CORONARY HEART DISEASE IN WOMEN:

NATURAL HISTORY

AND

SIGNIFICANCE OF LIPIDS AS RISK FACTORS

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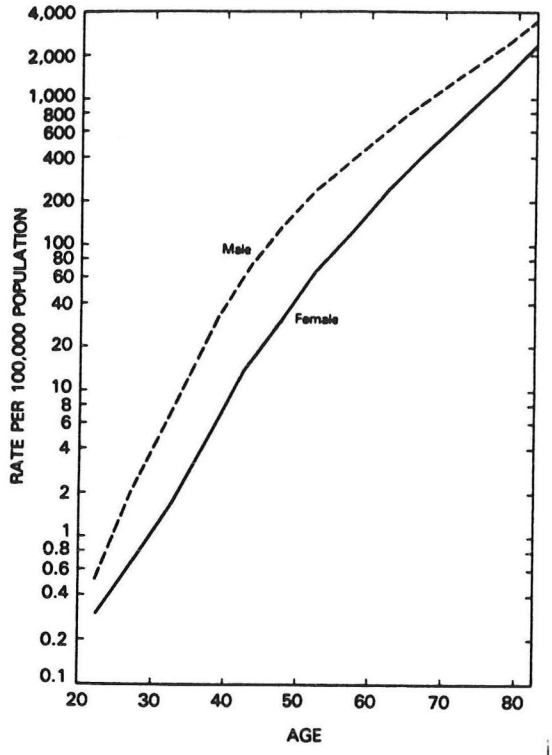
Coronary heart disease (CHD) is the number one cause of death and disability in westernized countries. Although CHD has been popularized as a cause of premature death in young men, CHD more commonly affects elderly men, and even "old women".[1] Confusion concerning the importance of CHD in women has been generated by incidence statistics that suggest that CHD is 1.5 times more common in men as women. This is amply illustrated in Figure 1 data taken from the U.S. Bureau of the Census.



Death rates associated with coronary heart disease among men and women, according to age: United States, 1983. From the National Center for Health Statistics: Vital Statistics of the United States.

This male:female ratio of 1.5 is consistent with cross-cultural autopsy findings documenting fewer coronary artery atherosclerotic plaques in women than men.[2]

Table I. Percent of Intimal Surface of Coronary Arteries With Raised Atherosclerotic Lesions, Subjects 25 to 64 Years of Age

Study Location	Mean % of Intimal Surface With Raised Lesions		
	Men	Women	M/F Ratio
White			
New Orleans	22.3	10.0	2.23
Oslo	20.2	13.8	1.46
São Paulo	11.1	7.0	1.59
Puerto Rico	9.7	7.3	1.33
Santiago	9.3	5.0	1.86
Costa Rica	8.2	5.3	1.55
Black			
New Orleans	14.3	13.6	1.05
Jamaica	9.1	8.2	1.11
Puerto Rico	8.4	5.2	1.62
São Paulo	6.0	6.9	0.87
Durban	5.7	5.1	1.12

M = male; F = female.

These lower incidence rates of CHD in women raise the question whether CHD is a significant cause of morbidity and mortality among women. Incidence statistics by age may not accurately represent the importance of CHD among the female population. Although the absolute rate of CHD among women is less than that of men of the same age, the number of deaths due to CHD are similar because more old women are alive than old men. CHD is by far the number one cause of death among women. CHD as a cause of death is five times more common than the second most common cause of death among women, breast cancer, and two to three times as common as death from all cancers.

TABLE 2

DEATHS FROM ISCHEMIC HEART DISEASE
U.S. BUREAU OF THE CENSUS
NATIONAL CENTER FOR HEALTH STATISTICS
1988

AGE	MEN		WOMEN	
	NUMBER OF DEATHS	% OF TOTAL	NUMBER OF DEATHS	% OF TOTAL
THRU 34	1,023	0.39	322	0.13
35-39	1,789	0.68	397	0.16
40-44	3,719	1.41	888	0.36
45-49	6,246	2.36	1,630	0.67
50-54	9,561	3.61	2,943	1.20
55-59	15,986	6.04	5,860	2.39
60-64	25,310	9.57	11,111	4.53
65-69	34,814	13.16	18,203	7.43
70-74	41,203	15.58	26,893	10.97
75-79	43,514	16.45	37,684	15.38
80-84	38,112	14.41	46,227	18.86
85-89	25,463	9.63	44,755	18.26
90-94	12,943	4.89	31,955	13.04
95-99	4,089	1.55	13,327	5.44
99+	704	0.27	2,870	1.17
NO AGE	30	0.01	22	0.01
TOTALS	264,506	100.00	245,087	100.00

