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Changing Drivers of Mortality Among Patients Referred for Cardiac Stress Testing

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Abstract

Objective: To identify temporal shifts in coronary artery disease (CAD) risk factor profiles, clinical parameters, and corresponding mortality rates among patients referred for radionuclide stress testing over 22 years.

Patients and Methods: We assessed 39,750 patients with suspected CAD ("diagnostic" patients) and 10,982 patients with known CAD who underwent radionuclide stress testing between January 2, 1991, and December 31, 2012, and were followed up for at least 5 years (median, 12.7 years).

Results: Among both diagnostic patients and those with known CAD, there was a marked temporal decline in typical angina and myocardial ischemia. However, several risk factors for disease progressively increased, including diabetes, obesity, and hypertension. In addition, the need to perform pharmacological testing in lieu of exercise increased markedly between the first and fourth epochs among both diagnostic patients (from 26.5% [1634 of 6176] to 53.0% [5781 of 10,908]; $P<.001$) and patients with known CAD (from 31.1% [999 of 3213] to 75.5% [1405 of 1860]; $P<.001$). The net effect of these competing positive and negative risk factor trends was no change in the adjusted annualized rate of mortality over the temporal span in our study, ranging from 1.57% per year in 1991-1995 to 1.76% per year in 2006-2012 among diagnostic patients and from 2.46% per year to 2.75% per year during the same intervals among patients with known CAD.

Conclusion: Our findings suggest a marked contemporary shift in the drivers of all-cause mortality among patients undergoing cardiac stress tests away from such factors as typical angina and inducible myocardial ischemia, which are declining in prevalence, and toward such factors as diabetes and an inability to perform exercise, which are increasing in prevalence.

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Since the 1970s, mortality from cardiovascular disease (CVD) has declined markedly,[1] and the sequelae of CVD have been reduced. These changes include a diminished prevalence of myocardial infarction,[2,3] peripheral vascular disease,[4] and typical angina[5] and a substantial reduction in inducible myocardial ischemia among patients referred for cardiac stress testing.[6-9] However, a progressive worsening of important risk factors for clinical diseases has emerged over recent decades, including the advent of a worldwide obesity epidemic,[10] a concomitant increase in diabetes,[11] and an increase in sedentary behaviors.[12-14] To date, it is not known whether and to what extent these adverse health trends might retard or reverse the gains in longevity that have resulted from improving health care.

The study of effects of these competing risk factor trends on all-cause mortality among patients undergoing stress testing is of clinical interest because both positive cardiovascular trends, such as reduction in angina and ischemia, and negative risk factor trends that promote clinical diseases, such as increasing obesity and diabetes, can be measured within the same population. In addition, the adverse risk factor trends that are present within society tend to be even more concentrated within patient cohorts referred for cardiac testing, resulting in a priori clinical risk that is substantially higher than that of the general population. Thus, study of changes in the

distribution of competing risk factor trends and its association with mortality can be assessed within a shorter temporal span among patient cohorts than would be possible by studying general populations. Accordingly, in this study, we assessed the relationship between dynamic changes in the prevalence of coronary artery disease (CAD) risk factors, concomitant clinical cardiac parameters such as ischemia, and all-cause mortality rates among patients with suspected and known CAD referred for radionuclide stress testing at our institution between 1991 and 2012 and then followed up for a minimum of 5 years.

PATIENTS AND METHODS

Study Population and Design
The Cedars-Sinai Cardiac Imaging Registry is a prospective registry of patients who have undergone stress/rest myocardial perfusion imaging (MPI), coronary computed tomographic angiography, and/or coronary artery calcium scanning since 1991 and consented to be followed up. For this study, we identified 54,009 patients from this registry who were referred for stress/rest single-photon emission computed tomography (SPECT) MPI between January 2, 1991, and December 31, 2012. Patients were identified as having known CAD based on a history of prior myocardial infarction, percutaneous intervention, and/or coronary artery bypass surgical procedure. Exclusion criteria included a history of valvular heart disease (n=771), cardiomyopathy (n=386), lost to follow-up (n=411), missing clinical data (n=138), or age less than 30 or greater than 85 years (n=2071). If a patient underwent more than one SPECT-MPI test, only the earliest test was considered. A total of 50,732 patients thus met the inclusion criteria for our study. We divided this cohort into 2 groups: 39,750 patients without a history of CAD, hereafter referred to as *diagnostic* patients, and 10,982 patients with known CAD. We further divided both groups into 4 successive temporal subgroups: those tested between 1991-1995, 1996-2000, 200l-2005, and 2006-2012. All patients were followed up for the occurrence of all-cause mortality. The study was approved by the Cedars-Sinai Institutional Review Board.

Data Collection
At the time of testing, patients completed a comprehensive questionnaire concerning demographic information, clinical symptoms, cardiac risk factors, and medications. Patients were asked about the location and precipitants of chest pain and whether the pain was relieved with rest or nitroglycerin. Based on their response, patients were classified as either being asymptomatic or having nonanginal, atypical, or typical angina. Asymptomatic patients who reported dyspnea were considered a separate group. A family history of premature CAD was considered present if a primary relative had diagnosed CAD or a cardiac event at less than 55 years of age. Current smoking was defined as either currently smoking cigarettes or having stopped smoking for less than 1 year. Hypertension, hypercholesterolemia, and diabetes were defined based on self-reported history. Recorded information regarding medication use was initiated in 2000.

Patients underwent either treadmill exercise or pharmacological testing using adenosine, regadenoson, or dobutamine stress testing if vasodilator testing was contraindicated. Exercise was performed according to the symptom-limited Bruce protocol. Patients who began exercise but could not achieve 85% of their maximal predicted heart rate were routinely studied using pharmacological testing after patients' heart rate and blood pressure returned to baseline.

Stress/rest SPECT imaging was performed according to previously described standard protocols. Semiquantitative visual interpretation of SPECT-MPI images was performed by experienced observers according to a 5-point score (0 = normal to 4 = absence of tracer uptake) for each myocardial segment, with division of images into 20 myocardial segments before February 2005 and 17 myocardial segments thereafter. Summed stress, rest, and difference myocardial perfusion scores were generated and converted to percent abnormal and ischemic myocardium by dividing summed scores by 80 for studies involving 20-segment analysis or by 68 for studies

involving 17-segment analysis, and then multiplying by 100. A summed difference score of less than 5% defined the presence of no ischemia, and scores of 5% to 9.9%, 10% to 14.9%, and 15% or greater defined the presence of mild, moderate, and severe myocardial ischemia, respectively.

