Clinical Utility of a Novel Coronary Heart Disease Risk-Assessment Test to Further Classify Intermediate-Risk Patients

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ABSTRACT

Background: Current coronary heart disease (CHD) risk assessments inadequately assess intermediate-risk patients, leaving many undertreated and vulnerable to heart attacks. A novel CHD risk-assessment (CHDRA) tool was developed for intermediate-risk stratification using biomarkers and established risk factors to significantly improve CHD risk discrimination.

Hypothesis: Physicians will change their treatment plan in response to more information about a patient's CHD risk level provided by the CHDRA test.

Methods: A Web-based survey of cardiology, internal medicine, family practice, and obstetrics/gynecology physicians (n = 206) was conducted to assess the CHDRA clinical impact. Each physician was shown 3 clinical vignettes representing community-based cohort participants randomly selected from 8 total vignettes. For each, the physicians assessed the individual's CHD risk and selected preferred therapies based on the individual's comorbidities, physical examination, and laboratory results. The individual's CHDRA score was then provided and the physicians were queried for changes to their initial treatment plans.

Results: After obtaining the CHDRA result, 70% of the physician responses indicated a change to the patient's treatment plan. The revised lipid-management plans agreed more often (74.6% of the time) with the current Adult Treatment Panel III guidelines than did the original plans (57.6% of the time). Most physicians (71.3%) agreed with the statement that the CHDRA result provided information that would impact their current treatment decisions.

Conclusions: The CHDRA test provided additional information to which physicians responded by more often applying appropriate therapy and actions aligned with guidelines, thus demonstrating the clinical utility of the test.

Introduction

Coronary heart disease (CHD) remains the leading cause of death and morbidity in the United States. Accurately identifying individuals with subclinical disease who may benefit from early interventions is a key to CHD prevention. The American College of Cardiology Foundation and American Heart Association (ACCF/AHA) guidelines recommend formal risk stratification based on clinical characteristics such as the Framingham Risk Score to calculate 10-year risk for individuals.[1,2] Yet such risk-factor models are known to be inaccurate, especially in the intermediate-risk group.[3,4] This may explain why fewer than 20% of surveyed physicians report using a risk calculator, with many physicians believing that the current risk-assessment tools are inadequate and time consuming, and that they exclude important risk factors.[5,6] As a result, most physicians misclassify a patient's CHD risk, with nearly two-thirds underestimating risk.[7]

Common risk-assessment tools place many individuals into an intermediate-risk category where many cardiac events occur, treatment guidelines are unclear, and patients require further risk stratification.[8] To better define the

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intermediate-risk group, a 5-year CHD risk-assessment (CHDRA) algorithm (MIRISK VP; Aviir, Inc., Irvine, CA) was developed to combine serum levels of 7 biomarkers associated with the biology underlying vulnerable plaque formation and rupture, along with age, sex, family history of myocardial infarction (MI), and diabetic status. The performance and clinical validation of the CHDRA algorithm to assess 5-year CHD risk in the intermediate-risk population has been reported.[9] The current study was undertaken to determine the clinical utility of the CHDRA test by measuring its impact on physicians' treatment choices when provided the CHDRA results for intermediate-risk individuals. A secondary aim was to measure physician adherence to clinical guidelines for cholesterol management.

Methods

Study Design

A Web-based, cross-sectional survey was administered to 206 physicians from 40 states in the United States, distributed equally across cardiology, internal medicine, family practice, and obstetrics/gynecology (OB/GYN) specialties. Of 1113 physicians invited to participate, 639 started and 206 completed the survey. An honorarium of $65 was provided per completed survey; the survey was estimated to take 30 to 40 minutes to complete. The physicians provided practice information and were queried about their CHD risk-assessment tool use and opinions (see Supporting Information, Appendix, in the online version of this article). They were asked to report their usual follow-up appointment frequency, laboratory testing, and other primary-prevention measures for patients based on age, sex, clinical characteristics, and formal CHD risk category. The study was conducted in accordance with the applicable US laws and regulations.