TABLE 3

FEMALE
DEATHS FROM BREAST CANCER
U.S. BUREAU OF THE CENSUS
NATIONAL CENTER FOR HEALTH STATISTICS
1988

AGE	NUMBER OF DEATHS	% OF TOTAL
35-39	1,259	2.97
40-44	1,879	4.43
45-49	2,473	5.82
50-54	3,146	7.41
55-59	4,172	9.83
60-64	5,270	12.41
65-69	5,512	12.98
70-74	5,379	12.67
75-79	4,668	10.99
80-84	3,829	9.02
85-89	2,344	5.52
ALL OTHERS	2,530	5.96
TOTALS	42,461	100.00

Another way to express gender differences in the rate of a disease that increases in its prevalence with age is to state the age of onset for a given rate of disease. Carefully executed prospective studies such as the Framingham Study mirror the U.S. Bureau of the Census incidence statistics in that CHD rates in men are 1.5 times as common as in women.[3] Suggested by authors of the Framingham analysis is that men at age 60 have the same incidence of CHD as women

age 75, i.e. that CHD in women lags behind that in men by 15 years. Since women at age 75 are "old women", it has been argued that CHD deaths in women are a natural consequence of the aging process, rather than a consequence of modifiable factors.

The predominant effect of aging on CHD rates cannot be understated. Age has consistently been a strong risk factor for CHD independent of gender.[4 5 6 7 8 9 10] Fully 2/3 of the CHD deaths in women occur over age 75.

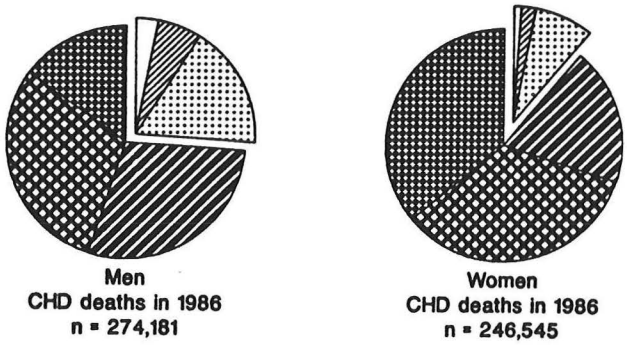


Figure 1. Deaths from ischemic heart disease in 1986 by age and sex (U.S. Bureau of the Census). Pie slices represent age groups: open = under 45 years of age; light stripes = 45 to 54; small closed circles = 55 to 64; heavy stripes = 65 to 74; crisscross = 75 to 84; and large closed circles = over 85. CHD = coronary heart disease.

Although one might conclude that CHD in women is only seen with advancing age, one might also speculate that even death at age 75 is premature. In addition, since CHD symptoms precede death, although age of death may not be alterable because of concurrent diseases of old age, the quality of life may be improved through a reduction, delay, or elimination of CHD symptoms.

It is important, then, to question whether women die of CHD because they are "old women", or whether women die of CHD because they have increased risk for CHD. If the later is the explanation, CHD in women, like CHD in men, could be an environmentally modifiable disease. Since CHD is the most common route of death, its cause is probably multi-factorial and therefore CHD itself might not be preventable. Its onset, however, might be delayed through risk factor intervention if the presence of risk factors promote the onset of CHD.

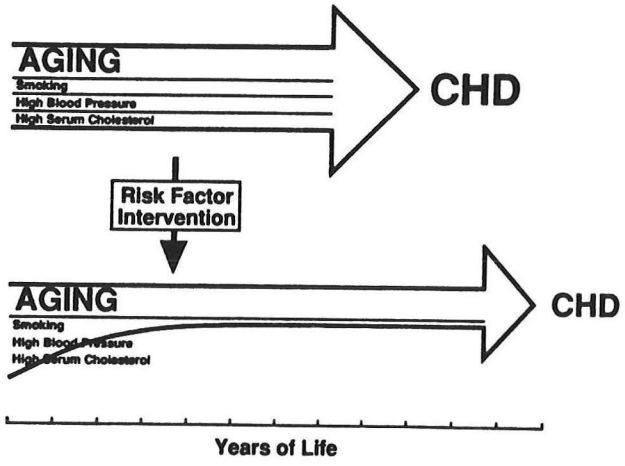


Figure 5. The effect of risk factor intervention on coronary heart disease (*CHD*). Aging is a potent risk factor leading to coronary heart disease, but development of coronary heart disease might be delayed through modification of risk factors.

