1474−1480.
4. Krivokapich J, Child JS, Walter DO, Garfinkel A. Prognostic value of dobutamine stress echocardiography in predicting cardiac events in patients with known or suspected coronary artery disease. *J Am Coll Cardiol* 1999;33:708−716.
5. Marwick TH, Case C, Sawada S, Rimmerman C, Brenneman P, Kovacs R, Short L, Lauer M. Prediction of mortality using dobutamine echocardiography. *J Am Coll Cardiol* 2001;37:754−760.
6. Sicari R, Pasanisi E, Venneri L, Landi P, Cortigiani L, Picano E. Stress echo results predict mortality: a large-scale multicenter prospective international study. *J Am Coll Cardiol* 2003;41:589−595.
7. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *J Am Coll Cardiol* 2014;63:2889−2934.
8. Lloyd-Jones DM. Cardiovascular risk prediction: basic concepts, current status, and future directions. *Circulation* 2010;121:1768−1777.
9. Shiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358−367.
10. Chaudhry FA, Tauke JT, Alessandrini RS, Vardi G, Parker MA, Bonow RO. Prognostic implications of myocardial contractile reserve in patients with coronary artery disease and left ventricular dysfunction. *J Am Coll Cardiol* 1999;34:730−738.
11. Stamm RB, Carabello BA, Mayers DL, Martin RP. Two-dimensional echocardiographic measurement of left ventricular ejection fraction: prospective analysis of what constitutes an adequate determination. *Am Heart J* 1982;104:136−144.
12. National Cholesterol Education Program (U.S.), National Heart, Lung, and Blood Institute, National Institutes of Health. Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Final Report. Bethesda: National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health, 2002.
13. Frijling BD, Lobo CM, Keus IM, Jenks KM, Akkermans RP, Hulscher ME, Prins A, van der Wouden JC, Grol RP. Perceptions of cardiovascular risk among patients with hypertension or diabetes. *Patient Educ Couns* 2004;52:47−53.
14. Pignone M, Phillips CJ, Elasy TA, Fernandez A. Physicians' ability to predict the risk of coronary heart disease. *BMC Health Serv Res* 2003;3:13.
15. Bangalore S, Yao S, Puthumana J, Chaudhry FA. Incremental prognostic value of stress echocardiography over clinical and stress electrocardiographic variables in patients with prior myocardial infarction: "warranty time" of a normal stress echocardiogram. *Echocardiography* 2006;23:455−464.
16. Exercise electrocardiogram and coronary heart disease mortality in the multiple risk factor intervention trial. Multiple Risk Factor Intervention Trial Research Group. *Am J Cardiol* 1985;55:16.
17. Yao S, Qureshi E, Syed A, Chaudhry FA. Novel stress echocardiographic model incorporating the extent and severity of wall motion abnormality for risk stratification and prognosis. *Am J Cardiol* 2004;94:715−719.
18. Yao S, Shah A, Bangalore S, Chaudhry FA. Transient ischemic left ventricular cavity dilation is a significant predictor of severe and extensive coronary artery disease and adverse outcome in patients undergoing stress echocardiography. *J Am Soc Echocardiogr* 2007;20:352−358.
19. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB III, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV. 2012 ACCF/AHA/ACP/AATS/PCNA/SCA/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. *J Am Coll Cardiol* 2012;60:e44−e164.
20. Yao S, Bangalore S, Chaudhry FA. Prognostic implications of stress echocardiography and impact on patient outcomes: an effective gatekeeper for coronary angiography and revascularization. *J Am Soc Echocardiogr* 2010;23:832−839.
21. National Heart, Lung, and Blood Institute (NHLBI) International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA). Clinicaltrials.gov 2011.
22. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE; COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008;117:1283−1291.