



## The Mona Lisa smiles: Impact of risk factors for coronary artery disease in women

**W**hat was Mona Lisa smiling about? For hundreds of years scholars and poets have speculated about what thought inhabited the mind of the woman who posed with the most enigmatic smile in history. Enigmatic too, is the significance of gender relative to the biologic traits and behaviors that contribute to the development and progression of coronary artery disease.<sup>1</sup> Does gender in and of itself impart risk? Anita Zeiler Arnold, DO and colleagues<sup>2,3</sup> probe this mystery in two papers that retrospectively analyze the large database of patients who underwent cardiac catheterization at the Cleveland Clinic. Their results corroborate several previously observed findings, question others, provide some new insights, and point out several issues that need further investigation.

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■ See Arnold and Underwood, p. 387, and Arnold and Moodie, p. 393

Arnold and Underwood<sup>2</sup> found by stepwise logistic regression that older age, diabetes, long-standing hypertension, elevated total serum cholesterol levels, cigarette smoking, and a family history of coronary artery disease constitute the major risks for women. These findings differ notably from the classic Framingham profile, in which women aged 35 to 64 years were more vulnerable to high systolic blood pressure (but not the duration of the systolic hypertension), high blood glucose levels, and excess weight. Although cigarette smoking was highly correlated in men, it was not a significant risk factor in women in the Framingham experience.<sup>4</sup> Arnold and Underwood<sup>2</sup> did not find body weight to constitute

a risk, possibly due to the confounding influence of cigarette smoking in this population. This finding is consistent with the tendency of smokers to weigh less than nonsmokers,<sup>5</sup> and for weight gain to occur after smoking cessation,<sup>6</sup> but is inconsistent with the findings of many other studies. Perhaps, for women, weight per se is not as important as the distribution of body fat.<sup>7-9</sup>

Arnold and Moodie<sup>3</sup> address the issue of gender differences in coronary disease of young women ( $\leq 30$  years). They identify smoking, a positive family history, insulin-dependent diabetes, long duration of hypertension, oral contraceptive use, and elevated total serum cholesterol levels as the major risks on the basis of univariate analysis. Follow-up was available in most of the women identified ( $9.8 \pm 6.4$  years). In general, prognosis for these patients was good. Only 7% had a subsequent myocardial infarction and only one patient has required repeat bypass surgery.<sup>9</sup> All the patients who died had hypertension and 80% had nephropathy requiring dialysis.

One prevailing finding in both men and women is that the greater the number of risk factors, the greater the risk of developing coronary artery disease. While individual risk factors are nominally the same, there appears to be a greater impact in women when multiple risk factors are present. For example, a 55-year-old woman who smokes and has elevated cholesterol and high blood pressure has roughly three times the normal risk for a subsequent myocardial infarction, whereas a 55-year-old man with the same risk factors has only twice the normal risk.<sup>10</sup>

The Cleveland Clinic data are derived from a time when cholesterol fractionation into low-den-

sity lipoprotein (LDL) and high-density lipoprotein (HDL) subtypes was not commonly performed clinically. Thus, the analyses are restricted to total cholesterol values. In Arnold and Underwood's<sup>2</sup> overall population, 52.5% of women with coronary atherosclerosis had total cholesterol levels greater than 250 mg/dL, but 34% of women without CAD also had similarly high levels. Why do so many women without CAD have high total cholesterol levels? Conversely, why do so many women with CAD not have high cholesterol levels? Some of this discrepancy relates to the definition of what constitutes coronary artery disease. However, the Framingham data also show an overlap in total cholesterol levels related to the subsequent occurrence of acute myocardial infarction.<sup>11,12</sup> These observations emphasize the value of measuring HDL and LDL subtypes. Interestingly, only one woman with less than 50% obstruction (ie, "normal" in this series) had a total cholesterol level in excess of 350 mg/dL, whereas 27 women (5.5%) with similarly high levels had coronary artery disease.

In women, elevated total cholesterol levels are often age-dependent. A high total cholesterol level in a woman in her third decade often reflects the presence of a high HDL level. In Arnold and Moodie's<sup>3</sup> younger patients with coronary atherosclerosis the mean cholesterol value was 259 mg/dL (range 155 to 500 mg/dL). In the patients who did have fractionation performed, the average HDL level was 49 mg/dL (range 29 to 78 mg/dL) and the LDL level averaged 178 mg/dL (range 120 to 305 mg/dL). The Framingham data suggest that a total-to-HDL cholesterol ratio exceeding 7.5 poses the same risk in men and women.<sup>10</sup> In Arnold and Moodie's<sup>3</sup> study of young women, the total-to-HDL cholesterol ratio overall was only 5.2, probably reflecting the higher HDL values normally observed in the young. HDL appears, however, to still be a better single predictor of subsequent coronary events in women than in men.<sup>13</sup>