Studies evaluating potential risk factors for CHD require a definition of CHD. This definition becomes central to our understanding of CHD in women. The definition of CHD could be based on historical information; for example, a history of chest pain classic for angina by Rose criterion. Alternatively, the definition of CHD could be based on more objective criteria, such as CHD manifest by positive exercise tolerance test (ETT) or coronary arteriography. Lastly, the definition of CHD could be based on the occurrence of terminal events, such as documented myocardial infarction (MI) or death from CHD. The definition chosen for CHD in women should be based on our understanding of the natural history of CHD in women.

NATURAL HISTORY OF CHD IN WOMEN

CHD is due to a process of atherosclerotic narrowing of coronary arteries which requires decades to become clinically manifest. The classic end point of CHD is death due to coronary disease, as documented by autopsy or death certificate. A study of risk factors for CHD death in women would require either a large number of older subjects or an even larger number of younger subjects who can be studied for a long period of time (see Figure 2). Ways to enrich the number of end points is to add additional CHD events, such as MI, angiographic evidence of coronary vessel narrowing, or non-invasive evidence for CHD such as positive exercise testing, or symptoms of angina pectoris. The addition of more subjective endpoints increase the margin of error in estimating the true prevalence of CHD in women. An example of this is readily available when considering the inclusion of angina as a manifestation of CHD.

ANGINA AS A SYMPTOM OF CHD IN WOMEN

Although just as many women develop CHD during their lifetime as men, the classic symptoms of angina in women is not as sensitive and specific a predictor of CHD in women as it is in men. Several studies have evaluated the sensitivity and specificity of angina in women for predicting CHD. The largest series containing both men and women is data collected from the Coronary Artery Surgery Study (CASS).[11] CASS provided data on 8,157 patients who underwent coronary arteriography for evaluation of chest pain. The chest pain was classified into 3 categories; definite angina, probable angina, and non-specific chest pain. The prevalence of documented coronary artery stenosis (>70% of a single vessel or >50% left main) for each of the chest pain categories for both men and women in listed in Table 4.

TABLE 4

PERCENT OF MEN AND WOMEN WITH THREE CATEGORIES OF CHEST PAIN WHO HAD CORONARY ARTERY STENOSIS ON CARDIAL CATH

	DEFINITE ANGINA	PROBABLE ANGINA	NON-SPECIFIC CHEST PAIN
MEN	93% (n = 1,919)	66% (n = 2,146)	14% (n = 1,282)
WOMEN	72% (n = 401)	36% (n=1012)	6% (n = 1397)

While 93% of men who had definite angina by history had documented coronary disease by angiography, only 72% of women with definite angina had angiographically proven coronary disease. This reduced specificity of angina to predict the prevalence of coronary disease in women was attributed to the lower prevalence rate, as expressed in Figure 1.

Because cardiac catheterization is an invasive procedure, the hope would be that non-invasive testing such as ETT would reduce the number of diagnostic catheterizations by improving sufficiently the ability to predict which patients with angina have CHD by angiography. Unfortunately, ETT by standard protocols adds little predictive information to discriminate between women with and without CHD. The ineffectiveness of ETT as a predictor of CHD in women is aptly illustrated by two studies.

In the first study[12], patients with typical angina pectoris were evaluated by standard ETT and coronary angiography. While 94% of the men with a positive ETT had at least a 50% stenosis of one vessel on coronary angiography, only 62% of females with similar presenting complaints and ETT had significant stenosis. Again, these results were ascribed to lower prevalence rates of CHD in women.

TABLE 5

ABILITY OF ETT TO PREDICT CHD AS DOCUMENTED BY CORONARY ANGIOGRAPHY

	FALSE POSITIVE	FALSE NEGATIVE
MEN	7%	40%
WOMEN	38%	19%

In a second study[13] subjects with similar incidences of CHD, underwent both ETT and coronary angiography. ETT by standard criteria of ST segment depression was no more effective than a coin toss in predicting CHD in women (Table 6). This

study suggested that, for some reason, ST segment changes on exercise in women were not as predictive of CHD as they were in men. Therefore, the inability to predict CHD in women may be due not only to lower prevalence rates of CHD in women, but also to the lack of specific and effective non-invasive screening tests.

