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Projected Morbidity and Mortality from Missed Diagnoses of Coronary Artery Disease in the United States

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Coronary artery disease (CAD) is the leading cause of death worldwide, and cardiac stress testing is the principal clinical tool used to evaluate stable patients with symptoms suggestive of myocardial ischemia.¹ In the United States alone, more than 6 million cardiac stress tests were performed on Medicare beneficiaries in 2008, and the growth rate of stress tests with nuclear imaging exceeded 300% from 1999–2008.² Although these numbers have raised concerns for possible overuse,¹ an equally concerning problem is raised by recent literature suggesting that, despite its wide diffusion, cardiac stress testing has poor sensitivity for obstructive CAD (> 50% luminal coronary artery stenosis),^{3,4} a finding with implications for the number of patients with missed diagnoses of obstructive CAD each year. These findings have been reported in several recent head-to-head comparisons with cardiac computed tomography (CT) angiography, and in a meta-analysis that adjusted exercise echocardiography and myocardial perfusion imaging (MPI) performance for cardiac catheterization referral rates.^{3–5} In total, this body of literature suggests that up to

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Disclosures

Dr. Joseph Ladapo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contributions

Dr. Ladapo conceived the study, performed statistical analysis, data interpretation, and manuscript preparation. Dr. Goldfeld performed data interpretation and manuscript preparation. Dr. Douglas performed data interpretation, manuscript preparation, and provided overall supervision.

half of patients with CAD referred for cardiac stress testing receive falsely negative results—and are therefore at risk for missed diagnoses and suboptimal therapy.

In light of this evidence and the development of alternative imaging and gene-expression technologies to diagnose CAD,⁴ we sought to provide national estimates of the morbidity and mortality from missed diagnoses of CAD in patients with falsely negative cardiac stress tests. We believe these estimates will help frame debates over optimal approaches to diagnose heart disease—each with its own assortment of risks and benefits—and guide strategies to reduce its associated morbidity and mortality.

We analyzed the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey from 2008–2010 to identify patients referred for cardiac stress testing without prior history of CAD (data and methods summarized in Table 1). Based on the 27,125 patient Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry (CONFIRM) registry,⁶ we assumed obstructive CAD prevalence was 23.5% in this population and used the referral bias-adjusted meta-analytic sensitivity of cardiac stress testing to estimate the number of patients with falsely negative results (missed diagnoses). Then, based on the Reduction of Atherothrombosis for Continued Health (REACH) Registry,⁷ we used estimates of the benefits of aspirin and statin therapy in patients with CAD, prevalence of this therapy prior to cardiac stress testing, and observed changes in treatment when patients become diagnosed with CAD, to project 1-year cardiovascular event rates in patients with missed diagnoses, and how these event rates would change if patients with falsely negative stress tests were instead correctly diagnosed. We also adjusted for the observation that, among patients with CAD, those with normal cardiac stress results have a better prognosis than those with abnormal results.³

Cardiac stress testing is performed in 3.8 million adults without prior history of CAD each year (mean age 58.7 years, 51.9% are women, 53.4% have hypertension, 16.2% have diabetes, and 15.6% are obese), and we estimate that 571,755 have a falsely normal result. At the time of testing, 29% and 26% of patients overall are already taking aspirin or a statin, respectively. Using intermediate parameters for the sensitivity of cardiac stress testing and the hazard ratio for adverse events in patients with normal vs. abnormal cardiac stress test results, we estimate that 13,710 of 571,755 patients with a falsely negative cardiac stress test will experience a cardiovascular event annually, but up to 2,202 of these events could be prevented if those patients were correctly diagnosed and treated (Table 2).

The economic burden of these falsely negative tests includes \$210.2 million in testing costs, \$19.4 million in hospital costs for nonfatal myocardial infarction and stroke, and \$89.0 million in lost productivity, for a total of \$318.6 million, not including downstream costs associated with premature death or other preventable cardiovascular events.

Our study shows that a substantial number of patients in the US with undiagnosed CAD have a falsely negative stress test each year—with many also experiencing a preventable cardiovascular event. While morbidity and mortality from these missed diagnoses is attenuated by high rates of pre-existing aspirin and statin use, the public health implication is

that many patients who would likely benefit from further risk stratification and risk factor modification may go undiagnosed.

Our work highlights the potential public health value of studying the comparative effectiveness of alternative diagnostic technologies for CAD. A large study that reported lower rates of nonfatal myocardial infarction in patients initially evaluated with cardiac CT angiography vs. stress testing implicitly supports the notion that more sensitive diagnostic tests may yield incremental health benefits,⁸ and several observational studies—and one randomized trial⁹—have reported higher rates of aspirin or statin use in similar patient populations initially evaluated with cardiac CT angiography vs. stress testing. A major comparative effectiveness study (PROMISE; Prospective Multicenter Imaging Study for Evaluation of Chest Pain; NCT01174550) recently demonstrated that anatomic and functional testing were associated with similar outcomes at 2 years, though event rates in this study were very low, and comparative differences in use of cardiovascular medications have not yet been reported.¹⁰ Other diagnostic options currently available for patients with suspected CAD include cardiac magnetic resonance imaging (MRI), though both the technology's availability and cost may limit its use, and a genomic blood-based test⁴ with a small evidence base compared to other existing technologies. Access to all of these technologies in low-income countries is also a challenge.