Following an explanation of the CHDRA test and its performance characteristics, each physician was presented with 3 clinical vignettes. The vignettes were randomly selected from 8 total vignettes and reflected participants in the Marshfield Clinic Personalized Medicine Research Project.[10] The Marshfield Clinic Research Foundation Institutional Review Board reviewed and approved the use of de-identified subject data for the clinical vignettes. Each vignette included the individual's current health status, clinical characteristics, physical examination results, medications, and recent laboratory results. The physicians could select a management strategy for an individual based upon the provided information, including lipid-lowering therapy, low-density lipoprotein cholesterol (LDL-C) goals, lifestyle changes, frequency of lipid testing and follow-up appointments, antihypertensive therapy, and aspirin therapy. Lipid questions were designed to analyze the concordance between physician recommendations and the Adult Treatment Panel III (ATP III) guidelines.[11]

After a treatment plan was chosen, the CHDRA test score was provided and physicians were asked the same clinical-management questions. Physicians were prompted with their previous answers and asked to make any necessary changes based on the CHDRA test score. After each vignette, the CHDRA test utility in deciding the appropriate treatment plan for that individual was queried. After completing all 3 clinical vignettes, an overview chart was shown including the physician's original risk classification, the CHDRA classification, and whether or not the individual had a coronary event (MI or unstable angina) within the 5-year study period. Questions about the CHDRA results were based on a 4- or 5-point Likert scale.

The Coronary Heart Disease Risk Assessment Test

The CHDRA blood test, developed and validated in independent cohorts where it significantly reclassified intermediate-risk individuals, is available to identify an intermediate-risk individual's absolute 5-year CHD risk.[9] The test determines the serum levels of 7 protein biomarkers (cutaneous T-cell–attracting chemokine, eotaxin, Fas ligand, hepatocyte growth factor, interleukin 16, monocyte chemotactic protein 3, and soluble Fas) within pathways associated with vulnerable atherosclerotic plaque production. The biomarker levels, along with the age, sex, family history of MI, and diabetic status, are used to reclassify individuals to high or low risk to more accurately identify their CHD risk profile.

Selection of the Clinical Vignettes

The 8 clinical vignettes were deemed to be intermediate risk (5-year risk of a CHD event, 3.50%–7.49%) based on a recalibrated Framingham 10-year CHD risk range of 10% to 20%.[2] The CHDRA test reclassified 5 cases to high risk and 2 cases to low risk, and 1 case remained at intermediate risk.

Statistical Analysis

The physicians' vignette responses, before and after seeing the CHDRA result, were assessed for agreement with the ATP III guidelines for LDL targets and lipid-lowering therapies.[12] A permutation approach was used to test for differences in physician decision percentages (see Supporting Information, Appendix, in the online version of this article). The significance of changes in cholesterol targets, lipid-testing frequency, and antihypertensive medication prescribing, in cases 1, 2, 3, 4, and 7, which were reclassified to high risk after seeing the CHDRA results, were assessed using the Bhapkar test (SAS version 9.3; SAS Institute Inc., Cary, NC). Values in cross-table cells with zero counts were imputed with a very small number (0.00001). All other analyses were completed using R (version 2.14.2). Statistical significance was set at 0.05.

Results

Out of 639 attempted surveys, 206 were completed (Table 1). These were divided nearly equally among the 4 medical specialties. Respondents were more likely to be male, yet well distributed across age and region. An overview of the 8 clinical vignettes is shown in Table 2. The mean age among vignette patients (balanced by sex) was 63 years. Each vignette was reviewed by 64 to 82 different physicians, giving a total 615 responses.

