levels of BH_4, and that the mechanism by which estrogen improves vascular compliance may involve an increase in bioavailable BH_4, thus leading to increased NO synthesis by e-NOS.

Neither estrogen treatment nor BH_4 supplementation restored compliance or FMD to premenopausal levels. Thus, additional factors must contribute to the vascular stiffening in large elastic vessels noted after menopause. These may include other vasoconstrictors, as well as structural changes of the arterial wall, which do not respond to short-term intervention. Further research looking at the dose response of BH_4 would be helpful in determining the degree of improvement in vascular function that can be achieved by supplementing this cofactor.

BH_4 has also been tested in patients with coronary artery disease, and has been found to prevent vasoconstriction induced by acetylcholine in angiographically normal vessel segments.[2] This study suggests several additional lines of future research, including the effects of BH_4 on the microvasculature of women with ischemic microvascular disease, and a possible pharmacologic role to improve large vascular function in women in whom hormone replacement is contraindicated. ■

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Age, Sex, Symptoms, and the Prevalence of Significant Coronary Artery Disease by Coronary Computed Tomographic Angiography

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The concept of "pretest probability" of coronary artery disease (CAD) is central dogma in the teaching and practice of cardiology. The likelihood of the presence of obstructive CAD based on age, sex, and quality of angina, as adopted by the Clinical Practice Guidelines for Management of Chronic Stable Angina by the American College of Cardiology (ACC) and American Heart Association (AHA) for predicting the presence of $>$ 50% stenosis, is challenged by Cheng and colleagues[1] in a recent analysis from the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry (CONFIRM) registry.

Long before the work of Cheng and colleagues,[1] Diamond and Forrester[2] retrospectively collected data from angiograms performed in the 1960s and 1970s and discerned that the variables of age, sex, and type of pain were important in predicting the probability of CAD. Prospective studies from Duke University (Durham, NC) and Stanford University (Stanford, CA) in men and women who underwent cardiac catheterization[3,4] or stress testing[5] confirmed the power of these basic clinical variables. The Diamond and Forrester prediction model was compared with data from the large multicenter Coronary Artery Surgery Study, containing the angiographic data of more than 20,000 patients.[6] In both studies, age, sex, and character of pain were incorporated into probability tables, with an average difference of 5%. These similar results led to the adoption of one unified table that has served as the primary substrate in forecasting the likelihood of CAD (Table 1).

The large multinational CONFIRM registry studied 14,048 consecutive patients enrolled at the time of clinically indicated coronary computed tomography (CT) angiography. Patients with known CAD, suspected acute coronary syndrome, or age $<$ 30 years were excluded. Patients had their symptoms categorized as angina, atypical chest pain (ATCP), or nonanginal chest discomfort based on established criteria for angina pectoris, and were then grouped based on the current prediction score for $>$ 50% stenosis (CAD50). Those age $>$ 70 years and with a history of diabetes, smoking, and dyslipidemia were algorithmically placed into groups that projected a probability of $>$ 70% stenosis (CAD70).

CT angiography based on standardized protocols was performed to evaluate for coronary artery stenosis. A single-source 64-slice or dual-source scanner was used along with β-blockers and nitrates to enhance image quality prior to scanning. A concomitant noncontrast CT was performed in 11,727 (83%) patients for coronary calcium scoring. Data were processed in mid-diastole and end-systole (if available) with image enhancement if needed, and were then sent to an experienced reader who had interpreted at least $\geq$ 1000 prior CT angiograms to assess for the CAD50 or CAD70 in visible segments $\geq$ 1.5 mm in diameter. Images were read on an intent-to-diagnose basis, adherent to standards from prior studies. A 16-segment American Heart Association

TABLE 1

Pretest Likelihood of Coronary Artery Disease in Symptomatic Patients According to Age and Sex*

	Nonanginal Chest Pain		Atypical Angina		Typical Angina	
Age (Y)	Men	Women	Men	Women	Men	Women
30-39	4	2	34	12	76	26
40-49	13	3	51	22	87	55
50-59	20	7	65	31	93	73
60-69	27	14	72	51	94	86

*Each value represents the percent with significant coronary artery disease on catheterization.
Data from Diamond and Forrester[2] and Chaitman BR et al.[6]

coronary artery tree model, along with a modified Duke CAD Prognostic Index Score, was used to characterize disease.

