Clinical application of genetic risk assessment strategies for coronary artery disease: genotypes, phenotypes, and family history

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Coronary artery disease (CAD) is the leading cause of death and premature disability in the United States and other industrialized countries [1]. Individuals with genetic predisposition to atherosclerosis have substantial risk for developing CAD, especially at early ages [2]. As a result, they may have the most to gain from preventive interventions [3]. This article reviews the role of genetics in the development and progression of CAD; available genetic risk assessment strategies for CAD; and clinical application of genetic risk information for CAD prevention, including recommendations for risk factor modification and early detection and the role of genetic counseling and education.

Role of genetics in development and progression of coronary artery disease

The accumulation of atherosclerotic plaque in an artery wall is a chronic disease that begins early in life [4]. This process seems to be initiated or facilitated by chronic injury to the endothelium [5]. Plaques may become symptomatic when they are large enough to restrict blood flow, leading to tissue ischemia. Acute coronary syndromes, such as unstable angina, myocardial infarction (MI), and sudden death, occur when thrombus forms...
on a thrombogenic plaque or when unstable plaques rupture or ulcerate leading to thrombus formation and possible vessel occlusion [6,7].

CAD is a complex disorder resulting from many risk factors. Multiple biochemical processes are involved, including lipid and apolipoprotein metabolism, inflammatory response, endothelial function, platelet function, thrombosis, fibrinolysis, homocysteine metabolism, insulin sensitivity, and blood pressure regulation [2]. Each of the biochemical processes associated with CAD comprises enzymes, receptors, and ligands, which are encoded by genes. Variations in these genes can alter the function of the constituents within a metabolic pathway. These genetic variations interact with each other and with nongenetic factors, resulting in variable susceptibility to the development and progression of atherosclerosis and thrombosis [2]. Non-genetic risk factors for CAD include exposures, such as tobacco smoke, and behaviors (eg, exercise and dietary patterns), many of which may be culturally determined. Similar to genetic factors, environmental and behavioral risk factors often aggregate in families.

Dozens of candidate genes have been associated with CAD or MI [8], although some associations have conflicting results (eg, angiotensin-converting enzyme, methylenetetrahydrofolate reductase [MTHFR], platelet glycoprotein receptor IIIa, and factor VII) [9–18]). The variable results may be due to chance; to errors in estimating the frequency of polymorphisms in the case or control group; to not matching the race/ethnicity of cases and controls; or to studying related but distinct phenotypes, such as the presence of atherosclerosis versus the occurrence of MI. Investigations using genome scan approaches have found novel genetic loci associated with CAD, which might provide additional insight to genetic factors contributing to atherosclerosis and coronary events [19–23]. There also are numerous studies that have found genetic associations or linkage with related disorders, such as hypertension [24–29], obesity [30–38], diabetes [39–49], lipids [50–53], and oxidative stress [54].

Genetic risk assessment strategies to assess coronary artery disease and myocardial infarction susceptibility

CAD is a complex disorder. Generally the manifestations of CAD arise from the interaction of several predisposing genetic or environmental factors. Global risk assessment has been recognized as an effective approach in preventing CAD and its manifestations [55]. Through global risk assessment, a more accurate estimation of absolute risk can be determined based on the summation of risks contributed by each risk factor. Subsequently the intensity of managing modifiable risk factors can be adjusted by the severity of the overall risk.

Most people are served well by existing global risk assessment methods and prevention guidelines. Genetic susceptibility to CAD is not addressed adequately by these methods, however, and underestimation of risk and
missed opportunities for prevention can result for people who are genetically predisposed to CAD. The Framingham Risk Score is a widely used risk assessment method for prediction of CAD risk [56]. It considers the established risk factors of gender, age, smoking, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and diabetes, but not family history of CAD or related disorders. The National Cholesterol Education Program Expert Panel [57] provides algorithms for treatment of lipid disorders in adults. The established risk factors of hypertension, diabetes, smoking, gender, age, and minimal family history information (parental history of MI before age 55) are used to determine risk and recommend lipid-lowering treatment. The risk associated with additional family history of CAD or related disorders is not included, however.

**Family history collection and interpretation**

The systematic collection and interpretation of family history information is currently the most appropriate screening approach to identify individuals with genetic susceptibility to CAD and MI. Family history of CAD and related conditions reflects the interactions of genetic, environmental, cultural, and behavioral risk factors shared among family members.

Family history of CAD is a significant risk factor for CAD. On average, there is a two to three fold increase in risk for CAD in first-degree relatives of affected individuals [58–62]. Having two or more first-degree relatives with CAD is associated with a three to six fold increase in risk [63,64]. The earlier the age of onset, the greater is the risk of CAD to relatives [63–66]. In addition, the risk of disease is typically greater in relatives of female cases compared with male cases, suggesting greater genetic burden in female cases [61,66–68].