After obtaining the CHDRA result, 69.9% of the physician responses indicated a treatment- and management-plan change (63.3% changed appropriately with the direction

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Table 1. Survey-Respondent Demographics

	Physician Specialty			
	Cardiology, %, n = 50	Internal Medicine, %, n = 51	Family Practice, %, n = 54	OB/GYN, %, n = 51
Age, y[a]				
25–34	4.0	7.8	5.6	0.0
35–44	28.0	33.3	31.5	31.4
45–54	36.0	35.3	20.4	35.3
≥55	32.0	23.5	42.6	33.3
Male physicians[b]	84.0	74.5	68.5	62.7
Practice region				
Northeast	54.0	45.1	24.1	21.6
Midwest	6.0	9.8	24.1	13.7
South	28.0	29.4	25.9	35.3
West	12.0	15.7	25.9	29.4
Practice type, solo	8.0	25.5	16.7	23.5
Practice duration, >10 years	68.0	72.5	77.8	84.3

Abbreviations: OB/GYN, obstetrics and gynecology.
[a] $P = 0.4$ permutation χ^2 test of age and across the physician specialties.
[b] $P = 0.1$ χ^2 test of sex and across the physician specialties.

of risk-score change). Any change to the frequency of lipid testing, glucose testing, medical examination, referrals, lipid-lowering therapy, LDL-C target level, antihypertension therapy, or further testing was counted as a change.

For lipid-lowering therapy, physicians could choose a LDL-C target and prescribe medical therapy alone (ie, statins or other drugs), lifestyle change, or a combination of therapy and lifestyle change. For cases reclassified to high risk by CHDRA, there was a shift from lifestyle-only to medical therapy and a shift to more aggressive LDL-C targets (Table 3). In 35% of the physician responses, changes were to a more aggressive management plan ($P < 0.0001$), defined as either a lower LDL-C target or a switch from a lifestyle to a medical therapy.

Among patients reclassified to high risk, there was also an increase in the frequency of recommended lipid testing, with the majority moving to every 3 or 6 months ($P < 0.0001$) (Table 4). Respondents also increased follow-up appointment frequency for patients reclassified to high risk by the CHDRA score (see Supporting Information, Appendix Table 1, in the online version of this article).

When comparing physician recommendation concordance with the ATP III guidelines, 57.6% were concordant at baseline and 74.6% were concordant after the CHDRA test ($P < 0.001$). Concordance was measured as the physician's accuracy in relation to the LDL-C target chosen either at baseline or after the CHDRA result considering the subject's LDL-C, high-density lipoprotein cholesterol, total cholesterol, smoking status, blood pressure, family history of CHD, and age. For those cases classified to low risk, no significant change occurred from the baseline recommendations after the CHDRA result was provided (82.4% vs 78.6%, $P = 0.14$).

All patients reclassified by CHDRA were already on ≥1 antihypertensive agent. After seeing the CHDRA score, the physicians recommended adding ≥1 antihypertensive agent (Table 5). No significant change in aspirin therapy occurred after providing the CHDRA score.

When asked to identify the utility of the CHDRA to risk-stratify intermediate-risk patients, 19% responded "extremely valuable," 52% said "valuable," 26% responded "slightly valuable," and 3% said "not valuable at all" (see Supporting Information, Appendix Table 2, in the online version of this article). There were no significant differences between specialties. Of the family practice and OB/GYN physicians, 57.4% and 60.7%, respectively, stated they were at least "likely" to recommend CHDRA to their colleagues, whereas cardiologists (46.0%) and internists (54.9%) responded as "likely" or "extremely likely" to recommend (see Supporting Information, Appendix Table 3, in the online version of this article). Overall, 81% indicated some likelihood of recommending the test to a colleague. In addition, 71.3% agreed or strongly agreed that CHDRA would significantly impact their management choices. Similarly, OB/GYN (94.1%), family practice (87.0%), internist (76.4%), and cardiologist (62%) physicians agreed or strongly agreed that the CHDRA test "provides valuable information that they did not know before," whereas 73.3% agreed or strongly agreed that the CHDRA and its results are "likely to have a significant impact on patient behavior by presenting the information to patients" (see Supporting Information, Appendix Table 4, in the online version of this article).

Discussion

Using clinical vignettes drawn from real patient cases in the Marshfield Clinic Personalized Medicine Research Project, adding the CHDRA test to traditional CHD risk assessments resulted in significant changes in physicians' clinical management of cardiovascular (CV) risk factors. More aggressive and targeted risk-factor management for patients reclassified from intermediate risk to high risk of experiencing a cardiac event was consistent across physician specialties, including internists, family practitioners, OB/GYNs, and cardiologists. The changes included appropriate cholesterol management, with a significant proportion of respondents lowering LDL targets, adding medical therapy to reach those targets, and increasing the frequency of follow-up. Physicians across all 4 specialties were more likely to prescribe additional antihypertensive therapies among patients reclassified upward. In general, most physicians found the tool valuable to assist in the clinical management of intermediate-risk patients, and most would recommend the test to their colleagues.