Baseline demographics and cardiovascular risk factors were similar between patient groups. The study population included 14,048 patients, 7719 men (mean age 57 ± 11 years) and 6329 women (mean age 60 ± 11 years). In this large sample, 60% of men (4605) and 75% of women (4752) were symptomatic at the time of testing. ATCP was the most common chest pain type, present in 57% of symptomatic men and 55% of symptomatic women. In all symptom categories, CAD severity scores were higher for men than for women. Patients with angina received the highest severity scores for both genders. The rates of high-risk CAD (score ≥ 5) and overall mean CAD severity scores increased with age, with patients ≥ 70 with angina representing the highest CAD severity subgroup along with prevalence of high-risk CAD. Logistic regression revealed age as seen by increase in decade (odds ratio [OR] 1.82, 95% confidence interval [CI], 1.70-1.94), male sex (OR 2.98; 95% CI, 2.57-3.45), and presence of typical angina (OR 2.45; 95% CI, 2.08-2.88) to be independently linked to high-risk CAD.

The authors form important conclusions that merit further discussion. The presence of CAD50 and CAD70 was much lower than those predicted by ACC/AHA guideline pretest probabilities (18% vs 51% for CAD50, $P < .001$; 10% vs 42% for CAD70, $P < .001$). There were major differences in observed versus predicted stenosis in patients with atypical angina (15% vs 47% for CAD50, 7% vs 37% for CAD70) and typical angina (29% vs 86% for CAD50, 19% vs 71% for CAD70). The presence of typical angina was the most predictive of CAD50 (40% in men, 19% in women) and CAD70 (27% in men, 11% in women).

The trend to over-predict the prevalence of significant coronary artery stenosis based on the current prediction model has been corroborated by previous studies.[7] Høilund-Carlsen and colleagues[7] found an absence of 50% stenosis in 52% of patients with typical angina where guidelines predicted a > 80% probability of CAD.[7] Patel and associates[8] observed that in > 130,000 registry patients, 50% of patients had 50% stenosis, whereas in 145,000 patients in the same registry with ATCP and noncardiac pain, the presence of 50% stenosis was only 25%. Recent work from Genders and associates[9] revealed the overestimation of 50% stenosis based on the Diamond-Forrester model in patients with typical angina, particularly women. In addition, despite any type of symptoms, the prevalence of CAD with a 50% stenosis was 20% to 35% for women and 35% to 50% for men age > 70 years, suggesting that additional factors need to be considered before noninvasive imaging in this elderly group (Figure 1).

The authors put forth potential explanations for their findings. Initial guideline models were predicated on studies in patients who were already at high risk based on abnormal stress test results. Also, the current study assessed the quality of chest pain based on fixed questions, whereas prior studies that created the current prediction guidelines varied by physician or were uncovered in chart reviews. Additionally, public health efforts aimed at disseminating information related to cardiovascular disease may be influencing lower-risk patients to present for earlier evaluation for CAD. This study also highlights the potential need for sex-specific prediction models based on the finding that men with increasing age were more likely to have more observed and expected CAD50 than women. Findings from the South Korean site, where observed-to-expected ratios were lowest, suggest a strong cultural element in the characterization of chest pain.

As demonstrated in recent meta-analyses, a major limitation of CT angiography continues to be its positive