Triglycerides were not a major focus of these two papers, but this lipid entity most likely ties together findings concerning the importance of obesity, diabetes, and, possibly, high blood pressure of long duration. Central or truncal obesity is associated with both higher blood pressure and hyperinsulinemia, which is thought to result in increases in atherogenic lipoproteins and decreases in HDL.<sup>14</sup> The importance of obesity as a determinant of coronary artery disease in women was confirmed in a prospec-

tive cohort study of 115 886 U.S. women 30 to 55 years of age. In this study, after controlling for cigarette smoking, the investigators found that even mild-to-moderate obesity increased the risk of coronary disease.<sup>15</sup>

In the Framingham experience, obesity was often associated with increased coronary artery disease risk in women,<sup>4</sup> and contrary to the case in men, triglyceride levels appeared to contribute to risk, at least in older women.<sup>10</sup> The Framingham data further suggest that the impact of diabetes is greater for women than for men and varies with the number of accompanying risk factors.<sup>16</sup> This is confirmed in the Rancho Bernardo Study, in which the relative hazard of ischemic heart disease death in patients with diabetes compared with patients without diabetes was 1.9 in men, but 3.3 in women, after adjusting for age, systolic blood pressure, cholesterol, body mass index, and cigarette smoking using the Cox regression model.<sup>17</sup>

In a study of young adult men and women aged 20 to 24 years, multivariate analysis revealed fasting serum insulin to be an independent predictor of systolic blood pressure.<sup>18</sup> In a large epidemiological survey, compared with younger women, postmenopausal women had higher plasma triglyceride and cholesterol levels, higher total-to-HDL cholesterol ratios, higher insulin levels, higher body mass index, and higher waist-to-hip ratios. Age-related changes in men were absent or less marked in this study. These investigators developed a case for insulin as a mediating factor in several coronary risks.<sup>19</sup>

Cigarette smoking in women is an especially serious risk,<sup>20</sup> with important biologic and social implications. The prevalence of smoking in Arnold's series was 36% in women with CAD and 14% in women without CAD ( $P < .001$ ).<sup>2</sup> In her series of young patients with infarction, 71.8% smoked.<sup>9</sup> This serious association has been reported earlier.<sup>21,22</sup> Cigarette smoking carries increased hazards for young women because it is often accompanied by oral contraceptive use, a combination that promotes thrombogenesis.<sup>1,23</sup>

Young women constitute the major group in which the prevalence of smoking is increasing.<sup>24-26</sup> The reasons for this are complex.<sup>27</sup> First, more than one third of women who smoke perceive that they must smoke to control their weight,<sup>4</sup> and more than two thirds believe they will gain weight if they quit.<sup>5,28</sup> Browse through almost any women's magazine and you will see advertising<sup>29</sup> that equates smok-

ing with attractiveness, social desirability, and even feminine self-assertion and independence.<sup>27</sup> There is evidence that cigarette advertising in magazines is associated with diminished coverage of the hazards of smoking, particularly in magazines directed to women.<sup>30</sup> "Low yield" cigarettes, which are specifically targeted at women with the implication that lower levels of tar and nicotine are safer, have been shown not to impart a lower risk of a first nonfatal myocardial infarction than higher-yield brands.<sup>31</sup>

Cigarette smoking is a good example of a modifiable risk in which there is strong interplay between the biology of gender and social behavior and in which the risk of coronary artery disease associated with an apparently inherited predisposition may be substantially modifiable.<sup>32</sup> This interplay may be relevant to other risks, including socioeconomic factors, educational attainment, social roles, physical activity, and stress. Although many articles about stress have appeared in the popular literature, and stress appears a major health concern of women,<sup>33</sup> very little prospective research has been published that characterizes the nature of stress as a coronary artery disease risk for women.

Until recently, conventional wisdom held that

risk factors for coronary disease are similar in women and men, except for those that affect only women such as menopause and the use of oral contraceptives and postmenopausal hormones.<sup>34-36</sup> A variation of this theme is that although men and women share a number of coronary risk factors, the overall impact of these factors on the incidence and clinical manifestations of coronary artery disease may differ between the sexes.<sup>37-39</sup> However, the more we learn, the more valid appears Leaf's<sup>40</sup> observation that gender differences do exist in most risk factors, and that an appreciation of these differences is important to better prevent coronary artery disease in women and to define directions for future research.

With the passage of time, our understanding of gender differences in coronary artery disease improves and the enigma appears to resolve. No matter how clever we are, however, or how many riddles we solve, many more mysteries remain. Maybe that is the message behind Mona Lisa's smile.

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