Cardiovascular Disease

A resident asks....

Why should a primary care doctor want to know about genetics and cardiovascular (CV) disease?

Key Points:

- CV disease is common.
- Coronary heart disease (CHD) results from an interplay of genetic and environmental factors.
- Relatively uncommon genetic disorders can dramatically increase the risk of heart disease, and its occurrence at an earlier age.
- Interventions are effective at reducing morbidity and mortality.
- A family history may identify others who would benefit from screening and preventive interventions.

Learning Objectives for Cardiovascular Disease Module

Participants will be able to:

- Understand what constitutes a positive family history.
- Understand how family history helps to identify autosomal dominant CV disease.
- Understand how different screening protocols influence the importance of obtaining family history.
- Understand the need to consider prevention efforts for family members, whether positive family history is based on lifestyle or genetics.

CASE #1

A medical student you are precepting in clinic wants to know if she should check a cholesterol level on a 25-year-old man who is establishing care. The patient is a vegan who exercises regularly. He has no history of smoking, hypertension or diabetes. However, he has a family history of heart disease; his father had a heart attack at age 50. He notes that his father was overweight, ate a high fat diet and never exercised.

Questions for Discussion:

1. What is the relevance of the family history of heart disease for this patient?
2. Does the role of family history in clinic decision making change depending on the screening criteria used – American College of Physicians (ACP), U.S. Preventive Services Task Force (USPSTF) or National Cholesterol Education Program (NCEP)?

CASE #1 – Discussion

1. What is the relevance of the family history of heart disease for this patient?

A family history of early CHD increases personal risk. A search for modifiable risk factors is indicated. In particular, elevated cholesterol should be suspected in anyone with a strong family history of premature CHD, which **National Cholesterol Education Program** (NCEP) defines as a family history of premature CHD or sudden death occurring in a first degree female relative less than 65 years old or in a first degree male relative less than 55 years old (see **Table 1**).

Epidemiological, observational and interventional studies clearly demonstrate a causal role of hypercholesterolemia in CHD, a condition that affects approximately 7 million Americans and is the most common cause of death in both men and women in the United States. The risk of CHD rises 2-3% for every 1% increase in total serum cholesterol. Twenty percent of adult Americans have a cholesterol level of greater than 240 mg/dL, which in a middle-aged man indicates a 9-12% risk of developing symptomatic coronary artery disease within 7- 9 years. In general, elevated LDL cholesterol and inversely low HDL cholesterol are associated with higher risk of coronary events. Risk can be further defined by analysis of other factors such as lipoprotein(a) [Lp(a)]. Some data suggests that an elevated triglyceride level is an independent risk factor for coronary artery disease (Austin et al, 1998). Additionally, non-lipid cardiac risk factors such homocysteine, fibrinogen and c-reactive protein levels may influence risk status (Harjai, 1999).

Because of the association between cholesterol and increased CHD risk, routine screening of adults for hyperlipidemia is recommended by many advisory groups. The **US Preventive Services Task Force** (USPSTF) and **American College of Physicians** (ACP) recommendations (see **Tables 2.1, 2.2**) reflect concern about the potential risks of lipid lowering medication and suggest delaying the age of onset of laboratory cholesterol screening in order to focus screening on higher risks groups in whom the benefit-risk ratio and cost-effectiveness is greater. The **NCEP Adult Treatment Panel III** guidelines (see

Table 2.3) take a more aggressive approach to screening while recognizing the different risk-benefit ratios in primary and secondary prevention.

The NCEP definition of positive family history, intended to identify genetic risk for hyperlipidemia, is somewhat arbitrary but necessary for institution of national guidelines. In reality, a positive family history is a more ambiguous entity that takes into account both the interactions of lifestyle and genetics and the family structure, i.e. the number of relatives at risk and their biological relationship to the person whose risk is being assessed. For example, a history of early CHD in a parent may reflect a genetic predisposition, a mix of non-genetic risk factors, or both. Effective early prevention may result in a parent with a history of medically treated hypercholesterolemia rather than myocardial infarction. A strong family history on the mother's side may be more evident in her male relatives than in her own medical history, due to the later onset of disease. Family history information should be evaluated with these considerations in mind.