Limitations of our study include the fact that the REACH Registry may not be representative of care provided in the US, and the absence of accounting for adverse effects of aspirin and statin therapy, including bleeding, liver injury, and myopathy. Nonetheless, we conclude that a substantial number of patients in the US with undiagnosed CAD are estimated to have a falsely negative stress test each year. It may be possible to further reduce morbidity and extend the lives of these patients by using more sensitive technologies either instead of or in conjunction with cardiac stress testing for obstructive disease.

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References

1. Ladapo JA, Blecker S, Douglas PS. Physician Decision Making and Trends in the Use of Cardiac Stress Testing in the United States: An Analysis of Repeated Cross-sectional Data. *Ann Intern Med*. 2014 Oct 7; 161(7):482–490. [PubMed: 25285541]
2. Andrus BW, Welch HG. Medicare services provided by cardiologists in the United States: 1999–2008. *Circ Cardiovasc Qual Outcomes*. 2012 Jan 1; 5(1):31–36. [PubMed: 22235064]
3. van Werkhoven JM, Schuijf JD, Gaemperli O, et al. Prognostic value of multislice computed tomography and gated single-photon emission computed tomography in patients with suspected coronary artery disease. *J Am Coll Cardiol*. 2009 Feb 17; 53(7):623–632. [PubMed: 19215839]
4. Thomas GS, Voros S, McPherson JA, et al. A Blood Based Gene Expression Test for Obstructive Coronary Artery Disease Tested in Symptomatic Non-Diabetic Patients Referred for Myocardial Perfusion Imaging: The COMPASS Study. *Circ Cardiovasc Genet*. 2013 Feb 15.
5. Ladapo JA, Blecker S, Elashoff MR, et al. Clinical implications of referral bias in the diagnostic performance of exercise testing for coronary artery disease. *Journal of the American Heart Association*. 2013 Dec.2(6):e000505. [PubMed: 24334965]

6. Min JK, Dunning A, Lin FY, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol*. 2011 Aug 16; 58(8):849–860. [PubMed: 21835321]
7. Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA*. 2010 Sep 22; 304(12):1350–1357. [PubMed: 20805624]
8. Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. *JAMA*. 2011 Nov 16; 306(19):2128–2136. [PubMed: 22089720]
9. Min JK, Koduru S, Dunning AM, et al. Coronary CT angiography versus myocardial perfusion imaging for near-term quality of life, cost and radiation exposure: a prospective multicenter randomized pilot trial. *J Cardiovasc Comput Tomogr*. 2012 Jul-Aug;6(4):274–283. [PubMed: 22732201]
10. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease. *N Engl J Med*. 2015 Mar 14.

Table 1

Population Characteristics and Probabilities of Health Outcomes in Ambulatory Care Patients Referred for Cardiac Stress Testing*

Variable	Base Case Estimate	Equation Variable	Source
Annual no. patients in US referred for cardiac stress testing	3,805,463	$N_{referred}$	NAMCS/NHAMCS
Probability of CAD	0.235	P_{CAD}	Min et al (9)
Cardiac stress test sensitivity for CAD		S	
Electrocardiography [†]	0.340	S_{ecg}	Ladapo et al (5)
Echocardiography	0.340	S_{echo}	Ladapo et al (5)
Myocardial perfusion imaging;	0.380	S_{mpi}	Ladapo et al (5)
Prevalence of aspirin and statin use in REACH Registry [‡]			
Aspirin alone	0.188	P_a	Bhatt et al (7)
Statin alone	0.225	P_s	Bhatt et al (7)
Both aspirin and statin	0.504	$P_{a,s}$	Bhatt et al (7)
Neither aspirin nor statin	0.083	P_u	Bhatt et al (7)
Prevalence of aspirin and statin use prior to cardiac stress testing in US patients			
Aspirin alone	0.167	P_{a*}	NAMCS/NHAMCS
Statin alone	0.137	P_{s*}	NAMCS/NHAMCS
Both aspirin and statin	0.121	$P_{a,s*}$	NAMCS/NHAMCS
Neither aspirin nor statin	0.574	P_{u*}	NAMCS/NHAMCS
Hazard ratio for cardiovascular events in REACH Registry			
Aspirin use, no vs. yes	1.075	RR_a	Bhatt et al (7)
Statin use, no vs. yes	1.370	RR_s	Bhatt et al (7)
Normal cardiac stress test, yes vs. no	0.667	RR_{ns}	van Werkhoven et al. (3)
Health risks			
Annual event rate for cardiovascular events in REACH Registry [§]	0.031	R_{dx}	Bhatt et al (7)
Optimal event rate in REACH Registry (for patients on aspirin and statin)	0.027	$R_{a,s}$	Derived from Rdx
Attainable event rate in patients with undiagnosed CAD	$R_{dx} \times RR_{ns}$	$R_{undx, attainable}$	-
Expected cardiovascular event rate in patients with undiagnosed CAD [¶]	$R_{dx*} \times RR_{ns}$	$R_{undx, expected}$	-
Total number of patients with CAD and normal cardiac stress test results (undiagnosed CAD)	$N_{referred} \times P_{CAD} \times (1-S)$	$N_{total undx}$	-
Number of patients with cardiovascular events, attainable	$N_{total undx} \times (1 - R_{undx, attainable})$	$N_{CV event, attainable}$	-
Number of patients with cardiovascular events, expected	$N_{total undx} \times (1 - R_{undx, expected})$	$N_{CV event, expected}$	-
Event costs, \$ (2013)			
Stress Electrocardiography	80		Medicare Fee Schedule
Stress Echocardiography	234		Medicare Fee Schedule