Much of the familial aggregation of CAD might be explained by the familial aggregation of established risk factors, such as elevated LDL cholesterol, low HDL cholesterol, and diabetes [66]. In an analysis of the Third National Health and Examination Survey, adults with a parental history of CAD were more likely to have multiple risk factors (odds ratio [OR] for four or five risk factors compared with none = 2.9, 95% confidence interval [CI], 1.4–6.3) [66]. Even after adjusting for these established risk factors, the family history remains a significant independent risk factor for CAD [65,66,68–75]. An explanation for this remaining risk may be familial aggregation of emerging CAD risk factors, including hyperhomocysteinemia [76]; C-reactive protein (CRP) [77]; elevated fibrin D-dimer, tissue plasminogen activator, and fibrinogen [78]; and insulin resistance [79]. In addition, the interactions of the genetic, environmental, cultural, and behavioral risk factors shared by family members may be too complex to assess with usual statistical methods.

The estimated accuracy and prevalence of a family history of CAD and related disorders are high enough to justify using family history for risk
stratification and targeting screening and prevention to the level of familial risk. Several studies have shown that family history reports of CAD in first-degree relatives are generally accurate with sensitivity estimates of 67% to 85% [63,80,81]. The relatively high sensitivity values indicate that family history can be used with some confidence to stratify risk above average. The specificity estimates for family history reports are more than 90% [63,80,81], indicating a lack of overreporting disease in relatives. Similar sensitivity and specificity estimates are seen for diabetes and hypertension [81]. Prevalence rates of a positive family history of CAD are substantial, with estimates ranging from 14% among high school students [82] to 29% among healthy adults in their mid-30s (11% having a high familial risk and 18% having an intermediate familial risk) [83].

Individuals with familial risk for CAD can be identified by asking targeted family history questions, including the number of relatives affected with CAD; their age at diagnosis; their gender; their degree of relationship to each other and the patient; and the presence of other conditions in the family, such as stroke, hypertension, lipid abnormalities, and diabetes [83]. With this information, stratification into different familial risk groups is possible, which can inform prevention activities [83]. Pedigree analysis, which involves collection and interpretation of more comprehensive family medical history, is performed in a genetic evaluation for individuals with high familial risk of CAD or for individuals who may have mendelian forms of cardiovascular disease.

**Biochemical testing to assess coronary artery disease and myocardial infarction susceptibility**

Tests to assess genetic risk for CAD are primarily biochemical analyses that measure the different pathways involved in development and progression of coronary atherosclerosis. Several of these tests identify established risk factors, such as increased LDL cholesterol, decreased HDL cholesterol, and diabetes, which are known to be causally related to CAD [55]. Many others are considered emerging risk factors, which are strongly associated with CAD [84–93], but for most a causal relationship with CAD has not been determined. Examples of emerging risk factors for CAD include small dense LDL particles, hyperhomocystinemia, CRP, interleukin-6, and factors involved in fibrinolysis such as plasminogen activating factor inhibitor-1 and fibrinogen. Although treatment strategies exist for many emerging risk factors (see later), treatment for most of them so far has not been associated with primary prevention of CAD events. Nonetheless, measuring these risk factors can result in more accurate risk stratification. Currently, recognizing a higher level of CAD risk because of emerging risk factors allows patients and clinicians the opportunity to intensify the treatments that have been proved effective for CAD prevention.
Hyperhomocysteinemia

Extreme elevations in plasma homocysteine (>200 μmol/L), owing to deficiency of cystathionine β-synthase or other key enzymes involved in homocysteine metabolism, cause premature cardiovascular disease. More modest elevations of homocysteine (>10 to 15 μmol/L) are associated with increased risk for cardiovascular disease [93]. Homocysteine may increase the risk for cardiovascular disease by decreasing endothelium-dependent vasodilation, increasing platelet adhesiveness, activating certain clotting factors, and inhibiting fibrinolysis by promoting lipoprotein(a) binding to fibrin [94]. Homocysteine levels are increased by deficiency of the B vitamins that are cofactors for enzymes involved in homocysteine metabolism, including folic acid and vitamins B₆ and B₁₂. Homocysteine also increases with declining renal function, pernicious anemia, thyroid dysfunction, psoriasis, certain malignancies, anticonvulsant therapies, certain oral contraceptives, methotrexate, niacin, fibrates, and metformin [95,96]. Homocysteine levels often can be lowered to a desirable range with folic acid and vitamins B₆ and B₁₂ [97–99]. Lowering homocysteine with B vitamins was shown to decrease the incidence of major cardiovascular events in a double-blind, placebo-controlled trial in 533 subjects with coronary stenosis [100]. Another trial comparing high-dose versus low-dose B vitamins in 3680 patients with ischemic stroke [101] and a controlled trial of folate alone for patients with CAD [102] showed no effect of vitamin supplementation on subsequent coronary events or stroke, even though baseline homocysteine levels were associated with increased risk in these prospective studies. The preventive effect of vitamins before development of symptomatic atherosclerosis is unknown.