A small number of families have genetic conditions conferring very high risk of CHD – e.g., familial hypercholesterolemia (FH) and familial combined hyperlipidemia (FCH). These are autosomal dominant traits that cause a markedly increased risk of CHD with the first myocardial infarction occurring at a mean age of 40 years old in affected men and 10 years later in affected women. In familial hypercholesterolemia, an LDL receptor defect often results in cholesterol levels above 300 mg/dL. Familial hypercholesterolemia (seen in 1 in 500 people in its heterozygous state) causes 5% of myocardial infarctions occurring before age 60. In familial combined hyperlipidemia, estimated to occur in 1 in 100 people, increased production of apoprotein B causes elevated levels of triglycerides, cholesterol, or both. Approximately 15% of individuals with myocardial infarction before age 60 have familial combined hyperlipidemia (see Summary **Table 3**). While most individuals are identified with FH by a family history of premature CHD, the condition may occasionally be noted on physical exam by noting tendinous xanthomas, commonly found on the extensor tendons of the hand or as thickening (>7 mm) of the Achilles tendon, which are pathognomonic for familial hypercholesterolemia.

2. *Does the role of family history in clinic decision making change depending on the screening criteria used – American College of Physicians (ACP), U.S. Preventive Services Task Force (USPSTF) or National Cholesterol Education Program (NCEP)?*

The importance of a positive family history as a basis for screening or prevention efforts differs depending on the protocol the physician is using. According to ACP or USPSTF recommendations, men younger than 35 and women younger than 45 are screened for lipid disorders only if they are at increased risk, primarily assessed by a positive family history. Because NCEP recommends that all individuals be screened for lipid disorders beginning at age 21, the family history is not important in the decision to screen. However, family history does influence the interpretation of cholesterol level and management decisions.

The ACP and USPSTF lipid screening guidelines are based on studies indicating that beginning treatment at age 35 for men and age 45 for women results in a decrease in morbidity and mortality nearly equal to that of treatment started at an earlier age, and avoids unnecessary years of the costs and potential adverse effects of medication (Law et al, 1994). However, this result cannot be extrapolated to the relatively small number of people with FH or FCH because their risk of CHD begins early in adult life, underscoring the importance of using family history to identify them. Screening for smoking and hypertension is recommended for all adults, starting in early adulthood. Similarly counseling about a healthy lifestyle – regular exercise, low fat diet and avoidance of smoking – is recommended. However, the effect of such advice is not clear. One might expect that knowledge of increased risk would motivate behavioral efforts, but compliance with recommendations for lifestyle modifications is not significantly increased based on knowledge of one's cholesterol level (Elton et al. 1994; Hanlon et al. 1994; Robertson et al. 1992; Strychar et al. 1998).

Knowledge of genetic risk may be different from information about other risk factors. In a pilot study of the parents of 24 children with neonatal screening test result showing the child to be at increased risk of FH, the parents responded differently depending on their perception of the underlying cause of this risk. When they perceived the test as detecting raised cholesterol, their child's condition was seen as

"familiar, dietary in origin, controllable and less threatening." When it was viewed as a genetic problem, it was seen as "uncontrollable and, hence, more threatening" (Senior, Marteau & Peters 1999). These preliminary results suggest the need to consider the effect of a sense of fatalism that may be attached to risks perceived as genetic in origin.

CASE #2

A 47-year-old normotensive, non-diabetic man is admitted with an acute MI. After his hospitalization and subsequent recovery, he is found to have an elevated cholesterol of 300, HDL 35, LDL-C 195, TG 350. He is obese and smokes one pack per day and eats a high fat diet. He does not exercise. He has two younger brothers who have similar lifestyles. Family history is unknown, as they were raised by godparents after their parents were killed in an auto accident.