Improving risk stratification of intermediate-risk individuals is a primary goal of the major CV societies. Fewer than 20% of physicians report using a risk calculator, and most physicians misclassify patient risk for CHD events.[7,13] In addition, traditional risk-factor algorithms, such as the

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Table 2. Clinical Characteristics of the Patient Case Profiles

	Patient Case Profile							
	1	2	3	4	5	6	7	8
Age, y	62	75	59	66	77	43	67	56
Sex	M	M	F	F	F	M	M	F
Weight, kg	78.6	105	93.2	69.1	66.4	95.9	77.3	68.6
BMI, kg/m^2	25.6	36.2	43	26.1	22.9	26.4	28.3	26.8
SBP/DBP, mm Hg	136/80	136/88	120/80	164/80	194/102	140/82	122/80	152/82
TC, mg/dL	123	186	244	268	227	258	214	215
LDL-C, mg/dL	77	104	159	178	129	178	136	160
HDL-C, mg/dL	34	51	37	49	76	42	39	38
TG, mg/dL	73	90	260	115	89	153	189	104
CRP, mg/dL	8.3	6.3	7.2	6.7	5.8	5.4	6.7	5.4
Fasting glucose, mg/dL	89	84	79	72	126	90	115	—
Cr, mg/dL	0.8	1.4	0.8	1.2	0.8	1.1	1.2	0.7
Medical history	HTN	HTN, HLD	HTN, HLD	HTN, HLD	DM, HTN, HLD	HTN	HTN	None
Current medications	CCB, diuretic, ASA	α-Blocker, β-blocker, ASA	β-Blocker	ACEI	ACEI, ASA	ARB, CCB	β-Blocker, diuretic	—
Family history of CAD	No	No	Yes	Yes	Yes	No	No	Yes
Initial risk category	Int	Int	Int	Int	Int	Int	Int	Int
CHDRA risk category	High	High	High	High	Int	Low	High	Low

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid (aspirin); BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; CHDRA, coronary heart disease risk assessment; Cr, creatinine; CRP, C-reactive protein; DM, diabetes mellitus; F, female; HDL-C, high-density lipoprotein cholesterol; HLD, hyperlipidemia; HTN, hypertension; Int, intermediate; LDL-C, low-density lipoprotein cholesterol; M, male; SBP/DBP, systolic blood pressure/diastolic blood pressure; TC, total cholesterol; TG, triglycerides.

Framingham Risk Score, are known to be inadequate. It is likely that a biomarker-based approach improving risk stratification, particularly for intermediate-risk patients, would have value in clinical practice.[14] Indeed, the American College of Preventive Medicine specifically indicated that newer biomarker-based risk stratification might be helpful for intermediate-risk individuals by stimulating more favorable risk-factor modification and greater preventive effort to substantially reduce the number of CV deaths.[3,15]

Real-world clinical utility from identifying individuals at high risk for a CHD event and implementing primary prevention with aggressive risk-factor reduction is well established.[5,15] Yet intermediate-risk individuals are often given less aggressive primary-prevention goals because escalating treatment intensity also increases the risk of side effects from medications, and balancing benefits and risks is the hallmark of sound primary prevention.[12,16] Interestingly, no significant "relaxation" in risk-factor management occurred among those cases down-classified from intermediate to low risk. Such decisions are consistent with recent calls for prudent interpretation of novel risk-reclassification methods.[17]

Physicians from various specialties saw value in using the CHDRA test results, with family practitioners and OB/GYN physicians seeing the most value. That is not surprising, considering that these physicians typically are the primary physicians for many intermediate-risk patients, but they may have less formal training and experience with CHD risk-assessment tools than cardiologists and internists. A 2005 statin-usage study showed that cardiologists manage only 4% of the intermediate-risk patients and 11% of the high-risk patients. Internists manage 40% of intermediate-risk and 31% of high-risk patients, and family practice/general medicine and other physicians manage 56% of the intermediate-risk patients and 58% of the high-risk patients.[15] Providing user-friendly and appropriate risk tools to aid family practice and OB/GYN physicians is valuable. Internists and cardiologists also benefit from easy-to-use tools to further stratify intermediate-risk patients.