Follow-up

Follow-up for all-cause mortality within the first 5 years was obtained using the Social Security Death Index, National Death Index, and California Non-comprehensive Death File. The last date of access for the Social Security Death Index was April 9, 2012; the last date of access for the National Death Index was December 31, 2016; and the last date of access for California Non-comprehensive Death File was February 23, 2018. Patients were followed up for a median of 12.7 years (interquartile range, 10.0 to 17.4 years).

Statistical Analyses

All statistical analyses were performed using Stata statistical software, version 14 for Windows (StataCorp) except as noted. The main analyses were stratified by diagnostic patients and patients with known CAD. Continuous variables are presented as mean ± SD or median and interquartile range as noted and compared across 4 groups using the Kruskal-Wallis test and, for ordered groups, the Cuzick test for trend. Categorical variables are expressed as frequency (percentage) and compared using the Pearson χ^2 test, and the χ^2 test for trend added for ordered groups as well. Kaplan-Meier curves were used to visualize group survival and were compared using the log-rank test and test for trend for ordered groups. Annualized mortality rates were adjusted for age, sex, ethnicity, and risk factors using Poisson regression and expressed as percentage per year using the SAS 9.4 PROC GENMOD procedure (SAS Institute). Univariable and multivariable Cox proportional hazards models were used to assess the predictors of all-cause mortality with the predictors chosen based on both univariate statistical significance and clinical judgement. The predictors were further ranked by the χ^2 contribution from the likelihood ratio test—the full model minus the predictor vs the full Cox model (multivariable, Table 1

and Supplemental Table 1 [available online at http://mcpiqojournal.org]). A 2-sided P value of less than .05 was required for statistical significance.

RESULTS

Temporal changes in the clinical characteristics of our patient population are summarized in Table 2, divided according to 4 epochs. The volume of diagnostic patients increased from the first to subsequent epochs, and the volume of patients with known CAD decreased in the fourth epoch. Among the diagnostic patients, there was a decrease in mean age and the cohort became ethnically more diverse. Between the first and fourth temporal epochs, there was a marked decrease in patients with typical angina (from 12.6% [780 of 6176] to 2.1% [232 of 10,908]) but an increase in patients with dyspnea. Smoking rates decreased, but there was an increase in the frequency of hypercholesterolemia, diabetes, obesity, and hypertension. This increase in hypertension was noted within each ethnic group (Supplemental Table 2, available online at http://mcpiqojournal.org). In addition, the percentage of patients requiring pharmacological stress testing increased markedly (from 26.5% [1634 of 6176] to 53.0% [5781 of 10,908]; $P<.001$), while the frequency of mild, moderate, and severe ischemia all declined.

Among the patients with known CAD, similar trends were noted across the 4 temporal epochs, including a decrease in typical angina (from 22.1% [711 of 3213] to 4.3% [79 of 1860]) and an increase in dyspnea, hypertension, hypercholesterolemia, diabetes, and obesity. There was a marked increase in pharmacological testing (from 31.1% [999 of 3213] to 75.5% [1405 of 1860]; $P<.001$), while the frequency of mild, moderate, and severe ischemia declined substantially.

Among other parameters, various indices of cardiac abnormality declined over time in both patient groups, including a declining frequency of an abnormal rest ECG, left bundle branch block, and left ventricular hypertrophy, with the latter decreasing in all ethnic groups (Supplemental Table 2). In addition, both the presence of mild scar (5% to 9% of myocardium) and severe scar (≥10% of

TABLE 1. Multivariable Predictors of All-Cause Mortality

Variable	χ^2; P value	Hazard ratio (95% CI)
Diagnostic patients		
Pharmacological vs exercise testing	1381.39; <.001	3.74 (3.47-4.03)
Age, per 5 y	478.97; <.001	1.16 (1.15-1.18)
History of high cholesterol	262.78; <.001	0.60 (0.56-0.64)
Body mass index, per 5 units	223.04; <.001	0.82 (0.79-0.84)
Diabetes	170.49; <.001	1.61 (1.51-1.73)
Dyspnea[a]	99.84; p<0.001	1.53 (1.42-1.66)
% Myocardial scar, per 5%	69.18; <.001	1.15 (1.12-1.19)
Left ventricular enlargement (yes/no)	62.15; <.001	1.51 (1.37-1.66)
Ethnicity[b]	61.13; <.001	1.07 (1.05-1.09)
Smoking	59.64; <.001	1.43 (1.31-1.56)
Male	58.03; <.001	1.27 (1.19-1.35)
Family history	19.58; <.001	0.81 (0.74-0.89)
History of hypertension	14.57; <.001	1.13 (1.06-1.21)
% Myocardial ischemic, per 5%	12.04; <.001	1.05 (1.02-1.08)
Patients with known coronary artery disease		
Pharmacological testing	321.86; <.001	2.47 (2.23-2.75)
Age, per 5 y	317.06; <.001	1.23 (1.20-1.26)
Left ventricular enlargement (yes/no)	84.33; <.001	1.68 (1.51-1.88)
Dyspnea[c]	72.07; <.001	1.65 (1.48-1.84)
Diabetes	66.16; <.001	1.48 (1.35-1.63)
Body mass index, per 5 units	62.51; <.001	0.83 (0.79-0.87)
Hypercholesterolemia	58.37; <.001	0.72 (0.66-0.78)
% Myocardial scar, per 5%	42.16; <.001	1.07 (1.05-1.09)
Ethnicity[d]	33.31; <.001	1.04 (1.00-1.08)
% Myocardial ischemia, per 5%	14.68; <.001	1.05 (1.03-1.08)
Hypertension	6.34; .012	1.13 (1.03-1.23)
Smoking	4.32; .038	1.16 (1.01-1.34)
Male	0.29; .588	0.97 (0.89-1.07)
Family history	0.28; .597	0.97 (0.87-1.08)

[a]Among chest pain symptoms in the diagnostic patients, dyspnea was the only symptom with an increased adjusted hazard ratio (HR) for mortality vs asymptomatic patients: HR for nonanginal pain, 0.78 (95% CI, 0.71-0.86); for atypical angina, 0.55 (95% CI, 0.51-0.59); for typical angina, 0.58 (95% CI, 0.51-0.67); and for dyspnea, 1.11 (95% CI, 1.02-1.22).

[b]Among racial/ethnic groups, using White patients as a referent, an increased HR for mortality was noted for Black patients (1.28 [95% CI, 1.18-1.39]), Hispanics/Latinos (1.32 [95% CI, 1.18-1.47]), and other/unknown (1.28 [95% CI, 1.14-1.44]).