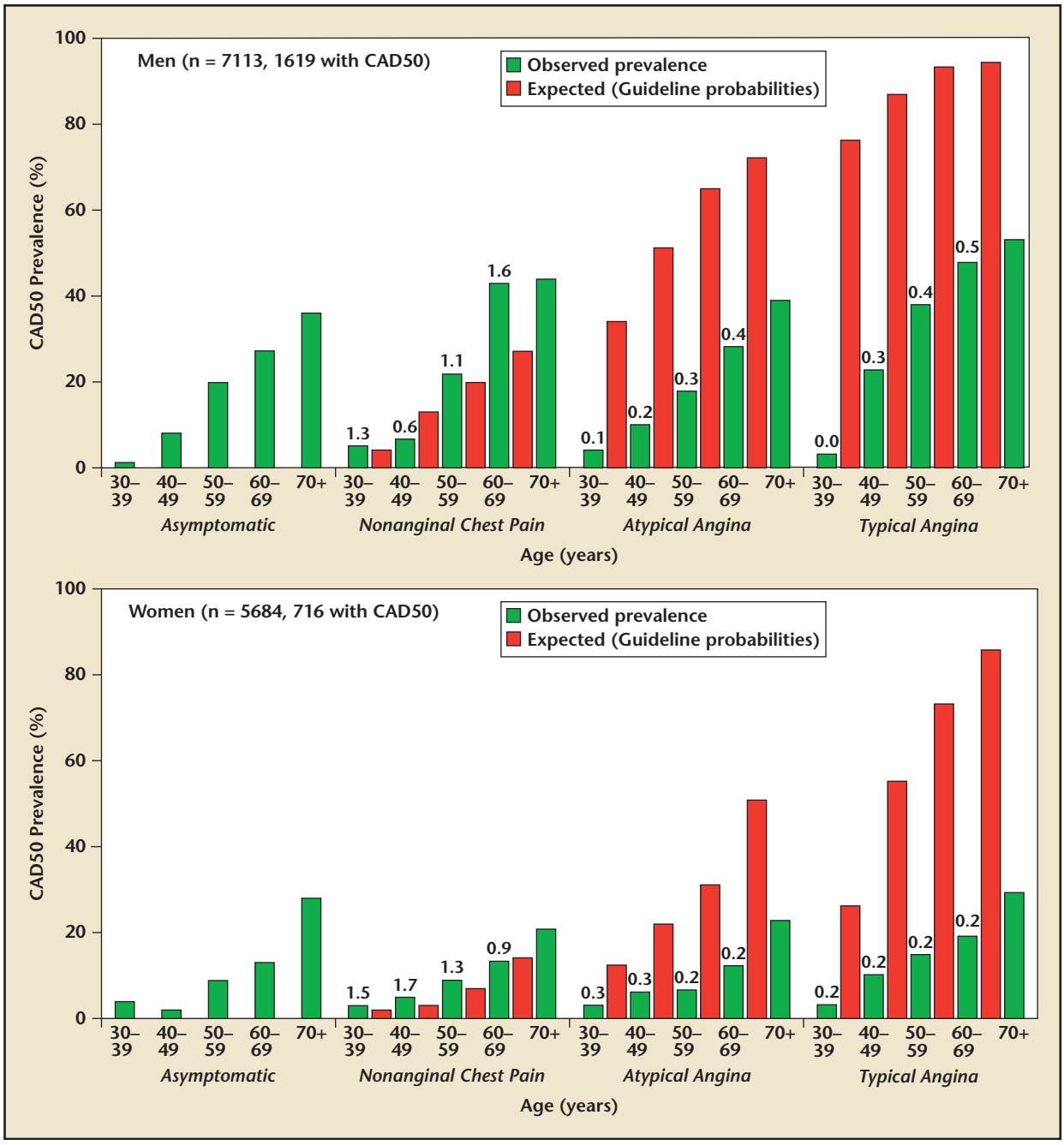

Figure 1. Observed prevalence (*green bars*) and expected prevalence (*red bars*) of angiographically confirmed CAD50 in study men (*top*) and women (*bottom*) with no symptoms, nonanginal chest pain, atypical angina, and typical angina in the CONFIRM study, using CT angiography. With increasing age, observed-to-expected ratios increased in men with atypical angina ($P < .001$) and typical angina ($P < .001$), but stayed unchanged in women. CAD50, 50% stenotic coronary artery disease; CONFIRM, Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry; CT, computed tomography. Reprinted with permission from Cheng VY et al.[1]

predictive value, ranging from 60% to 70%.[10,11] In models adjusted for these limitations, the maximum potential CAD50 prevalence of study patients was 28%, which still remains lower than that predicted by guideline probabilities. In this study, the reader was nonblinded and data were not collected regarding severity and duration of chest pain. The open-label nature of the study may have contributed to biased interpretation when known angina and risk factors were seen. Also, the intention-to-diagnose approach did not account for potential inaccuracies from coronary calcification and uninterpretable segments.

Conclusions

With the development of new technologies as well as the evolution of existing ones, the paradigm of testing for CAD may have to be revisited. Data used to construct

prior prediction models came from a time with a higher prevalence of disease without the medical therapy that is available today. Additional studies should look at cardiovascular endpoints in relation to the findings presented here. In the age of health care reform, and the nearly 10 million noninvasive cardiovascular tests performed annually,[12] more reliable pretest probability and risk assessment will help guide effective patient care. Cardiac CT angiography has revealed a clinical overestimation of significant CAD and may play a role in reducing the number of unnecessary stress tests and diagnostic coronary angiograms in the future. The data from CONFIRM suggest that we can use the history and cardiac CT angiography to find prevalent significant CAD with the aim of intensification of antiatherosclerotic therapies and revascularization in the ideal subset with the most likelihood of benefit. ■

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