The ACCF/AHA Guidelines for Screening of Asymptomatic Adults recommend further risk stratification of intermediate-risk individuals, who are generally defined as having a calculated 10-year risk of CHD in the 10% to 20% range.[1] The tests recommended for consideration, such as C-reactive protein and computed tomography,

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Table 3. Change in Cholesterol Targets and Prescribing in Cases 1, 2, 3, 4, and 7 That Were Reclassified From Intermediate to High Risk

	Therapy Choice After Seeing CHDRA Results								
	Drugs to Achieve					Lifestyle to Achieve			
	LDL-C <70 mg/dL	LDL-C <100 mg/dL	LDL-C <130 mg/dL	LDL-C <160 mg/dL	Any LDL-C Level	LDL-C <100 mg/dL	LDL-C <130 mg/dL	LDL-C <160 mg/dL	None
Therapy Choice, Initial									
Drugs to achieve									
LDL-C <70 mg/dL	42	1[a]	0[a]	0[a]	3[a]	0[a]	0[a]	0[a]	0[a]
LDL-C <100 mg/dL	36[b]	91	7[a]	1[a]	0[a]	2[a]	1[a]	0[a]	1[a]
LDL-C <130 mg/dL	6[b]	19[b]	20	1[a]	0[a]	1[a]	2[a]	0[a]	0[a]
LDL-C <160 mg/dL	0[b]	1[b]	2[b]	8	0[a]	0[a]	0[a]	0[a]	0[a]
Any LDL-C level	1[b]	1[b]	0[b]	0[b]	7	0[a]	1[a]	0[a]	0[a]
Lifestyle to achieve									
LDL-C <100 mg/dL	15[b]	12[b]	0[a]	0[a]	0[a]	23	0[a]	0[a]	1[a]
LDL-C <130 mg/dL	2[b]	9[b]	6[b]	0[a]	0[a]	0[b]	10	0[a]	0[a]
LDL-C <160 mg/dL	1[b]	0[b]	1[b]	2[b]	0[a]	1[b]	1[b]	2	0[a]
None	14[b]	3[b]	1[b]	0[b]	6[b]	1[b]	0[b]	0[b]	34

Abbreviations: CHDRA, coronary heart disease risk assessment; LDL-C, low-density lipoprotein cholesterol. $P < 0.0001$ from Bhapkar test calculated after substituting 0.00001 for 0 (null hypothesis that the proportion of doctors prescribing an LDL-C therapy is the same before and after seeing CHDRA results). [a]Total count = 22; indicates less appropriate (less aggressive) lipid targets and/or therapy. [b]Total count = 141; indicates more appropriate (aggressive) lipid targets and/or therapy.

Table 4. Change in Frequency of Lipid Testing in Cases 1, 2, 3, 4, and 7 That Were Reclassified From Intermediate to High Risk

	Frequency of Lipid Testing, After Seeing CHDRA Results						
	Each Month	Every 3 Months	Every 6 Months	Each Year	Every 2 Years	Every 5 Years	Never
Frequency of Lipid Testing, Initial							
1/month	7	0[a]	0[a]	0[a]	0[a]	0[a]	0[a]
1/3 months	6[b]	73	2[a]	0[a]	0[a]	0[a]	1[a]
1/6 months	3[b]	35[b]	125	5[a]	0[a]	0[a]	0[a]
1/year	1[b]	9[b]	45[b]	76	0[a]	0[a]	0[a]
1/2 years	0[b]	0[b]	1[b]	5[b]	4	0[a]	0[a]
1/5 years	0[b]	0[b]	0[b]	1[b]	0[b]	1	0[a]
Never	0[b]	0[b]	0[b]	0[b]	0[b]	0[b]	0