[c]Among chest pain symptoms in patients with known coronary artery disease, nonanginal chest pain and dyspnea were the only symptoms with an increased adjusted HR for mortality vs asymptomatic patients: HR for nonanginal pain, 1.18 (95% CI, 1.02-1.37); for atypical angina, 0.92 (95% CI, 0.82-1.04); for typical angina, 0.88 (95% CI, 0.76-1.02); and for dyspnea, 1.60 (95% CI, 1.40-1.82).

[d]Among racial/ethnic groups, using White patients as a referent, an increased HR for mortality was noted for Black patients (1.44 [95% CI, 1.26-1.64]).

myocardium) and the percentage of patients with reduced left ventricular ejection fraction (<45%) also decreased.

Relative Predictors of All-Cause Mortality

By multivariable analysis, the highest χ^2 contribution for mortality among both the diagnostic and known CAD groups was the use of pharmacological stress testing, followed by age (Table 1). In both groups, the presence of diabetes, dyspnea, degree of myocardial scar, left ventricular enlargement, and ethnicity were additional predictors of all-cause mortality. Among other clinical factors, hypertension, smoking, and inducible myocardial ischemia were modest predictors of mortality, and a history of high cholesterol and the presence of obesity were inversely related to mortality. When assessed on a temporal basis, the use of pharmacological testing

TABLE 2. Clinical Characteristics of the 50,732 Study Patients, Stratified by Temporal Periods[a,b]

Variable	1991-1995	1996-2000	2001-2005	2006-2012	Trend P value
Diagnostic patients (N=39,750)	6176	10,304	12,362	10,908	NA
Age (y)	63.2±12.2	62.8±12.4	60.1±12.6	58.9±12.3	<.001
Male	3460 (56.0)	5565 (54.0)	6472 (52.4)	5690 (52.2)	<.001
Ethnicity	NA	NA	NA	NA	NA
White	4858 (78.7)	7285 (70.7)	8284 (67.0)	6450 (59.1)	<.001
Black	497 (8.0)	987 (9.6)	1893 (15.3)	2180 (20.0)	<.001
Asian	233 (3.8)	348 (3.4)	591 (4.8)	717 (6.6)	<.001
Hispanic/Latino	126 (2.0)	391 (3.8)	942 (7.6)	1277 (11.7)	<.001
Other/unknown	462 (7.5)	1293 (12.6)	652 (5.3)	284 (2.6)	<.001
Symptoms	NA	NA	NA	NA	NA
Asymptomatic	1995 (32.3)	2847 (27.6)	2908 (23.5)	2615 (24.0)	<.001
Nonanginal pain	1605 (26.0)	1692 (16.4)	1308 (10.6)	429 (3.9)	<.001
Atypical angina	1529 (24.8)	3660 (35.5)	6717 (54.3)	6429 (59.2)	<.001
Typical angina	780 (12.6)	1133 (11.0)	435 (3.5)	232 (2.1)	<.001
Dyspnea only	267 (4.3)	972 (9.4)	994 (8.0)	1200 (11.0)	<.001
CAD risk factors	NA	NA	NA	NA	NA
Hypertension	2838 (46.0)	5167 (50.2)	6339 (51.3)	6317 (57.9)	<.001
High cholesterol	2527 (40.9)	4643 (45.1)	5476 (44.3)	5086 (46.6)	<.001
Smoking	1065 (17.2)	1273 (12.4)	915 (7.4)	944 (8.7)	<.001
Diabetes	829 (13.4)	1117 (10.8)	1943 (15.7)	2286 (21.0)	<.001
Family history of CAD	1426 (23.1)	2461 (23.9)	1513 (12.2)	1678 (15.4)	<.001
Weight (lb)	166.7±35.1	172.2±39.9	178.7±46.0	183.4±52.1	<.001
Mean BMI (kg/m^2)	26.4±4.7	27.3±5.5	28.1±6.5	28.9±7.3	<.001
<25	2539/6112 (41.5)	3716/10,252 (36.3)	4060/12,326 (32.9)	3360/10,889 (30.9)	<.001
25-29.9	2456/6112 (40.2)	4100/10,252 (40.0)	4659/12,326 (37.8)	3903/10,889 (35.8)	<.001
≥30	1117/6112 (18.3)	2436/10,252 (23.8)	3607/12,326 (29.3)	3626/10,889 (33.3)	<.001
Stress test mode	NA	NA	NA	NA	NA
Pharmacological	1634 (26.5)	4057 (39.4)	5867 (47.5)	5781 (53.0)	<.001
Rest ECG	NA	NA	NA	NA	NA
ECG abnormalities	3956 (64.1)	5558 (53.9)	5435 (44.0)	4678 (42.9)	<.001
LVH	717 (11.6)	1186 (11.5)	582 (4.7)	479 (4.4)	<.001
LBBB	165 (2.7)	255 (2.5)	210 (1.7)	179 (1.6)	<.001
Atrial fibrillation	142 (2.3)	244 (2.4)	240 (1.9)	216 (2.0)	.033
SPECT results	NA	NA	NA	NA	NA
% Ischemic MYO	NA	NA	NA	NA	NA
Any (ie, ≥5)	1550 (25.1)	1319 (12.8)	1136 (9.2)	578 (5.3)	<.001
5-9.9	673 (10.9)	579 (5.6)	630 (5.1)	346 (3.2)	<.001
10-14.9	348 (5.6)	309 (3.0)	220 (1.8)	129 (1.2)	<.001
≥15	529 (8.6)	431 (4.2)	286 (2.3)	103 (0.9)	<.001
% MYO scar	NA	NA	NA	NA	NA
Any (ie, ≥5)	622 (10.1)	445 (4.3)	319 (2.6)	324 (3.0)	<.001
5-9.9	405 (6.6)	260 (2.5)	180 (1.5)	179 (1.6)	<.001
10-14.9	105 (1.7)	79 (0.8)	61 (0.5)	69 (0.6)	<.001
≥15	112 (1.8)	106 (1.0)	78 (0.6)	76 (0.7)	<.001
LV function	NA	NA	NA	NA	NA
LV enlargement	623 (10.1)	541 (5.3)	515 (4.2)	657 (6.0)	<.001
Mean LVEF (%)	NA	60.9±12.7	64.9±12.2	65.0±11.4	<.001
>45	NA	4570/5020 (91.0)	11,595/12,247 (94.7)	10,360/10,866 (95.3)	<.001
35-45	NA	299/5020 (6.0)	408/12,247 (3.3)	326/10,866 (3.0)	<.001
<35	NA	151/5020 (3.0)	244/12,247 (2.0)	180/10,866 (1.7)	<.001