TABLE 6

	MEN			WOMEN	
	+ ETT	- ETT		+ ETT	- ETT
+ ANGIO	77%	19%	+ ANGIO	47%	22%
- ANGIO	23%	81%	- ANGIO	53%	78%
ETT SENSITIVITY FOR MEN		$\frac{77}{77 + 19} = 80\%$	ETT SENSITIVITY FOR WOMEN		$\frac{47}{47 + 42} = 68\%$
ETT SPECIFITY FOR MEN		$\frac{81}{81 + 23} = 78\%$	ETT SPECIFITY FOR WOMEN		$\frac{78}{78 + 53} = 59\%$

Complicating the lower specificity of non-invasive testing of CHD in women is the that fact that angina as a historical symptom of CHD is not specific for CHD and is quite common in women. The incidence of angina in the Framingham Study does not parallel the 15 year lag in CHD death rates. In fact, women at age 60 have equal prevalence of angina as men age 60.[10] (Figure 4)

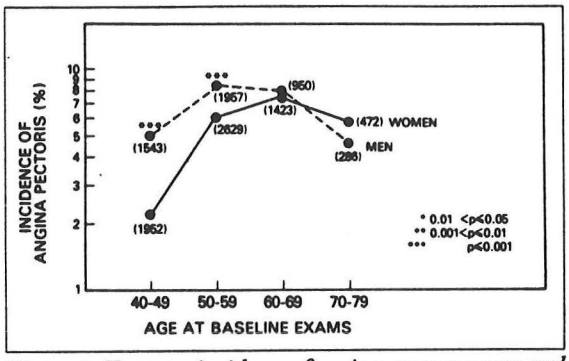


Figure 3. Ten-year incidence of angina among women and men by age, Framingham Heart Study.

From the Framingham Study, over a five year period one in eight women with classic symptoms of angina have a CHD event as compared to one in five men. Because the progession from anginal symptoms to other manifestations of CHD in women does not follow the same pattern as in men, and because angina has lower specificity rates for identifying women with CHD, angina may be an inferior marker of CHD. Why angina is more common in middle aged women is unclear. A naive interpretation of this statistic is that CHD is a more benign condition in women than men. However, alternative explanations exist.

The most popular explanation of the reduced specificity of angina predicting CHD in women is Bayes Theorem, i.e., that the ability of angina to predict CHD is limited by the lower prevalence rates of CHD.[14] In support of this hypothesis, the specificity of angina as a predictor of angiographic proven CHD increases with advancing age. From the CASS data[11], while only 64% of women younger than 40 who had classic symptoms of angina had CHD documented by angiography, 96% of women age 70 or older with these symptoms had angiographic evidence of CHD.

Another hypothesis is that women may be more aware of their bodies than men, and women experience and report angina earlier than men. This hypothesis would suggest that women have angina for a longer period of time before MI or CHD death. This hypothesis does not suggest that CHD is more "benign" in women, it simply suggests that it can be diagnosed earlier. This hypothesis, however, would only be supported if angiographic studies showed some atherosclerotic disease in women with angina. The presence of angina would then require an additional event such as endothelial dysfunction and coronary spasm. This scenario could be consistent with the diagnosis of "nonobstructive" coronary disease.

Yet a third hypothesis is that women have greater likelihood of having other diseases that cause a chest pain syndrome consistent with angina[15] (Table 7).

TABLE 7

DIFFERENTIAL DIAGNOSIS OF ANGINA IN WOMEN

Coronary Artery Disease

Coronary Vasospasm

Mitral Valve Prolapse

Chest Wall Disease

Esophageal Spasm

Esophageal Reflux

Hiatal Hernia

These diseases include mitral valve prolapse, coronary artery spasm, angina like symptoms from GI or chest wall sources. Since other chest pain disorders do not lead to myocardial infarction or sudden death, this would explain the Framingham findings that fewer women with angina have an MI. Following this argument, the rate of "progression" of CHD, as manifest by the time delay from the onset of angina to an MI could be expected to have a sex difference, since not all angina reflects CHD.

