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**G**ender differences and their diagnostic relevance are well recognized in angina, notably with regard to nausea, back pain, and response to effort. But how does gender impact the management of stable angina? Coronary artery disease (CAD) is the leading killer of women. Prevention guidelines were updated in 2004.<sup>1</sup> Female gender is protective, conferring lower age-specific incidence rates than in men. But CAD kills as many women as men: onset may be deferred by 10 years, but women's eventual prognosis is poorer.<sup>2</sup> Gender has little influence on the relative importance of risk factors, and none in primary prevention, whether regarding risk factor management or lifestyle changes.<sup>3</sup> Clinical assessment can be accurate in diagnosing significant obstructive CAD. However, women experience angina differently from men, reporting greater pain intensity and physical limitation, although scoring similarly in total sensory or affective intensity.<sup>4</sup> Noninvasive risk stratification is less accurate in women: not only does estrogen increase the false positive rate of stress electrocardiography (ECG), but because stress ECG has only 50% to 57% sensitivity in postmenopausal women, stress echocardiography or myocardial scintigraphy are preferable investigations. Absence of ST-segment deviation on ambulatory monitoring has a higher negative predictive value in women, although prognostic values do not differ.<sup>5</sup> Coronary angiography is needed for accurate assessment: it excludes obstructive CAD in 20% to 40% of women, as well as angina caused by microvascular dysfunction and the abnormal coronary flow reserve caused by higher values in the follicular phase and acute postmenopausal estrogen

administration.<sup>6</sup> Women are at lower risk of sudden death and episodes of ventricular tachycardia or fibrillation, but have higher resting heart rates. They are at higher risk of QT-interval prolongation and torsades de pointes, probably due to gender differences in ion channels and a greater susceptibility to QT-prolonging drugs.<sup>7</sup> Atrial fibrillation is less common in women. Estrogen does not affect the QT interval in healthy women, but decreases QT dispersion, perhaps explaining the gender difference in susceptibility to ventricular arrhythmia. The diagnosis and treatment of stable angina are similar in both sexes, as recent guidelines show.<sup>8</sup> However, management may be more difficult in women: thrombolysis involves more hemorrhage in older smaller women, and angioplasty and bypass carry greater risks. Blood viscosity may not be an independent risk factor, but could be a marker of CAD. Women with symptomatic disease have more thromboembolic complications than men, and their platelets bind more fibrinogen molecules, meaning that they may require stronger and more specific platelet inhibitors<sup>9</sup>; aspirin resistance rates (20% at rest and 22% during exercise) are gender-independent. Prothrombin fragment F1+2, a marker for thrombin generation, is higher in hyperlipidemic women than men, but responds to statins in both sexes, as do C-reactive protein, fibrinopeptide A, D dimer, and factor VIIa.<sup>10</sup> Statins lower major CAD events by ≈30% regardless of sex.<sup>11</sup> Estrogen enhances vasoreactivity and glucose tolerance, while decreasing atherosclerosis, hemostasis, and lipid and lipoprotein levels. In postmenopausal women, it lowers low-density lipoprotein (LDL) cholesterol, raises high-density lipoprotein (HDL)

cholesterol, and lowers some coagulation factors (fibrinogen) while increasing others (factor VII). In observational studies, eg, the Nurses' Health Study and Uppsala Study, hormone replacement therapy (HRT) lowered CAD risk. But prospective trials, eg, the Women's Health Initiative (WHI)<sup>12</sup> and the Heart and Estrogen/Progestin Replacement Study (HERS),<sup>13</sup> failed to confirm benefit, while an initial mid-term decreased risk failed to persist at follow-up despite a 35% reduction in diabetes. HRT also conferred no benefit on atherosclerosis progression in angiographic CAD.<sup>14</sup> Women have higher levels of glutathione peroxidase 1, one of several cellular antioxidant enzymes that may protect against atherosclerosis.<sup>15</sup> However, antioxidant vitamin supplementation combined with HRT had no benefit in postmenopausal women.<sup>16</sup> Androgens may play an underestimated role in this regard, since hypoandrogenemia in men and hyperandrogenemia in women are associated with increased CAD; androgens also upregulate atherosclerosis-related genes in macrophages from males but not females. Estrogen receptor polymorphism is another factor accounting for the positive effects of estrogens in certain subgroups: the ER.alpha IVS1-401 C/C genotype is associated with an

increased HDL response to estrogen,<sup>17</sup> and the ESR 1c.454-397 C/C genotype with an increased risk of infarction. Specific polymorphisms in eight genes are associated with a metabolic syndrome, with some gene associations being sex-specific. Sex bias affects some aspects of CAD management. Women are less likely to receive aspirin or aggressive lipid-lowering medication for secondary prevention in the primary care setting, but there is no bias in assessment and treatment by cardiologists or in revascularization rates.<sup>18</sup> In very young women, percutaneous revascularization is followed by much higher rates of vascular complications, 1-year mortality, and q-wave infarction than in men.<sup>19</sup> Bypass surgery is associated with more difficult recovery in women, independently of disease severity or prior health status; in women with angina, surgery is equal in efficacy to percutaneous stent-assisted intervention, while appearing superior in men with multivessel disease. Overall, women with CAD have a worse health-related quality of life outcome than men and a worse prognosis.<sup>20</sup> Thus, women need aggressive primary and secondary prevention, together with appropriate prophylaxis for subgroups with unfavorable left ventricular hypertrophy. □

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