Lipoprotein(a)

Lipoprotein(a) is a lipoprotein particle composed of an apolipoprotein B-100 particle covalently linked to an apolipoprotein(a) particle. Apolipoprotein(a) is homologous to plasminogen and may compete with plasminogen, limiting fibrinolysis [103]. Lipoprotein(a) also has been implicated in foam cell formation, endothelium-dependent vasodilation reduction, and LDL cholesterol oxidation promotion [104]. Levels of lipoprotein(a) are strongly genetically determined [105,106]. Lipoprotein(a) increases slightly with age and at the time of acute illness; also, females have greater values than males, with values increasing after menopause [107]. The distribution of levels varies widely among racial and ethnic groups [107]. Most of the associations with CAD have been found in white. Levels greater than 20 to 30 mg/dL are considered high. Lipoprotein(a) levels can be reduced with niacin [108]. Diet and exercise have no effect on lipoprotein(a) levels [109,110]. In postmenopausal women, estrogen replacement therapy can lower levels [111], and in men, testosterone can lower levels [112]. Reduction in lipoprotein(a) attributed to estrogen has been associated with a reduction in cardiovascular events in women [113].
(HRT) with either estrogen for women or testosterone for men is not the standard of care for reducing CAD risk, however. Aggressive LDL cholesterol lowering seems to abolish the CAD risk associated with elevated lipoprotein(a), even with unchanged lipoprotein(a) levels [114]. LDL cholesterol lowering should be the treatment goal for high-risk individuals with elevated lipoprotein(a).

**Atherogenic lipoprotein phenotype**

Atherogenic small, dense LDL cholesterol particles, reduced fraction of HDL2b, low HDL cholesterol, elevated triglycerides, and excess apolipoprotein B are characteristic of the atherogenic lipoprotein phenotype (ALP). ALP occurs in 25% of middle-aged men [115] and is associated with a threefold increase in CAD risk [116,117]. ALP can be improved with regular exercise, loss of body fat, restricted intake of simple carbohydrates and alcohol [118], medical therapy including niacin and fibrates [119,120], and avoidance of β-blockers if possible [121]. Fish oil supplementation also improves the lipid profile associated with ALP [122]. Modifying ALP with the aforementioned measures, particularly niacin alone or in combination with other lipid-lowering therapy, has resulted in regression or prevention of progression of coronary atherosclerotic lesions and reduced coronary risk [123].

**Insulin resistance**

Insulin resistance is associated with many traditional and emerging risk factors (hypertension, hypertriglyceridemia, small LDL cholesterol particles, decreased HDL cholesterol, elevated plasminogen activator inhibitor-1, fibrinogen, and CRP). It can be considered a risk factor predisposing to CAD [55]. An estimated 24% of adults in the United States have the metabolic syndrome associated with insulin resistance [124]. The third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [57] highlighted the importance of treating patients with the metabolic syndrome to prevent cardiovascular disease. Insulin resistance can be treated effectively with lifestyle changes and metformin [125].

**C-reactive protein**

Many studies have shown a strong association between CRP and future cardiovascular events [126,127]. Measurement of high-sensitivity CRP (hs-CRP) is a useful clinical marker of inflammation related to atherosclerosis [127]. Statin drugs used for cholesterol lowering have been associated with reduction in hs-CRP [128]. This reduction may be due in part to the anti-inflammatory effects of these drugs. A report has shown that HRT increases CRP levels [92], suggesting a possible mechanism for increased CAD risk due to HRT. hs-CRP could become a target of therapy for reducing CAD risk. At this time, measurement of hs-CRP is used primarily to stratify risk and guide recommendations for modification of other risk factors.
**Thrombophilia**

Several factors involved in promotion of thrombosis and inhibition of fibrinolysis are associated with CAD. (See the article by Feero in this issue for a review of inherited thrombophilias predisposing to venous thrombosis.) Among this group of CAD risk factors, fibrinogen is one of the most important. Fibrinogen levels are modifiable through smoking cessation, aerobic exercise, weight loss, fibric acid medications, and omega-3 fish oils [129,130]. Antiplatelet medications, such as aspirin and other forms of anticoagulants, also might reduce the thrombotic risk associated with elevated fibrinogen.

**DNA-based testing to assess susceptibility to coronary artery disease and myocardial infarction**

There are more than 30 mendelian disorders (single-gene disorders) that feature CAD or MI (Table 1) [131]. Genetic tests for many of these mendelian disorders are available and include DNA-based tests and biochemical analyses [132]. These conditions generally are associated with a substantial risk for CAD and MI at young ages. For most of these mendelian disorders, personal and family history characteristics are crucial for identifying individuals at risk. Specifically, early-onset CAD is usually present in multiple family members, and family members may have associated conditions, such as stroke, diabetes, thrombophilia, or cholesterol abnormalities. Collection and interpretation of family medical history is central to providing access to genetic testing services that are available for diagnosis of mendelian forms of CAD and MI.

Despite the success of identifying susceptibility genes for multifactorial, nonmendelian forms of CAD and associated conditions, the risk associated with any one of these gene variants is generally of small magnitude and by itself has little clinical significance [133]. Before testing for low-risk susceptibility genes has widespread clinical application, additional studies are needed to assess the prevalence and penetrance of these genotypes and the effect of other genes and environmental factors on their expression. The clinical utility of DNA-based testing for CAD susceptibility compared with other risk assessment strategies, including familial risk assessment and assessment of biochemical risk factors, must be proved. Nonetheless, testing for many CAD susceptibility genotypes is available. Subsequent examples describe the potential benefit and limitations of DNA-based testing for CAD susceptibility in the clinical setting.