Questions for Discussion:

1. What are the likely contributors to his cardiac risk status?
2. Should you encourage the patient to disclose his health status (and its implications for risk to others in the family) to his family members?

CASE #2 – Discussion

1. What are the likely contributors to his cardiac risk status?

In assessing cardiac risk in general, age is the best predictor of death from CHD, with a 100-fold increase between ages 40 and 80. Other established risk factors for CHD include dyslipidemia, hypertension, diabetes, and cigarette smoking. In addition, gender is a factor: women tend to develop CHD later than men. For a non-smoking, normotensive 55-year-old man with a total cholesterol level less than 200 mg/dL, the probability of having a heart attack within 8 years is 31/1000. If he smokes, the risk is 46/1000; if he has high cholesterol (>260 mg/dL) and smokes, it is 64/1000. With the addition of hypertension (systolic greater than 150 mmHg) to smoking and hypercholesterolemia, his risk of myocardial infarction within 8 years is 95/1000.

2. Should you encourage the patient to disclose his health status (and its implications for risk to others in the family) to his family members?

Because knowledge of a family history of FH or FCH influences screening and treatment decisions, it has the power to reduce events. Providers are encouraged to inform their patients to notify family members of the potential impact of their own health status on risk to biologic relatives. The patient's lipids raise the possibility of these genetic diagnoses. More likely, his lipids reflect his poor dietary habits, obesity and sedentary lifestyle. (Background genetic factors – normal variants in genes coding for apolipoproteins and other proteins related to lipid metabolism – probably contribute as well.)

Whether his CHD is due primarily to genetics or primarily to lifestyle, his family members are likely to benefit from information about cardiac risk reduction. Because discussions about talking to family members about risk have occurred primarily in the genetic community, less attention has been paid to the opportunity to use one patient's health status as a springboard to educate other family members about risk, and, in particular, about the impact of lifestyle on health. Yet lifestyle, like genetics, is often shared among family members.

CASE #3

A 40-year-old woman sees you to help direct her exercise and weight loss program. She is a non-smoker, has no diabetes or hypertension, and her BMI is 24. Her 62-year-old mother just died of a heart attack, and her brother was found to have elevated cholesterol. You obtain a fasting lipid profile that shows her LDL to be 142 and her HDL is 45. She tells you that according to the 1993 NCEP guidelines, she understands she doesn't need medications, but wonders whether newer data will prompt more strict guidelines. She'd also like you to explain the genetics of heart disease.

Questions for Discussion:

1. What is the appropriate management strategy for her?
2. What information about genetic risk is most relevant to her care?

CASE #3 - Discussion

1. What is the appropriate management strategy for her?

Although the patient is correct that NCEP III guidelines are stricter than previous NCEP guidelines (see **Table 2.3**), it is not clear that she should pursue more aggressive therapy. She falls into the 0-1 risk factor category (her one risk factor is her mother's heart attack). Thus her LDL goal, according to NCEP III, is < 160, which she has met (**Table 2.4**). With an additional risk factor (e.g., if her brother were to develop CHD, or she were to develop hypertension – or if she were ≥ 55 years), her NCEP III LDL goal would be ≥ 130. Thus no additional management is indicated now, but continued careful monitoring of cardiac risk factors is appropriate.

2. What information about genetic risk is most relevant to her care?

The patient may benefit from learning that the genetics of heart disease are complex. Both rare high risk mutations and relatively common genetic variants contribute to CHD risk. Many of the "background" common genetic variants influence the likelihood of developing risk factors such as hypertension or diabetes.

Personal efforts to reduce risk are helpful no matter what genetic risk is present: People with FH, for example, benefit significantly from avoiding smoking, exercising regularly, etc. This patient's family history (her mother's heart attack) points to an element of genetic risk. Her own efforts with exercise and diet are likely to be very helpful in further reducing her personal risk.