Since we do not know the reason why middle aged women have similar rates of angina but lower rates of CHD than men, another way to evaluate the time course of the CHD process in men and women is to compare death rates in individuals with documented CHD. Such analyses would compare the average time to death for men and women who have had a recent MI, for example, or had angiographically proven CHD.[16] On 20 year follow-up of the Framingham Study participants who had an MI, 38% of men died from CHD, while 54% of women died from CHD.[17] By the 30 year

follow-up, men and women post MI had similar mortality rates.[18] The difficulty of generalizing these data as evidence for similar progression rates of CHD is that they may reflect different pathophysiological events. Angina, disregarding causes other than coronary disease, may reflect plaque size, and/or endothelial dysfunction, while myocardial infarction and death may reflect platelet or thrombotic events. Nevertheless, CHD in women is not a benign condition, and should be a diagnosis entertained in women with angina who are older, and have other risk factors for CHD.

Although nonspecific for CHD, angina was the most common presentation for Framingham women with CHD under age 60, with 56% of women presenting with angina, 35% with a myocardial infarction, and only 9% presenting with sudden death. Among men similarly studied, 30% presented with angina, 54% with myocardial infarction, and 16% with sudden death. In other words, the clinical appearance of angina, although not specific, is an important clue in the development of CHD. The appearance of angina as a symptom may aid in early detection of CHD in women.

Despite the difficulty in diagnosing CHD short of coronary angiography in women, CHD is the overwhelming cause of death among women. CHD is of major importance when considering the health care of women. If physicians could be successful at reducing CHD, the health impact on women, and particularly older women, would be enormous. The traditional approach towards these issues is to identify risk factors that would be useful in predicting those women who would be most affected by CHD.

RISK FACTORS FOR CHD IN WOMEN.

The concept of risk factors and their ability to predict and modify disease has revolutionized our approach to CHD in men. Although risk factor analysis was designed as a population based approach to the CHD problem, this approach has been adopted by physicians as a means of identifying individuals appropriate for early and aggressive management. For example, reducing serum cholesterol levels, a strong risk factor for CHD in men, reduces rates of CHD manifestation[19 20] as well as progression of existing disease.[21 22 23 24]

A total of eight prospective trials have included women in their analysis (Table 8) and these studies form the base of our understanding about the similarities and differences in risk factors by gender for CHD. The significant risk factors for CHD in women by study are listed in Table 9.[25] In general, the same risk factors that predict CHD in men predict CHD in women.

TABLE 8

STUDY	WOMEN n	YR STUDY BEGAN	AGE AT ENTRY	EVENT OUT COME	TYPE OF DATA
Federal Women	4,727	1978	30-69	All cause mortality	Federal Records & Death Records
Tecumseh	2,203	1959	25-74	CHD	Comprehensive Examinations
Charleston County	1,192	1960	35 +	CHD mortality	Comprehensive Examinations
Alameda County	2,052	1965	40 +	CHD mortality	Questionnaire
LRC	2,270	1972	40-69	CVD mortality	Comprehensive Evaluation
Nurses Study	121,345	1976	30-55	CHD	Questionnaire Incidence Cause Medical Records Review
Rancho Bernardo	2,048	1972	50-79	CHD mortality	Comprehensive evaluation
Framingham	2,700	1949	40-79	CHD	Comprehensive evaluation

Risk Variable	Federal Women	Tecumseh	Charleston County	Alameda County	LRC	Nurses' Study	Rancho Bernardo	Framingham
Age	X	X	X	X	X	X	X	X
Hemodynamic								
SBP		X	X	X	X	X	X	X
DBP		X			X	X	X	X
Cholesterol (total)		X	X		X	X	X	X
LDL					X			X
HDL					X			X
Triglycerides					X		X	X
Body mass index		X	X	X	X		X	X
Uric acid		X						
FEV/ht²		X						
FVC/ht²		X						
LV hypertrophy		X						X
Heart rate		X						
History								
Diabetes		X	X	X		X	X	X
Chest pain and heart trouble†				X				
Previous MI					X		X	
Cigarette smoking		X	X	X	X		X	X
Alcohol		X		X	X			X
Physical activity				X	X			X
Family history of CHD		X					X	
Sleeping pattern				X				
Antihypertensive medication								X
Demographic								
Marital status		X		X			X	X
Isolation				X				
Group membership				X				
Life satisfaction				X				
Type A behavior								X
Education			X		X			X
Employment status		X						X
Occupation	X							X
Income	X			X				
Hormonal								
Oral contraceptives						X		
Noncontraceptive hormones					X	X	X	X
Menopause					X			
Hysterectomy status					X			