**Cholesterol ester transfer protein**

Kuivenhoven et al [134] found a significant association between variation at the cholesterol ester transfer protein locus and angiographic progression of coronary atherosclerosis in men with CAD. There was a dose-dependent relationship between one specific cholesterol ester transfer protein gene
Table 1
Mendelian disorders featuring coronary artery disease and myocardial infarction

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Mode of inheritance</th>
<th>OMIM entry*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity-metabolic syndrome</td>
<td>MF</td>
<td>605552</td>
</tr>
<tr>
<td>Apolipoprotein (a) polymorphism/lipoprotein A excess</td>
<td>AD</td>
<td>152200.0001</td>
</tr>
<tr>
<td>Apolipoprotein A-I deficiency</td>
<td>AD, AR</td>
<td>107680.0011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>107680.0012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>107680.0013</td>
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<tr>
<td></td>
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<td>107680.0015</td>
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<tr>
<td></td>
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<td>107680.0017</td>
</tr>
<tr>
<td></td>
<td></td>
<td>107680.0022</td>
</tr>
<tr>
<td>Atherosclerosis susceptibility/atherogenic lipoprotein phenotype (ALP)</td>
<td>AD, MF</td>
<td>108725</td>
</tr>
<tr>
<td>Coronary artery dissection, spontaneous</td>
<td>AD</td>
<td>122455</td>
</tr>
<tr>
<td>Cerebrotendinous xanthomatosis</td>
<td>AR</td>
<td>213700</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>XLR</td>
<td>301500</td>
</tr>
<tr>
<td>Familial combined hyperlipidemia</td>
<td>AD, MF</td>
<td>144250</td>
</tr>
<tr>
<td>Familial defective apo B</td>
<td>AD</td>
<td>144010</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>AD</td>
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<tr>
<td>Familial hypercholesterolemia, autosomal recessive</td>
<td>AR</td>
<td>603813</td>
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<tr>
<td>Familial partial lipodystrophy</td>
<td>AD</td>
<td>151660</td>
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<tr>
<td>Familial pseudohyperkalemia due to red blood cell leak</td>
<td>AD, AR</td>
<td>177720</td>
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<td>Fibromuscular dysplasia of arteries</td>
<td>AD</td>
<td>135580</td>
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<tr>
<td>Heparin cofactor II deficiency</td>
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<td>142360</td>
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<tr>
<td>Homocysteinemia</td>
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<tr>
<td>Homocystinuria</td>
<td>AR</td>
<td>236200</td>
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<tr>
<td>Homocystinemia/homocystinuria due to 5,10 methylenetetrahydrofolate reductase deficiency</td>
<td>AR</td>
<td>236250</td>
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<td>Hyperlipoproteinemia, type III</td>
<td>AR with pseudodominance</td>
<td>107741</td>
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<td>Protein C deficiency</td>
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<tr>
<td>Pseudoxanthoma elasticum</td>
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<td>Pseudoxanthoma elasticum, autosomal dominant</td>
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<td>Sitosterolemia</td>
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<td>Spontaneous coronary dissection</td>
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<td>Tangier disease</td>
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<tr>
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<tr>
<td>Vitamin B₁₂ metabolic defect with methylmalonic acidemia and homocystinuria</td>
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<tr>
<td>Werner’s syndrome</td>
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<tr>
<td>Williams syndrome</td>
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<td>194050</td>
</tr>
</tbody>
</table>

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; MF, multifactorial; XLR, X-linked recessive.

* OMIM, On-line Mendelian Inheritance in Man [132], a periodically updated reference to inherited disorders associated with alterations in single genes.

polymorphism (TaqIB) and the efficacy of pravastatin in slowing the progression of atherosclerosis. Although this cholesterol ester transfer protein association with CAD progression was significant, the finding has limited clinical utility. Although individuals with the B1B1 genotype derived the greatest benefit, treatment with pravastatin improved the outcome for all study subjects, abolishing any differences based on cholesterol ester transfer protein genotype.

**Apo E**

The ApoE4 allele has been associated with CAD in several populations [135–137]. ApoE2/E2 homozygous individuals are at risk for type III hyperlipoproteinemia, which is associated with an increased risk for atherosclerosis. In addition, apoE genotyping could come to play a role in recommending lipid-lowering diets [122,138–141]. Forty percent of the individual variation in response of LDL cholesterol levels to a low–saturated fat diet is familial [142]; this might be due in part to the apoE locus. Several studies have shown that carriers of the apoE4 allele tend to be more responsive to the LDL-lowering effects of low-fat dietary interventions compared with noncarriers [138–141]. Carriers of the apoE2 allele may be particularly susceptible to unfavorable changes in lipids and to coronary heart disease when they are exposed to diets high in saturated fat [141].

The apoE genotype influences the responsiveness to fish oil supplementation in subjects with an ALP [122]. Individuals with an apoE2 allele displayed favorable changes when given fish oil, including a marked reduction in the postprandial increase in triglycerides and a trend toward increased lipoprotein lipase activity compared with non-apoE2 carriers [143]. ApoE4 carriers had an unfavorable response compared with E3/E3 homozygotes with a significant increase in total cholesterol and a trend toward a reduction in HDL cholesterol [122].