Table 1

FOR PEOPLE WITH INCREASED TOTAL CHOLESTEROL

NCEP III risk factors used in determining goals for LDL

POSITIVE FACTORS (raise risk)

NON-MODIFIABLE	*MODIFIABLE*
Age: men ≥ 45 years, women ≥ 55 years or premature menopause without estrogen replacement	**Cigarette smoking**
Family hx of premature CHD CHD / sudden death in 1° female relative <65 year or in 1° male relative <55 years	**Hypertension**: ≥140/90 mmHg or treated
	HDL < 40 mg/dl
	Diabetes mellitus

NEGATIVE FACTOR

High HDL ≥ 60 mg/dl (If present, negates one positive risk factor in above determination)

Of note: Obesity and inactivity, while not considered risk factors in NCEP III classification, are seen as areas of intervention.

Table 2.1 American College Of Physicians - 1996 Cholesterol Screening Guidelines

Primary Prevention

Target population

Middle-aged Adults*

Men - age 35-65 years Women - age 45-65 years

Selective screening of young adults with history or physical examination suggesting a familial lipoprotein disorder or at least 2 other risk factors for coronary heart disease

Recommended approach

Screening of total cholesterol is not mandatory but is considered an appropriate strategy if done. Abnormal results should be confirmed with a repeat test.

Frequency: variable, depending on test results

If results normal, test once.
If results near treatment threshold, repeat at least every 5 years.

Secondary Prevention

Recommended approach

Screening with a lipoprotein analysis is recommended for any patient with a prior event.

Table 2.2 U.S. Preventive Services Task Force- 1995 Cholesterol Screening Guidelines

Primary Prevention

Target population

Middle-aged Adults*

Men - age 35-65 years Women - age 45-65 years

Selective screening of young adults with family history of very high cholesterol or premature coronary artery disease; or with other major risk factors for coronary heart disease

Recommended approach

Screening of total cholesterol recommended.
Abnormal results should be confirmed with a repeat test.

Frequency: variable, depending on test results

If results normal, test at least once.
Periodic screening most important during times of cholesterol increase (middle-aged men, perimenopausal women, weight gain).

Secondary Prevention

Recommended approach

Screening with a lipoprotein analysis is recommended for any patient with a prior event.

Table 2.3 NCEP Adult Treatment Panel III Cholesterol Screening Guidelines (http://www.nhlbi.nih.gov/guidelines/cholesterol/)

Step 1: Determine lipoprotein levels (LDL, total and HDL cholesterol) obtained after 9-12 hour fast

Optimal LDL = < 100; near optimal = 100 – 129

Step 2: Identify whether CHD or CHD-equivalent* is present

* peripheral artery disease, abdominal aortic aneurysm

Step 3: Identify whether other CHD risk factors are present

- smoking
- BP ≥ 140/90 or on BP meds
- HDL < 40
- Family history of premature CHD (CHD in male first degree relative < 55 years; CHD in female first degree relative < 65 years)
- Age (men ≥ 45 years; women ≥ 55 years)

Step 4: If 2+ risk factors (other than LDL ≥ 130), assess 10-year CHD risk (Web site refers reader to Framingham tables; most people with 0-1 risk factors have 10-year risk < 10%)

Step 5: Determine risk category to establish goals of therapy (see **Table 2.4**)

Step 6: Initiate lifestyle changes

Step 7: Consider adding drug therapy if LDL remains above goal

Step 8: (After 3 mos. of lifestyle changes)

Identify metabolic syndrome (defined by 3 or more of elevated waist circumference; elevated triglycerides; low HDL; BP ≥ 130 / ≥ 85; fasting glucose ≥ 110).

Step 9: Treat elevated triglycerides (≥ 150) through intensified weight management and increased physical activity

Table 2.4 LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories (http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm/)

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor**	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

** Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

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