TABLE 2. Continued					
Variable	1991-1995	1996-2000	2001-2005	2006-2012	Trend P value
Medications	NA	NA	NA	NA	NA
Lipid-lowering	NA	472/2454 (19.2)	3337/12,362 (27.0)	3888/10,902 (35.7)	<.001
Statins	NA	452/2454 (18.4%)	3180/12,362 (25.7%)	3542/10,902 (32.5)	<.001
Ezetimibe	NA	NA	60/2507 (2.4)	397/10,902 (3.6)	NA
Other lipid meds	NA	24/974 (2.5)	204/12,362 (1.7)	608/10,902 (5.6)	<.001
Antihypertensives	1111/6176 (18.0)	1673/10,304 (16.2)	5618/12,362 (45.5)	5894/10,902 (54.1)	<.001
β-Blockers	468/6176 (7.6)	984/10,304 (9.6)	2375/12,362 (19.2)	2664/10,902 (24.4)	<.001
ACE inhibitors	NA	171/1316 (13.0)	2126/12,362 (17.2)	2044/10,902 (18.8)	<.001
ARBs	NA	38/963 (4.0)	836/12,362 (6.8)	1667/10,902 (15.3)	<.001
Calcium blockers	760/6176 (12.3)	642/10,304 (6.2)	1342/12,362 (10.9)	1582/10,902 (14.5)	<.001
Diuretics	NA	126/974 (12.9)	1641/12,362 (13.3)	1794/10,902 (16.5%)	<.001
Aspirin	NA	193/2344 (8.2%)	3090/12,362 (25.0)	3333/10,902 (30.6)	<.001
Revascularization at ≤90 d	398 (6.4)	561 (5.4)	540 (4.4)	323 (3.0)	<.001
Revascularization by % ischemic MYO	NA	NA	NA	NA	NA
<5	29 (0.6)	64 (0.7)	94 (0.8)	95 (0.9)	.032
5-9.9	58 (8.6)	113 (19.5)	158 (25.1)	93 (26.9)	<.001
10-14.9	91 (26.2)	129 (41.8)	106 (48.2)	63 (48.8)	<.001
≥15	220 (41.6)	255 (59.2)	182 (63.6)	72 (69.9)	<.001
Annualized mortality, %/y (95% CI)	NA	NA	NA	NA	NA
Unadjusted	2.47 (2.30-2.66)	2.56 (2.42-2.71)	2.50 (2.38-2.63)	2.27 (2.14-2.40)	.021
Adjusted for age, sex, and ethnicity	1.75 (1.64-1.86)	1.90 (1.80-2.00)	1.97 (1.88-2.07)	1.88 (1.78-1.99)	NA
Additionally adjusted for all CAD risk factors	1.57 (1.47-1.68)	1.85 (1.75-1.95)	1.85 (1.76/1.95)	1.76 (1.66-1.86)	NA
Patients with known CAD (N=10,982)	3213	3553	2356	1860	NA
Age (y)	67.0±10.8	66.8±11.4	65.7±11.6	65.2±11.5	<.001
Male	2355 (73.3)	2547 (71.7)	1696 (72.0)	1351 (72.6)	.554
Clinical history	NA	NA	NA		NA
Post-MI	2228 (69.3)	2363 (66.5)	1369 (58.1)	1017 (54.7)	<.001
Post-PCI	1224 (38.1)	1688 (47.5)	1241 (52.7)	1113 (59.8)	<.001
Post-CABG	1291 (40.2)	1390 (39.1)	856 (36.3)	587 (31.6)	<.001
Ethnicity	NA	NA	NA	NA	NA
White	2744 (85.4)	2706 (76.2)	1776 (75.4)	1262 (67.8)	<.001
Black	192 (6.0)	284 (8.0)	259 (11.0)	282 (15.2)	<.001
Asian	90 (2.8)	123 (3.5)	92 (3.9)	115 (6.2)	<.001
Hispanic/Latino	51 (1.6)	144 (4.1)	117 (5.0)	132 (7.1)	<.001
Other/unknown	136 (4.2)	296 (8.3)	112 (4.8)	69 (3.7)	.072
Symptoms	NA	NA	NA	NA	NA
Asymptomatic	1001 (31.2)	847 (23.8)	519 (22.0)	433 (23.3)	<.001
Nonanginal pain	483 (15.0)	353 (9.9)	241 (10.2)	83 (4.5)	<.001
Atypical angina	862 (26.8)	1098 (30.9)	1118 (47.5)	1025 (55.1)	<.001
Typical angina	711 (22.1)	844 (23.8)	249 (10.6)	80 (4.3)	<.001
Dyspnea only	156 (4.9)	411 (11.6)	229 (9.7)	239 (12.8)	<.001