* The symbol X indicates studies in which a particular risk variable was examined.
† Based on self-report.
LRC = Lipid Research Clinics; SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL = low-density-lipoprotein; HDL = high-density-lipoprotein; FEV = forced expiratory volume; FVC = forced vital capacity; LV = left ventricular; MI =

SIGNIFICANT RISK FACTORS FOR OLDER WOMEN FROM PROSPECTIVE TRIALS

STUDY	SIGNIFICANT PREDICTORS
FEDERAL WOMEN	Age
TECUMSEH	Age Cigarette Smoking Systolic Blood Pressure Family Hist. Mother Death by CHD >65
CHARLESTON COUNTY	Age Systolic Blood Pressure Cholestserol Diabetes Smoking
ALAMEDA COUNTY	Age Systolic Blood Pressure History of Angina Diabetes Physical Inactivity Group Non-membership Smoking
LRC	Age Estrogen Use Systolic Blood Presure Diastolic Blood Pressure Triglycerides HDL Cholesterol Smoking
NURSES STUDY	Cigarette Smoking Early Menopause Hypertension Hypercholesterolemia Diabetes History Parental MI age 50-60 Post-menopausal hormone use
RANCH BERNARDO	Age Diabetes Personal History CHD Younger = Diastolic Blood Pressure Hypercholesterolemia Obesity Older = Hypercholesterolemia
FRAMINGHAM	Age Blood Pressure Relative Weight Serum Cholesterol LDL HDL Triglycerides

In addition to similar risk factors for both men and women, the Framingham Study suggests that the CHD risk factors are of similar magnitude.[26]

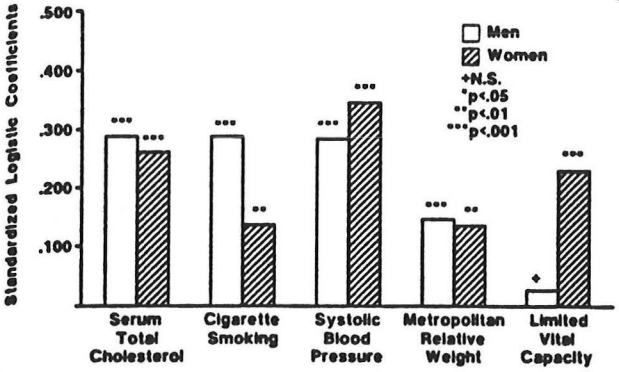
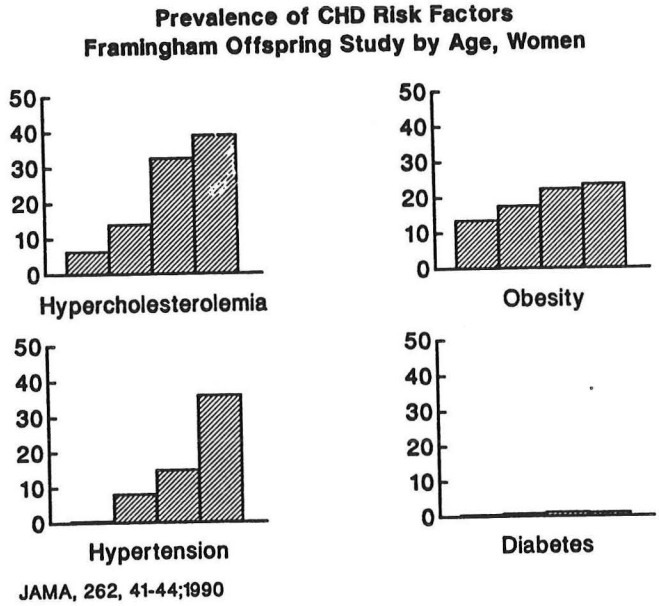


FIGURE 1. The relative importance of selected risk factors for CHD in the Framingham Study 30 year follow-up of men and women 35 to 64

IS IT AGE OR AN INCREASE IN RISK FACTORS WITH AGE THAT CAUSES CHD?