Despite these important associations relating response to diet and the apoE genotype, clinicians must proceed with caution when considering this particular genetic test as a means to assess CAD risk. The apoE4 genotype also is associated with increased risk for Alzheimer’s disease [144]. The American College of Medical Genetics (ACMG) and the American Society of Human Genetics (ASHG) have not endorsed apoE testing for diagnosis or prediction of Alzheimer’s disease [145]. Testing may be harmful because individuals discovering that they may have increased risk for Alzheimer’s disease currently do not have available clear actions for preventing the disease. Patients should be informed of the association of apoE genotype with Alzheimer’s disease if considering apoE genotyping for cardiovascular disease risk assessment.

**Methylenetetrahydrofolate reductase**

Homozygosity for the MTHFR C677T mutation has been associated with elevated levels of homocysteine [146]; homocysteine levels are...
associated with CAD risk [93]. A meta-analysis of case-control studies showed a significantly higher risk of CAD associated with the MTHFR C677T genotype, especially in the setting of low folate levels [147]. The ACMG/ASHG statement regarding measurement and use of total plasma homocysteine recommends that the specific basis for elevated homocysteine levels (>15 μM) be determined before treatment because inappropriate supplementation of folate, vitamin B₁₂, and pyridoxine possibly may cause harm [148].

**Prothrombin G20210A**

In a study of postmenopausal women, risk of MI was significantly increased (OR = 10.9, 95% CI, 2.15–55.2) in women with the prothrombin G20210A mutation who also had hypertension and were taking HRT [149]. Women with the prothrombin mutation had only a mildly increased risk of MI if they did not use HRT. Women without the prothrombin G20210A mutation were not at substantially increased risk for MI, even if they used HRT. These findings suggest a potential benefit of prothrombin G20210A mutation testing in women at high risk for MI who are considering use of HRT. Decision making regarding HRT use is complex, however, and it is uncertain how much value such testing would add in the clinical setting.

**Platelet glycoprotein Ia/IIa receptor**

Smoking is a significant risk factor for CAD and MI. Individuals with specific genotypes have greater risks for MI, however, associated with smoking. One example is the Gln-Arg192 polymorphism of the human paraoxonase gene [150]. Another is the 807T allele of the platelet glycoprotein Ia/IIa receptor [151]. Homozygosity for the platelet glycoprotein Ia/IIa receptor 807T by itself is associated with about a threefold increase in risk for MI; smoking alone is associated with a fourfold increase in risk [151]. These two risk factors interact with a greater than multiplicative effect, yielding an OR of 25 for MI among individuals who are homozygous for the 807T allele and also smoke [151]. Although knowledge of increased risk due to high-risk alleles might be expected to improve smoking cessation efforts, this has not been shown. The absence of these risk alleles does not allow one to smoke with impunity because smoking likely increases risk for MI through other mechanisms, and it is associated with other hazardous health effects.

**Platelet glycoprotein IIIa receptor**

Several studies have identified a strong association between the platelet glycoprotein receptor IIIa A2 allele and extensive CAD or occurrence of coronary thrombosis [12–14]. Other studies have failed to show an association, however, with CAD or MI [15–17]. Cooke et al [18] argued that differences in aspirin use might account for some of the discrepancies in studies investigating this polymorphism because aspirin has been shown to inhibit the increased platelet aggregation observed with this polymorphism.
Aspirin likely has other beneficial effects in the prevention of CAD and acute coronary syndromes. Its use is recommended for primary and secondary prevention of CAD [152]. The clinical utility of genotyping glycoprotein receptor IIIa would be limited because it seems unlikely that this test alone would distinguish who would benefit from chemoprevention with aspirin.

5-Lipoxygenase polymorphisms

5-Lipoxygenase converts dietary fatty acids to leukotrienes, potential inflammatory mediators of atherosclerosis. In a cross-sectional study of 470 healthy, middle-aged people, carotid artery intima-media thickness (measured as a marker of atherosclerosis) was increased in the 6% of people with a variant genotype (either of two polymorphisms) in the promoter region of the 5-lipoxygenase gene [153]. The increased thickening, adjusted for other risk factors, was comparable to the increase seen with diabetes. People with these polymorphisms also had doubled levels of CRP. Higher dietary intake of polyunsaturated n-6 fatty acid increased the effect of the gene variant, whereas higher intake of n-3 fatty acids (eg, from fish oils) lessened the effect [153]. Although this observation suggests a genotype-diet interaction that could identify people more likely to respond to fish oils for prevention of atherosclerosis, clinical use of 5-lipoxygenase genotyping would have to await prospective studies showing that individualized treatment prevents CAD.