TABLE 2. Continued					
Variable	1991-1995	1996-2000	2001-2005	2006-2012	Trend *P* value
CAD risk factors	NA	NA	NA	NA	NA
Hypertension	1578 (49.1)	2059 (58.0)	1639 (69.6)	1496 (80.4)	<.001
High cholesterol	1609 (50.1)	2213 (62.3)	1525 (64.7)	1340 (72.0)	<.001
Smoking	526 (16.4)	429 (12.1)	168 (7.1)	153 (8.2)	<.001
Diabetes	632 (19.7)	610 (17.2)	632 (26.8)	654 (35.2)	<.001
Family history	962 (29.9)	968 (27.2)	295 (12.5)	258 (13.9)	<.001
Weight (lb)	169.3±32.8	171.8±35.9	180.0±41.7	184.2±43.9	<.001
Mean BMI (kg/m^2)	26.3±4.3	26.9±4.8	28.0±5.8	28.6±6.0	<.001
<25	1291/3177 (40.6)	1291/3535 (36.5)	716/2346 (30.5)	511/1857 (27.5)	<.001
25-29.9	1350/3177 (42.5)	1489/3535 (42.1)	990/2346 (42.2)	711/1857 (38.3)	.012
≥30	536/3177 (16.9)	755/3535 (21.4)	640/2346 (27.3)	635/1857 (34.2)	<.001
Stress test mode	NA	NA	NA	NA	NA
Pharmacological	999 (31.1)	1966 (55.3)	1565 (66.4)	1405 (75.5)	<.001
Rest ECG	NA	NA	NA	NA	NA
ECG abnormalities	2722 (84.7)	2807 (79.0)	1605 (68.1)	1236 (66.5)	<.001
LV hypertrophy	417 (13.0)	511 (14.4)	155 (6.6)	99 (5.3)	<.001
LBBB	149 (4.6)	151 (4.2)	65 (2.8)	40 (2.2)	<.001
Atrial fibrillation	72 (2.2)	104 (2.9)	59 (2.5)	56 (3.0)	.193
SPECT results	NA	NA	NA	NA	NA
% Ischemic MYO	NA	NA	NA	NA	NA
Any (≥5)	1823 (56.7)	1550 (43.6)	891 (37.8)	507 (27.3)	<.001
5-9.9	691 (21.5)	662 (18.6)	445 (18.9)	261 (14.0)	<.001
10-14.9	450 (14.0)	369 (10.4)	245 (10.4)	143 (7.7)	<.001
≥15	682 (21.2)	519 (14.6)	201 (8.5)	103 (5.5)	<.001
% MYO scar	NA	NA	NA	NA	NA
Any (≥5)	1530 (47.6)	1240 (34.9)	730 (31.0)	568 (30.5)	<.001
5-9.9	551 (17.2)	430 (12.1)	278 (11.8)	203 (10.9)	<.001
10-14.9	330 (10.3)	262 (7.4)	161 (6.8)	123 (6.6)	<.001
≥15	649 (20.2)	548 (15.4)	291 (12.4)	242 (13.0)	<.001
LV function	NA	NA	NA	NA	NA
LV enlargement	782 (24.3)	743 (20.9)	360 (15.3)	336 (18.1)	<.001
Mean LVEF (%)	NA	52.3±14.8	56.3±14.9	57.4±15.1	<.001
>45	NA	1030/1409 (73.1)	1837/2328 (78.9)	1485/1856 (80.0)	<.001
35-45	NA	198/1409 (14.1)	271/2328 (11.6)	196/1856 (10.6)	.003
<35	NA	181/1409 (12.8)	220/2328 (9.4)	175/1856 (9.4)	.003
Medications	NA	NA	NA	NA	NA
Lipid-lowering	NA	218/668 (32.6)	1409/2356 (59.8)	1352/1860 (72.7)	<.001
Statins	NA	213/668 (31.9)	1355/2356 (57.5)	1278/1860 (68.7)	<.001
Ezetimibe	NA	NA	24/349 (6.9)	178/1860 (9.6)	NA
Other	NA	11/250 (4.4)	101/2356 (4.3)	232/1860 (12.5)	<.001
Antihypertensives	1086/3213 (33.8)	937/3553 (26.4)	1746/2356 (74.1)	1568/1860 (84.3)	<.001
β-Blockers	432/3213 (13.5)	676/3553 (19.0)	1110/2356 (47.1)	1184/1860 (63.7)	<.001
ACE inhibitors	NA	70/338 (20.7)	717/2356 (30.4)	630/1860 (33.9)	<.001
ARBs	NA	12/247 (4.9)	233/2356 (9.9)	366/1860 (19.7)	<.001
Calcium blockers	790/3213 (24.6)	312/3553 (8.8)	379/2356 (16.1)	322/1860 (17.3)	<.001
Diuretics	NA	34/250 (13.6)	426/2356 (18.1)	420/1860 (22.6)	.001
Aspirin	NA	112/639 (17.5)	1363/2356 (57.9)	1229/1860 (66.1)	<.001

TABLE 2. Continued					
Variable	1991-1995	1996-2000	2001-2005	2006-2012	Trend *P* value
Revascularization at <90 d	442 (13.8)	558 (15.7)	307 (13.0)	170 (9.1)	<.001
Revascularization by % ischemic MYO	NA	NA	NA	NA	NA
SDS <5	64 (4.6)	84 (4.2)	55 (3.8)	42 (3.1)	.033
SDS 5-9.9	89 (12.9)	110 (16.6)	91 (20.5)	42 (16.1)	.015
SDS 10-14.9	71 (15.8)	117 (31.7)	76 (31.0)	38 (26.6)	<.001
SDS ≥15	218 (32.0)	247 (47.6)	85 (42.3)	48 (46.6)	<.001
Annualized mortality, %/y (95% CI)	NA	NA	NA	NA	NA
Unadjusted	4.0 (3.73-4.38)	4.9 (4.55-5.24)	4.7 (4.28-5.11)	5.0 (4.49-5.46)	.004
Adjusted for age, sex, and ethnicity	2.65 (2.47-2.84)	2.88 (2.71-3.07)	2.99 (2.80-3.19)	2.86 (2.67-3.06)	NA
Additionally adjusted for all CAD risk factors	2.46 (2.30-2.64)	2.89 (2.72-3.08)	2.90 (2.72-3.10)	2.75 (2.56-2.95)	NA

[a]ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockade; CABG, coronary artery bypass graft; CAD, coronary artery disease; BMI, body mass index; ECG, electrocardiographic; LV, left ventricular; LVEF, LV ejection fraction; LVH, LV hypertrophy; LBBB, left bundle branch block; MI, myocardial infarction; MYO, myocardial; NA, not available; PCI, percutaneous coronary intervention; SDS, summed difference score; SPECT, single-photon emission computed tomography.
[b]Data are presented as mean ± SD or No. (percentage) of patients unless indicated otherwise.

and age were also the strongest predictors of mortality within each epoch of our study (Supplemental Table 1).

Table 3 shows the comparative adjusted hazard ratios for mortality among patients stratified according to mode of stress testing, ischemic status, and number of CAD risk factors (among hypertension, diabetes, and smoking). The need for pharmacological testing accentuated the hazard ratios associated with any combination of risk factors and ischemic status.

Temporal Trends in Mortality

Assessing the diagnostic and known CAD cohorts according to their mode of stress testing revealed a temporal decline in annualized mortality rates among patients undergoing either exercise or pharmacological testing within each cohort, adjusted for age, sex, ethnicity, and CAD risk factors (Figure 1). Among exercise patients in the diagnostic group, annualized adjusted mortality decreased from 1.3% per year in 1991 to 0.5% per year in 2012. Among diagnostic patients undergoing pharmacologic testing, annualized mortality decreased from 4.6% per year in 1991 to 2.0% per year during the same time period. A similar pattern of decline in annualized mortality was also noted among the exercise and pharmacological groups of patients with known CAD.