A mistaken impression concerning the importance of risk factors is that risk factors are a static variable that once determined do not change with time. An obvious example of this is cigarette smoking, which is under the voluntary control of the individual. Cigarette smoking can stop, start, increase or decrease in intensity, and these changes appear to alter the strength of CHD prediction.[27] For example, several studies state that a previous history of smoking does not increase the likelihood of CHD events, but a history of current cigarette smoking, no matter how little, dramatically increases risk.[28,29]

Less commonly thought of as dynamic are risk factors that are not as subject to voluntary control, i.e. blood pressure and cholesterol levels. Although diet may alter blood pressure and serum lipids to some extent, these risk factors are also strongly influenced by age and genetics. The effect of genetics is an understandable focus in today's molecular society, but the effects of age has received less attention. Age is a powerful affector of the two major risk factors for CHD, cholesterol and blood pressure. This is most aptly illustrated in a recent report from the Framingham off-spring study which shows that the prevalence of hypertension in women increases from 0.5% (ages 30-39) to 36% (age 60-69) and hypercholesterolemia increases over a similar age period from 6% to 39%.[30]



Whether these dramatic increases in prevalence of risk factors with age explain the reason why age is such a powerful and consistent predictor of CHD cannot be assessed. Certainly it makes sense that the aging artery might be more susceptible to disease.[31] It would, however, not be inconceivable that part of the predictive power of aging is due to the rise in risk factors with age. Epidemiologic studies typically determine risk factor status at time A and disease incidence at some distant time B. Since risk factors may change from time A to time B, part of the strength of "age" as a risk factor could be the effects of increasing risk factors with age. Age remains an overwhelming CHD predictor that is gender independent.

LIPIDS AS A RISK FACTOR:

Six studies have evaluated lipids as a risk factor for coronary heart disease in women. These studies are the Tecumseh Community Health Study,[5] the Charleston Heart Study,[6] the Lipid Research Clinic's Follow-up Study,[8] the Nurses' Health Study,[32] the Rancho Bernardo Study,[9] and the Framingham Study.[10] While each study has different characteristics that make it unique (see Table 8), and while some studies rely on reported cholesterol levels rather than those measured for the study, the overwhelming evidence is that the lipids predict coronary disease in women. The specific findings for each study are reviewed below and summarized in Table 10.

1. TECUMSEH COMMUNITY HEALTH STUDY, 1959-1980.

   White women, age 25 or more (n = 2,708) were free of CHD at the initial examination. CHD endpoints were angina, EKG changes, history of MI, and death due to CHD. There was a direct association between serum cholesterol levels and risk for CHD.

2. CHARLESTON HEART STUDY, 1960-1985

   Women, age 35 or more (n = 1,196) were evaluated for study. 1.9% had on initial examination a history of angina pectoris. Endpoints were CHD mortality. Serum cholesterol levels were a significant predictor of all cause mortality, but only in black women (n = 454) was serum cholesterol a significant predictor of CHD death.

3. LIPID RESEARCH CLINICS FOLLOW-UP STUDY,1972-1986

   White women, age 40 to 69 (n = 2,270) were evaluated, and in this study both total serum cholesterol and lipoprotein levels were determined. Endpoints were cardiovascular disease mortality. On univariate analyses, total cholesterol and LDL cholesterol were not associated with CHD mortality, but triglycerides and HDL cholesterol were. On multivariate analyses, HDL cholesterol level remained a significant predictor of CHD mortality, but triglycerides did not. When HDL cholesterol was included in the multivariate analysis, the effect of estrogen replacement therapy on CHD mortality was diminished by 50%, suggesting that a good proportion of the effects of estrogen therapy on CHD mortality was mediated by the effects of estrogen on HDL cholesterol levels.