α-Adducin variant

A population-based, case-control study of patients treated for hypertension found a significant interaction between the α-adducin gene variant, Trp460, and diuretic therapy in the risk of MI or stroke [154]. The α-adducin gene variant was identified in more than one third of the participants. The risk of MI or stroke in individuals with the wild-type genotype did not depend on the type of antihypertensive therapy. In carriers of the α-adducin variant, however, diuretic therapy was associated with a lower risk of MI and stroke than other antihypertensive therapies (OR = 0.49; 95% CI, 0.32–0.77). Other traditional cardiovascular disease risk factors did not influence this interaction. These results suggest a role for genotyping hypertensive individuals for the α-adducin variant allele, Trp460, to determine benefit from diuretic therapy. These findings need to be confirmed in other studies, however, and other benefits and risks of diuretic therapy need to be considered before such testing translates to clinical practice.

Alcohol dehydrogenase type 3

Alcohol consumption has been associated with reduced risk of CHD. People with an alcohol dehydrogenase type 3 allele metabolize alcohol more slowly. This genetic variant in men also is associated with a lower risk of MI (relative risk [RR] = 0.65; 95% CI, 0.43–0.99) [155]. A significant interaction between this allele and alcohol intake has been found. People who are
homozygous for this allele and drink at least one drink a day have the greatest reduction in risk for MI (RR = 0.14; 95% CI, 0.04–0.45) and the highest HDL cholesterol levels (for interaction $P = .05$). This finding has limited clinical utility because all men in this study seemed to benefit from consuming at least one drink per day regardless of their genotype. In addition, many other variables need to be considered when counseling about alcohol intake.

**Estrogen receptor-α gene**

Herrington et al [156] showed that sequence variation of the estrogen receptor-α gene (IVS1-401 C/C genotype) is associated with the magnitude of increase in HDL cholesterol levels when estrogen or combination HRT is administered to women with CAD. This response has not been linked yet to variation in the risk of cardiovascular disease, however.

**Approach to individuals with high familial risk**

This section reviews the process of genetic evaluation for an individual referred because of personal or family history characteristics suggesting a strong genetic susceptibility to CAD or MI (Box 1). The process includes (1) genetic counseling and education; (2) risk assessment using personal and family medical history, physical examination, laboratory testing, and screening for early detection of CAD; and (3) recommendations for risk factor modification.

**Box 1. Characteristics of genetic susceptibility to coronary artery disease (CAD)**

Consultation for genetic risk assessment and specialized risk reduction should be considered for individuals with at least one of the following characteristics:

- Early-onset CAD, men age <55 and women age <65
- More than one close relative with CAD, especially female relatives
- Multiple atherosclerotic vessels (eg, coronaries, carotids, aorta) with multifocal involvement (ie, angiographic severity)
- Presence of multiple CAD risk factors in family members with CAD
- Presence of related disorders in close relatives (eg, diabetes, stroke, hypertension, peripheral vascular disease)

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a Close relative, first- or second-degree relative from the same lineage.
Genetic counseling and education regarding coronary artery disease susceptibility

An important goal of genetic evaluation for CAD is the development of individualized preventive strategies based on the genetic risk assessment and the patient’s personal medical history, lifestyle, and preferences. Genetic counseling is crucial for delineating a patient’s motivation and likely responses to learning of a genetic risk. Through genetic consultation, patients are educated about the role of behavioral and genetic risk factors for CAD, their mode of inheritance, and the options for prevention and risk factor modification. This communication process ensures the opportunity to provide informed consent, including discussion of the potential benefits, risks, and limitations of genetic risk assessment and options for prevention [157].

Although family history of CAD has been shown to be a significant predictor of CAD risk, a report has shown that this familial risk does not translate into spontaneous improvement in lifestyles of at-risk relatives [158]. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, CAD risk factors were assessed over two consecutive 5-year follow-up periods among 3950 participants aged 18 to 30 years. Kip et al [158] found that the occurrence of a heart attack or stroke in a young adult’s immediate family member did not lead to self-initiated, sustained change in modifiable risk factors. These results argue that primary care clinicians may need to intervene actively with people with a family history of CAD, in whom the opportunities for prevention are substantial [3].

Because most of the established and emerging risk factors for CAD aggregate in families, a family-based approach to risk factor modification ought to be an effective strategy, and this has been shown in a few studies [159–161]. Lifestyle changes, such as dietary modification, weight control, and smoking cessation, are likely to be more effective when delivered to the family than to an individual because family members can influence each other and provide ongoing support to one another.

Risk assessment

Review of the personal medical history should include diagnoses of CAD, MI, peripheral vascular disease, stroke (including transient ischemic attacks), thrombosis, arrhythmia, heart failure, pulmonary disease, diabetes, and hypertension. Medical records, particularly procedure reports, are reviewed for confirmation. The review of systems focuses on cardiorespiratory function, including questions regarding angina, shortness of breath, dyspnea on exertion, paroxysmal nocturnal dyspnea, pedal edema, claudication, and exercise tolerance. Inquiry regarding tobacco exposure, history of alcohol use, exercise, and diet also should be performed.