However, because of the progressive increase in patients requiring pharmacological testing between the first and fourth epochs, the overall annualized mortality rates did not change substantially over time within the diagnostic and known CAD cohorts. Among our entire diagnostic cohort, the annualized mortality rate was 1.57% per year in the first epoch and 1.76% per year in the fourth epoch. Among the patients with known CAD, the annualized mortality rate was 2.46% per year in the first epoch and 2.75% per year in the fourth epoch.

As further illustration of this counterbalancing trend, Figure 2 shows the contrasting temporal trends for inducible myocardial ischemia, the need to perform pharmacological testing in lieu of exercise testing, and annualized mortality rates among the diagnostic and known CAD cohorts on a year-by-year basis. Although there was a progressive temporal decline in the frequency of inducible myocardial ischemia and an increase in the frequency of pharmacological testing, the concomitant mortality rate remained relatively constant over time among both groups.

DISCUSSION

Although mortality from CVD has declined substantially over recent decades, important negative health trends have emerged that have the potential to retard future health gains. These

TABLE 3. Adjusted Hazard Ratios for All-Cause Mortality According to Patients' Mode of Stress Testing, Presence or Absence of Inducible Ischemia, and Risk Factor Burden[a,b]						
Variable			Diagnostic patients		Patients with known CAD	
Mode of stress testing	Ischemia	No. of RFs[c]	No. of patients	Hazard ratio (95% CI)	No. of patients	Hazard ratio (95% CI)
Exercise	SDS <5%	0-1	18,299	1.0 (Referent group)	2433	1.0 (Referent group)
	SDS ≥5%		1767	1.87 (1.56-2.25)	1832	1.52 (1.25-1.86)
	SDS <5%	2-3	1979	2.30 (1.91-2.76)	398	2.08 (1.52-2.85)
	SDS ≥5%		366	3.81 (2.85-5.08)	384	2.15 (1.58-2.93)
Pharm	SDS <5%	0-1	11,715	4.59 (4.19-5.02)	2435	3.22 (2.72-3.81)
	SDS ≥5%		1705	5.92 (5.22-6.71)	1805	3.86 (3.25-4.58)
	SDS <5%	2-3	3174	7.30 (6.55-8.13)	945	4.84 (4.01-5.85)
	SDS ≥5%		745	10.24 (8.83-11.86)	750	5.74 (4.74-6.96)

[a]CAD, coronary artery disease; Pharm, pharmacological; RF, risk factor; SDS, summed difference score.
[b]Adjusted for age, sex, family history, high cholesterol, body mass index, and symptoms.
[c]Based on consideration of 3 risk factors: hypertension, smoking, and diabetes.

trends include a global increase in obesity[10] and diabetes[11] and increasing sedentary behavior.[12-14] In this study, we identified the temporal trends in various cardiac parameters, risk factors associated with clinical disease, and rates of mortality over 2 decades among patients with suspected and known CAD referred for radionuclide stress MPI.
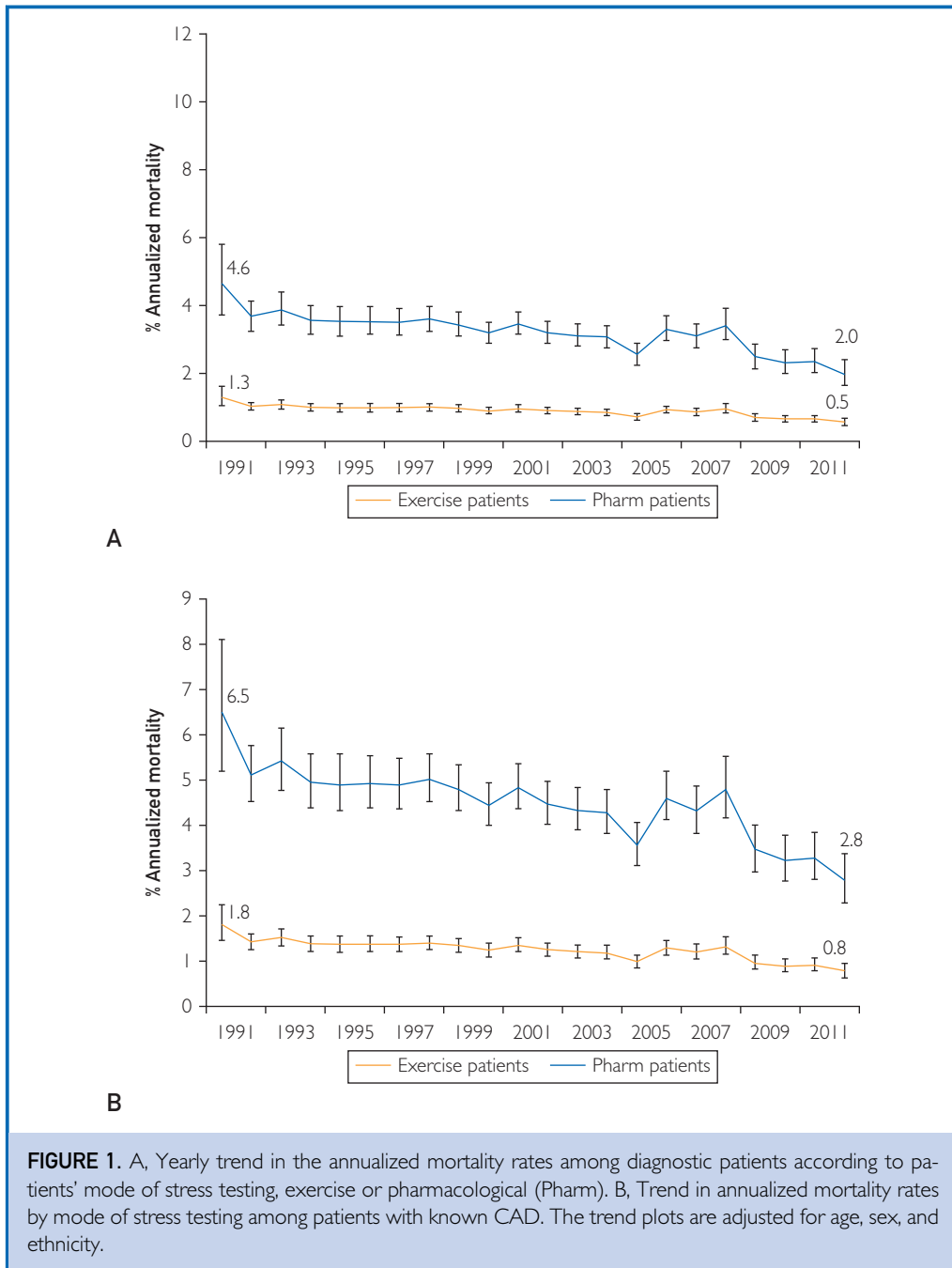
The clinical profiles of both our diagnostic and known CAD cohorts improved substantially over the temporal period of our study. By our fourth epoch (2006-2012), the frequency of typical angina declined to only 2.1% among diagnostic patients and 4.3% among known CAD patients. There was also a substantial temporal decline in the frequency of mild and moderate to severe myocardial ischemia in both groups. Other favorable temporal trends included a decline in smoking, resting electrocardiographic abnormalities, and frequency and size of myocardial scar. A risk factor that increased substantially over time among our patients was self-reported hypertension. This temporal increase was noted in all racial/ethnic groups and contrasts to a reported population decrease in the prevalence of hypertension in the United States.[15] This difference serves to emphasize inherent differences that may exist in risk factor trends within patient populations, in whom risk factors drive both disease risk and an increasing likelihood for testing, and community populations, which are not subject to such selection bias.