Variable	Base Case Estimate	Equation Variable	Source
Stress Myocardial perfusion imaging	582		Medicare Fee Schedule
MI hospitalization	22,322		HCUP
Stroke hospitalization	15,500		HCUP
Productivity loss time estimates [¶]			
Stress Electrocardiography	110 mins		HeartSite.com
Stress Echocardiography	170 mins		HeartSite.com
Stress Myocardial perfusion imaging	230 mins		HeartSite.com
MI hospitalization length of stay	5 days		HCUP
Stroke hospitalization length of stay	5.8 days		HCUP

Abbreviations: No, number; CAD, coronary artery disease; ECG, electrocardiography; HCUP, Healthcare Cost and Utilization Project; MI, myocardial infarction; NAMCS, National Ambulatory Medical Care Survey; NHAMCS, National Hospital Ambulatory Medical Care Survey; REACH, Reduction of Atherothrombosis for Continued Health

* All results reported in this study can be reproduced using equations and values in Table 1.

[†] Sensitivity of stress echocardiography used for stress ECG because referral bias-adjusted sensitivity for stress ECG unavailable

[‡] Estimated by assuming independence between aspirin and statin use (overall rates = 0.682 and 0.729, respectively)

// Hazard ratio for normal cardiac stress test = 3.8%/6% = 0.64 but rounded to 0.667 for ease of analysis interpretation

[§] Four year event rate in REACH Registry (12.2%) converted to annual rate; $R_{dx} = P_{a,s} \times R_{a,s} + P_s \times R_{a,s} \times RR_a + P_a \times R_{a,s} \times RR_s + P_u \times R_{a,s} \times RR_a \times RR_s$

[€] $R_{dx}^* = RR_{ns} \times (P_{a,s} \times R_{a,s} + P_s \times R_{a,s} + P_a \times R_{a,s} \times RR_s + P_u \times R_{a,s} \times RR_a \times RR_s)$

[¶] Includes 50 minutes of round-trip travel time for stress testing; productivity loss based on average hourly wage and weekly earnings for employees in the US (\$22.74 and \$798, respectively)

Table 2

Annual Incidence Of Missed Diagnoses Of Obstructive Coronary Artery Disease And Associated Morbidity/Mortality Among Patients Referred For Cardiac Stress Testing In The U.S.

	Sensitivity of Cardiac Stress Testing [*]		
	Low (27–31%)	Intermediate (34–38%)	High (41–44%)
Annual no. of patients referred for stress testing who have obstructive CAD[†]	892,419	892,419	892,419
Abnormal result	258,194	320,663	378,823
Normal result	634,225	571,755	513,596
Event risk in patients with undiagnosed CAD, compared to patients with diagnosed CAD^{‡§}			
Low (67% lower)			
1-year CV events (expected)	7,650	6,897	6,195
1-year CV events (attainable)	6,415	5,783	5,195
Events prevented	1,235	1,113	1,000
Intermediate (33% lower)			
1-year CV events (expected)	15,208	13,710	12,316
1-year CV events (attainable)	12,766	11,508	10,338
Events prevented	2,442	2,202	1,978
High (0% lower)			
1-year CV events (expected)	22,675	20,442	18,362
1-year CV events (attainable)	19,052	17,175	15,428
Events prevented	3,623	3,266	2,934

Abbreviations: No, number; CAD, coronary artery disease; CV, cardiovascular; REACH, Reduction of Atherothrombosis for Continued Health; HR, hazard ratio

^{*} Range derived from 95% confidence intervals for exercise myocardial perfusion imaging or echocardiography sensitivity in a meta-analysis that adjusted for referral bias

[†] Assumes an obstructive CAD prevalence of 23.5% in the 3,805,463 US ambulatory care patients referred each year for cardiac stress testing to diagnose CAD

[‡] Attainable CV mortality is mortality rate in REACH Registry multiplied by risk reduction associated with having a normal stress test

[§] Expected CV mortality ascribes higher risk to patients not taking aspirin or statins based on HRs in REACH Registry