During genetic consultation, a pedigree is constructed by obtaining demographic and medical information for all first-degree and second-degree
relatives, including current age or age at death; cause of death if deceased; history of CAD, other forms of heart disease, and related conditions such as stroke, peripheral vascular disease, aortic aneurysm, hypertension, diabetes, and lipid abnormalities; and associated risk factors, such as smoking. Additional questioning can be helpful regarding procedures that might have been performed, such as coronary artery bypass surgery, angioplasty, echocardiogram, or pacemaker placement. When available, medical records and autopsy reports of family members are reviewed to verify diagnoses and document test results. The family history should include ethnicity and country of origin because certain conditions might be more prevalent in certain ethnic groups. The prevalence of insulin resistance is high among individuals of Native American admixture [162,163].

When this information is collected, pedigree analysis is performed to determine the most likely mode of inheritance (ie, mendelian versus multifactorial) and the risk of disease to the patient and to unaffected relatives. If a mendelian disorder is suspected, this analysis helps to elucidate the differential diagnosis. This process can inform recommendations for appropriate diagnostic tests and individualized management and prevention strategies.

An inherited susceptibility to thrombosis may be suspected in a pedigree that features multiple affected relatives with early onset of CAD, stroke, and other thromboembolic events [164]. Testing of thrombotic markers might reveal important risk factors in the family. Recommendations can be made to avoid factors that may aggravate that risk, such as use of oral contraceptives, HRT, and prolonged periods of immobility, and for prophylactic use of anticoagulants in high-risk situations. (See Feero article in this issue.)

A physical examination focused on CAD risk should include blood pressure in the arms and the ankles. In addition to identifying hypertension, these measurements can be used to calculate the ankle/brachial blood pressure index (ABI). ABI values less than 0.9 are correlated with atherosclerosis. In addition, a blood pressure of 130/85 mm Hg or greater is a criterion for the metabolic syndrome [57]. Weight and height should be obtained, and body mass index should be calculated. Theses data can be helpful in identifying a need for achieving an ideal weight and monitoring diet and exercise interventions. Waist circumference should be obtained because it can be a factor in identifying the metabolic syndrome [57]. Evaluation of lipid disorders should include examination of the eyes, assessing corneal arcus and lipemia retinalis. Examination of the skin should include assessment for xanthelasma and tendinous xanthomas. The cardiovascular examination should include careful assessment of the heart and lungs; listening for bruits at major vessels in the neck, abdomen, and groin; and palpation of the aorta and distal pulses. Any abnormalities can be followed up with additional studies, such as ultrasound. Physical signs of mendelian disorders that feature cardiovascular disease (eg, Marfan syndrome, Ehlers-Danlos syndrome type IV, pseudoxanthoma elasticum, and Fabry’s disease) also should be sought.
Laboratory testing to detect traditional and emerging risk factors for CAD includes fasting lipid panel, lipoprotein(a), LDL cholesterol particle size, HDL cholesterol fractionation, apolipoprotein B, hs-CRP, glucose, and homocysteine measurements. The atherogenic lipoprotein phenotype can be identified if there is a preponderance of small dense LDL cholesterol, decreased fraction of HDL2b (<15%), elevated triglycerides, and elevated apolipoprotein B. ALP can be treated effectively with lifestyle changes or medications (niacin or fibrates) as reviewed earlier [118–120]. Fasting insulin can be checked if there is evidence of impaired glucose tolerance. The metabolic syndrome can be identified if at least three of the following criteria are met: blood pressure 130/85 mm Hg or greater, waist circumference greater than 102 cm in men and greater than 88 cm in women, HDL cholesterol less than 40 mg/dL in men and less than 50 mg/dL in women, and triglycerides 150 mg/dL or greater [57]. If the metabolic syndrome is present or if there are signs of insulin resistance or impaired glucose tolerance, oral glucose tolerance testing should be considered for detection of diabetes.

DNA-based testing may be considered in specific situations for high-risk individuals. MTHFR mutation analysis for the C677T allele can be performed if hyperhomocysteinemia is detected. Factor V Leiden mutation analysis can be performed for premenopausal women with other high-risk factors for MI who are considering use of oral contraceptives. If the Factor V Leiden mutation is identified, oral contraceptives may be avoided because of an associated risk for MI in premenopausal women [164]. Prothrombin G20210A mutation analysis can be considered for high-risk, postmenopausal women considering HRT. The combination of HRT and the G20210A mutation is associated with risk for MI [149]. ApoE genotyping can be considered if there is a question about the diagnosis of type III hyperlipoproteinemia or if the apoE genotype would influence dietary recommendations significantly.

Early detection strategies for CAD might be useful to stratify risk further in asymptomatic individuals at increased risk for CAD [55], especially if the identification of subclinical atherosclerosis would alter recommendations regarding risk factor modification or adherence to risk-reducing strategies. Noninvasive tests, such as carotid artery duplex scanning to measure intima-media thickness, ABI, electron-beam CT (EBCT) to detect coronary artery calcification, ultrasound-based endothelial function studies, MRI techniques, and testing for hs-CRP, offer the potential for measuring and monitoring atherosclerosis in asymptomatic people. Several of these methods are highly valid and predictive of CAD events (eg, ABI, carotid intima-media thickness, and EBCT) [55]. When a higher risk is confirmed with these methods, aggressive medical therapies for primary prevention can be recommended.