Nevertheless, this increase in hypertension was accompanied by a decreased prevalence of left ventricular hypertrophy, perhaps reflecting more effective antihypertensive management of our patients. The use of both antihypertensive medications and statins progressively increased within our cohort.

Based on these positive cardiovascular trends, an accompanying decline in mortality would have been expected but did not materialize within either the diagnostic or known CAD cohorts. Rather, the annualized mortality rates remained relatively flat. Among diagnostic patient, the annualized adjusted mortality rate was 1.57% per year in the first epoch and 1.76% in the last epoch. Among patients with known CAD, the annualized mortality rate was 4.0% per year in the first epoch and 5.0% per year in the last. Thus, given the marked decline in ischemia, angina, and other adverse cardiac parameters, counterbalancing factors appear to have prevented a temporal decline in mortality.

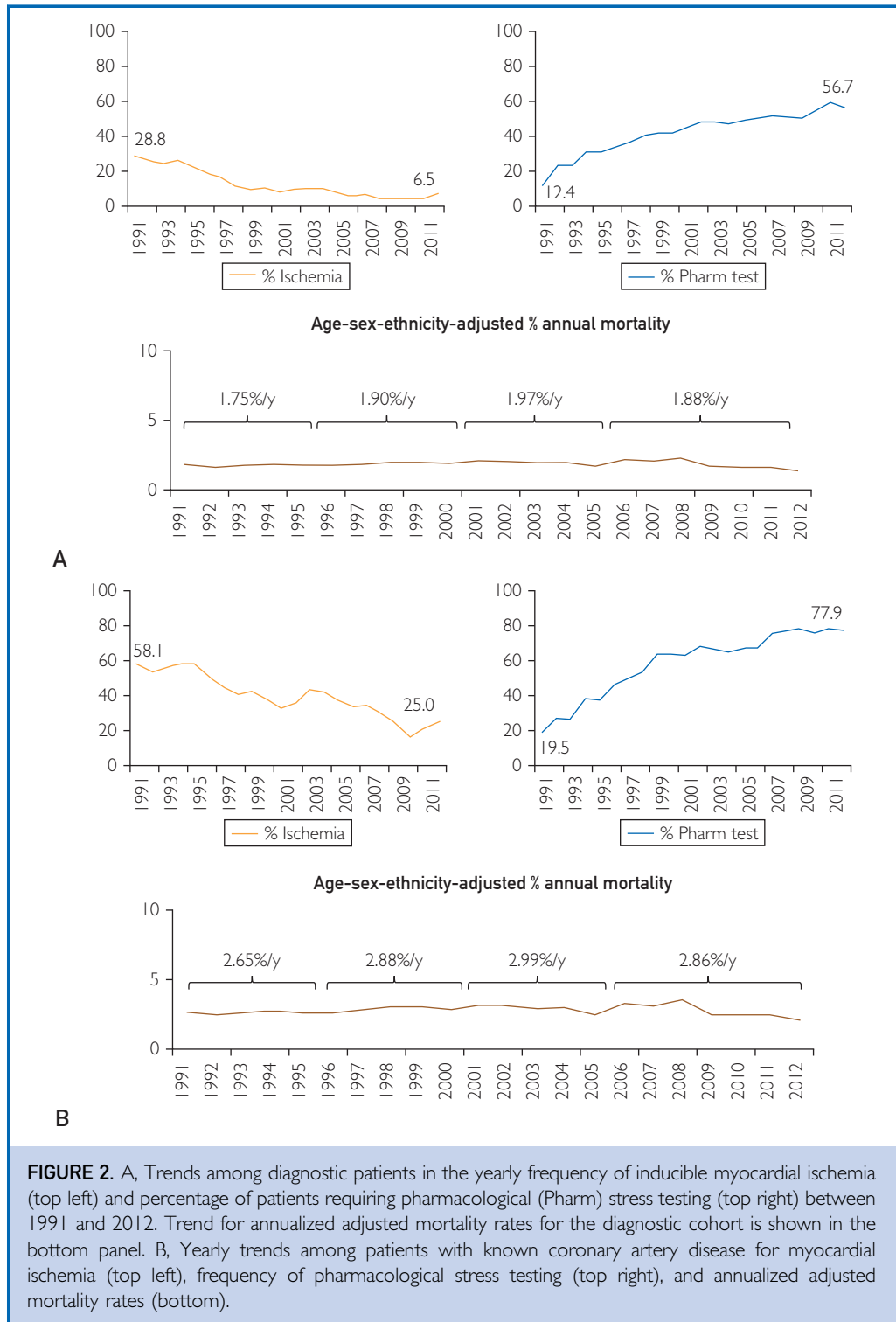## Comparative Predictors of Mortality

To evaluate these potential factors, we assessed the most potent predictors of mortality. In both the diagnostic and known CAD cohorts, pharmacological testing was the strongest predictor of mortality by χ^2 analysis, exceeding age. Among other variables, the presence of diabetes, dyspnea, left ventricular

FIGURE 1. A, Yearly trend in the annualized mortality rates among diagnostic patients according to patients' mode of stress testing, exercise or pharmacological (Pharm). B, Trend in annualized mortality rates by mode of stress testing among patients with known CAD. The trend plots are adjusted for age, sex, and ethnicity.

enlargement, and percentage of myocardial scar were also important predictors of mortality.