Abbreviations: CHDRA, coronary heart disease risk assessment.
$P < 0.0001$ from Bhapkar test calculated after substituting 0.00001 for 0 (null hypothesis of the same frequency of lipid testing prescribed before and after seeing CHDRA results).
[a]Total count = 9; indicates less appropriate (less aggressive) lipid testing frequency. [b]Total count = 106; indicates more appropriate (aggressive) lipid testing frequency.

have shown only modest improvement in clinical utility as assessed by clinical net reclassification of intermediate-risk individuals. The need for greater risk discrimination remains.

The guidelines are clear for treating high-risk individuals, or those with preexisting CHD, by considering lipid therapy, aspirin, antihypertensives, diabetes control, nutrition, physical activity, and influenza vaccine.[18] Yet there are numerous individuals within the intermediate-risk category who may actually be at high risk and would benefit from appropriate therapy. Using statins, aspirin, angiotensin-converting enzyme inhibitors, and β-blockers has been estimated to reduce recurrent cardiac events by as much as 80%.[19] If everyone received recommended prevention activities, MIs would be reduced by 63% in the next 30 years.[20] The call for improved risk assessment in asymptomatic individuals is a

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Table 5. Change in Number of Hypertensive Medications Prescribed in Cases 1, 2, 3, 4, and 7 That Were Reclassified From Intermediate to High Risk

	No. of Medications, After Seeing CHDRA Results				
No. of Medications, Initial	0	1	2	3	4
0	97	35[a]	2[a]	0[a]	0[a]
1	1[b]	185	8[a]	4[a]	0[a]
2	0[b]	4[b]	41	4[a]	0[a]
3	0[b]	2[b]	0[b]	12	2[a]
4	0[b]	1[b]	0[b]	0[b]	2

Abbreviations: CHDRA, coronary heart disease risk assessment.
$P < 0.0001$ from Bhapkar test calculated after substituting 0.00001 for 0 in above table (null hypothesis of the same number of medications prescribed before and after seeing CHDRA results).
[a]Total count = 55; indicates more appropriate (aggressive) number of medications. [b]Total count = 8; indicates less appropriate (less aggressive) number of medications.

persistent theme in clinical practice guidelines as a means to improve healthcare effectiveness and outcomes.[1]

Achieving optimal levels of serum cholesterol as set forth by the ATP III guidelines has a well-documented impact and is a key feature of the American Heart Association 2020 strategic goals (a 20% improvement in CV health and a 20% reduction in disease).[21] By demonstrating an impact on the actions physicians take in response to improvements in patients' CHD risk assessment, the CHDRA tool may help to achieve the American Heart Association goals.

This study has limitations. Because the risk-stratification tool is an assessment of CV risk-factor management based on clinical vignettes, some physicians may respond differently than they would to a physical examination. Although the 206 physicians who completed the survey represent a diverse sample of US physicians, nonparticipating physicians may have different perceptions, knowledge, and practice patterns. This focused survey contained some questions that forced the respondent to choose a best answer within a finite set of possibilities. A physician's clinical experience is seldom as unambiguous. Physicians were also focused on CHD in this survey and therefore may have done better than with typical asymptomatic patients. Although this demonstrates that using the CHDRA test prompted shifts in therapy that increased compliance with guidelines, changes in patient behavior and adherence to therapy recommendations were not assessed. Although it is believed that early detection of CHD risk will aid in preventing cardiac events, changing physician behavior supports, yet does not ensure, changes in patient behaviors.

Conclusion

The CHDRA test, a biomarker-based risk-stratification tool, has a positive clinical utility leading physicians to substantially change their management of CV risk factors for patients reclassified from intermediate to high risk. Given these findings, this tool could be a valuable addition to the risk-stratification arsenal for patients at intermediate risk of a CHD event. Although we did not evaluate patient-level findings in this study, there is evidence that additional information about risk stratification may positively affect patient behavior.[22] Future research should prospectively measure the CHDRA test impact on clinical management and patient behavior.

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