The EBCT is the most popular of these early detection methods. There is consistent evidence that coronary calcification correlates with the presence and degree of plaque at autopsy, by intravascular ultrasound [165], and by
angiography [166,167]. Coronary calcification also is correlated with non-fatal MI and need for subsequent coronary revascularization in asymptomatic individuals [168–170] and patients undergoing coronary angiography [171]. A prospective study has shown that EBCT identifies a high-risk group of asymptomatic subjects with clinically important silent ischemia as shown by stress myocardial perfusion single-photon emission CT (SPECT) [172]. Abnormal SPECT was seen in 11.3% of patients with coronary calcium scores of 101 to 399 and 46% with scores of 400 or greater. Until more recently, however, the added value of the coronary calcium score beyond the usual risk assessment methods had not been shown. In a study of sibships at high risk for hypertension, a coronary artery calcium score above the 70th percentile was significantly associated with occurrence of coronary events, over an average of 5 years, after adjusting for Framingham Risk Scores (OR = 2.8; 95% CI, 1.2–6.4) [173]. For individuals with a greater than average CAD risk (eg, people with a significant family history), the coronary calcium score obtained with EBCT has potential to detect advanced but asymptomatic coronary atherosclerosis, leading to recommendations for aggressive risk factor modification. At least one study has shown that knowledge of coronary calcium scores positively influenced behavior in self-referred subjects [174], although additional outcomes research regarding the utility of this approach is necessary. In addition, low coronary calcium scores may be valuable in defining a lower CAD risk [55], which could provide some reassurance to individuals assigned a high risk because of their family history. Risk factor modification could be relaxed some for them, on the basis of EBCT.

Risk factor modification

Genetic information about CAD risk has value in guiding decision making regarding lifestyle and other disease management and prevention strategies. Individuals with a strong genetic susceptibility to CAD, as determined by family history and the presence of established and emerging risk factors, may derive the greatest benefit from traditional preventive strategies, such as smoking cessation and screening and treatment for elevated cholesterol and blood pressure. Individuals with CAD also might benefit from targeting emerging risk factors with specific interventions and lifestyle changes. For the most part, however, evidence regarding primary prevention of clinical cardiovascular events in individuals who have modified emerging risk factors effectively is lacking, and prospective clinical trials are necessary. It is crucial to discuss these potential benefits and limitations with any patient undergoing assessment of emerging CAD risk factors.

Cholesterol lowering is an important clinical strategy in primary and secondary prevention of CAD [57]. Use of cholesterol-lowering agents has been effective in reducing atherosclerosis incidence, disease progression, and CAD mortality [174–180]. In high-risk individuals, hypercholesterolemia
should be treated initially with lifestyle changes and, if necessary, with lipid-lowering medications to achieve a risk-appropriate LDL cholesterol value. Even when there is effective lipid lowering, however, a substantial proportion of individuals develop CAD or have progression of their disease [181]. Considering treatment of additional biochemical risk factors in high-risk individuals is a reasonable approach.

If there are small LDL cholesterol particles, niacin should be considered. Niacin can be used in combination with a statin drug if LDL cholesterol is elevated. Niacin also can be prescribed in similar doses to treat elevated lipoprotein(a) levels [108], or if estrogen replacement therapy is an option, this can be considered [111]. Niacin also can raise HDL cholesterol [182], as do exercise [183] and moderate alcohol intake [184]. With niacin therapy, transaminases, uric acid, and blood glucose should be monitored because abnormalities can arise [185]. Transaminases and creatinine kinase levels also can increase with statin drugs, although the usefulness of routine measurement is questionable [186]. If there is evidence of hyperhomocysteinemia, nongenetic factors should be assessed (eg, measurement of B vitamins, renal function, thyroid function, and review of medications), and B vitamin supplementation should be considered, titrating the amount of folic acid to the fasting homocysteine level [97–100]. Homocysteine levels can become abnormal with niacin, fibrac acid derivatives, and metformin [96], drugs that often are used in individuals at risk for CAD. Insulin resistance can be treated effectively with lifestyle changes or metformin [125].

Summary

Several lines of evidence support the contribution of genetic variations to the development and progression of CAD and to response to risk factor modification and lifestyle choices. Genetically predisposed individuals generally have the highest risk for CAD and develop disease at an earlier age. The best method to identify and stratify genetic risk for CAD is collection and interpretation of the family history. Additional information from the medical history, physical examination, and biochemical and DNA testing, interpreted in the context of the family history, can refine the genetic risk assessment further. Knowledge of genetic susceptibility to CAD has value in providing risk information and can influence lifestyle choices and management options. Genetically susceptible individuals might benefit the most from aggressive treatment of established CAD risk factors. In addition, many emerging risk factors are modifiable, and targeting these risk factors with specific therapies may result in improved CAD prevention. Family-based prevention might be most effective for genetically predisposed individuals because many established and emerging risk factors aggregate in families, and most are amenable to lifestyle changes. Early detection of CAD may be appropriate for genetically susceptible individuals to guide decision making about risk factor modification. Studies are needed to
generate evidence regarding the feasibility, validity, and utility of using familial risk assessment to inform CAD prevention strategies and the ethical, legal, and social issues that may arise.

References