To further assess mortality trends, we divided patients according to their mode of stress testing, exercise or pharmacological. Among the diagnostic patients who exercised, the adjusted rate of mortality declined from 1.3% per year for patients studied in 1991 to only 0.5% per year for patients studied in 2012. Similarly, among patients with known CAD who exercised, annualized mortality declined from 1.8% per year to 0.8% per year over the same period. Although

FIGURE 2. A, Trends among diagnostic patients in the yearly frequency of inducible myocardial ischemia (top left) and percentage of patients requiring pharmacological (Pharm) stress testing (top right) between 1991 and 2012. Trend for annualized adjusted mortality rates for the diagnostic cohort is shown in the bottom panel. B, Yearly trends among patients with known coronary artery disease for myocardial ischemia (top left), frequency of pharmacological stress testing (top right), and annualized adjusted mortality rates (bottom).

mortality rates also declined among the diagnostic and known CAD cohorts undergoing pharmacological testing, the mortality rates remained substantially elevated in pharmacological vs exercise groups in each epoch of our study.

Why Overall Mortality Did Not Decline for the Entire Cohort

The relatively flat mortality rates noted in our study appear to be the consequence of the counterbalancing positive vs negative risk trends noted in our patient cohorts. Factors that would be expected to lower mortality risk were highly predominant in our stress testing population, including a marked temporal decline in ischemia, angina, and other cardiac abnormalities, and a progressive intensification of disease-altering medical therapies, such as increased statin use. The decline in these factors probably reflects an underlying decrease in the magnitude of obstructive CAD disease in our population, a factor that likely explains why the traditional Diamond-Forrester estimation of pretest likelihood of CAD[16] is no longer valid. This old algorithm now consistently overestimates CAD prevalence within current clinical populations.[17,18]

During this time, however, factors that are associated with greater all-cause mortality risk, according to our multivariable analysis, also increased, including diabetes, hypertension, dyspnea, and pharmacological testing. The need for performing pharmacological testing in lieu of exercise, which was the most potent multivariable predictor of mortality in our patient cohorts, was particularly marked. Among both our diagnostic and known CAD cohorts, the frequency of performing pharmacological testing in lieu of exercise testing more than doubled over the course of our study.

Assessment of Other Clinical Factors

Among other factors, obesity and hypercholesterolemia were inverse risk predictors for mortality, and myocardial ischemia was only a modest predictor. Our finding with respect to obesity may be reflective of a well-characterized but poorly understand "obesity paradox"—the unexpected finding of a relatively reduced mortality rate among obese patients within many patient populations, including stress test cohorts.[19] It is possible that the lack of prognostic significance associated with a history of hypercholesterolemia was influenced by the high utilization of lipid-lowering therapies among our patients. Similarly, treatment bias also may have influenced the apparent mild prognostic significance of myocardial ischemia in this study. Both medical therapies and performance of myocardial revascularization can substantially reduce myocardial ischemia when present,[20] and in our study, there was a progressively greater use of the latter with increasing baseline ischemia.

A Call to Study the Increasing Need for Pharmacological Testing

Our study results suggest that a marked shift has occurred in the drivers of mortality among patients undergoing cardiac stress testing, away from such factors as ischemia and angina and toward such factors as diabetes and a need to perform pharmacological testing in lieu of exercise. However, although the pathophysiology of such factors as diabetes have been well studied, there has been a dearth of studies to identify the principle pathophysiologic factors governing the increased mortality risk associated with pharmacological testing. Such study is hampered by the variety of clinical conditions that underlie the need for performing pharmacological testing in lieu of exercise. Three lines of prospective investigation are needed to elucidate the factors contributing to the heightened risk for patients requiring pharmacological testing. First, although pharmacological testing has now been employed for nearly 4 decades, there is little reported study information that characterizes patients according to the reasons for such testing. In the only reported study to date, these reasons were diverse, including such factors as physical deconditioning, musculoskeletal limitations, and frailty symptoms.[21] Second, there is a need to assess how clinical outcomes vary according to the underlying reasons for performing pharmacological testing. For instance, a patient who cannot exercise because of pre-frailty is likely to be at substantially higher clinical risk than a patient who cannot exercise because of a transient orthopedic condition. Third, there is a need to determine the upstream mediators that are driving the increasing need for pharmacological testing among patients undergoing stress testing, noted not only in our study but in other recently reported stress testing cohorts as well.[7,8,22,23] Candidate variables include such factors as increasing obesity,[10] diabetes,[11] and physical

inactivity.[12-14] Although physical activity patterns are not generally evaluated within cardiac stress test populations, recent findings indicate that such evaluations can be applied using practical questionnaires that enhance the prediction of mortality risk among patients referred for cardiac testing.[24-26]

Another potential factor may be an increasing prevalence of musculoskeletal disorders within society,[27,28] perhaps due to the increase in these other risk factors.

Study Limitations
Our study has important limitations. Because it is a single-center study, it is subject to selection biases that may not reflect the experience of other medical centers because differences in racial, ethnic, socioeconomic, and other diverse factors can influence the distribution of clinical risk factors and the quality of health care. Therefore, replication of our findings among other populations is required. We did not collect information regarding cause-specific mortality. Prior studies have indicated that the need for pharmacological stress testing is associated with an increased risk for both cardiovascular and all-cause mortality,[29-31] but prospective study should investigate how competing risk factor trends within current stress test populations may be differentially affecting cardiac vs noncardiac mortality rates and even the various causes of cardiac mortality (eg, ischemic heart disease mortality vs heart failure mortality). In this study, we did not risk-stratify our pharmacological cohort according to whether they could perform limited exercise, but prior studies have indicated that patients undergoing pharmacological testing who perform limited exercise protocols are at lower mortality risk vs those undergoing pharmacologic testing who cannot perform any exercise at all.[32,33] In addition, we did not collect information regarding the reasons for performing pharmacological testing or noncardiac comorbidities that may have influenced outcomes in our patient cohort. We also could not assess the influence of medical therapies initiated in patients between baseline testing and follow-up. Finally, because our study is only observational in nature, the changing risk factor trends noted herein do not prove causal relationships between these risk factors and

mortality. Moreover, it is possible, if not probable, that other unmeasured factors, such as evolving changes in patient referral patterns and unmeasured confounders, also may have been operative in our patient population.

CONCLUSION
In this study spanning over 22 years, there was a marked decline in typical angina and inducible myocardial ischemia among patients referred for radionuclide stress testing but an increase in patients requiring pharmacological testing in lieu of exercise, diabetes, obesity, dyspnea, and hypertension. As a net effect, mortality did not decline, suggesting a profound change in the drivers of clinical risk among current patients referred for cardiac stress testing.

SUPPLEMENTAL ONLINE MATERIAL
Supplemental material can be found online at http://mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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