TABLE 10

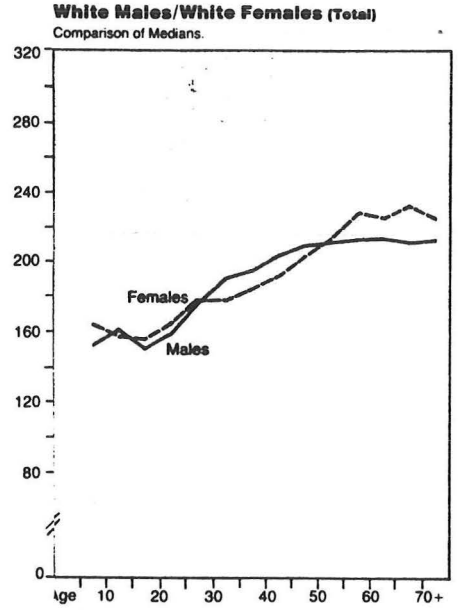
LIPIDS AS A PREDICTOR OF CHD
PROSPECTIVE TRIALS

STUDY	FINDINGS
LIPIDS REPORTED:	
NURSES HEALTH STUDY	Self-reported elevations in total cholesterol was associated with significant 2-fold increase in relative risk.
LIPIDS MEASURED:	
TECUMSEH (Chol)	High cholesterol levels are predictive of CHD on univariate analysis, but not on multivariate analysis except for women age group 50-64 years.
CHARLESTON COUNTY (Chol)	Cholesterol was a predictor of all cause mortality in black and white women, and a predictor of CHD mortality in black women.
RANCHO BERNARDO (Chol, TG)	Cholesterol was a significant predictor of CHD death in women age 65-79 and 50-79 but not 50-64. Triglycerides were a significant predictor of CHD death in women age 50-64 but not older ages. Cholesterol, but not triglycerides, was significant contributor to Relative Risk (Cox Model)
LIPIDS AND LIPOPROTEINS MEASURED:	
LIPID RESEARCH CLINIC FOLLOW UP STUDY	Cholesterol and LDL are not significant predictors of CHD death. TG is on univariate analysis only. HDL is predictor on both univariate and multivariate. The strength of estrogen as a predictor of risk is diminished when LDL and HDL are considered in the analysis.
FRAMINGHAM HEART STUDY	Total cholesterol is predictive of CHD risk in age 40-49 and 50-59. Triglycerides are predictive in age 60-69. LDL, HDL is predictive age 50-59 and 60-69 but not 70-79. On multivariate analysis, total cholesterol predictive of 10 year risk in age 40-49.

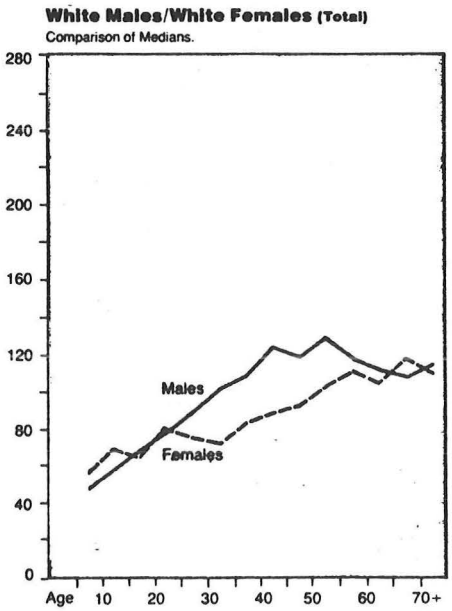
LIPIDS AS A RISK FACTOR - DYNAMIC WITH AGE

The increase in lipids with age have been described in several cross-sectional studies, the most carefully done from a lipid standpoint is the Lipid Research Clinics Prevalence Study (LRCPS).[33]

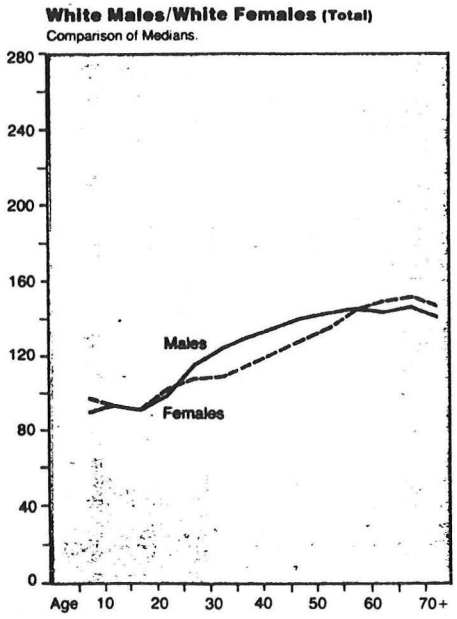
TOTAL CHOLESTEROL: From LRCPS, total cholesterol levels rise 30-50 mg/dl with age. This rise with age appears to be enhanced with the rise of body weight with age. This, however, is clearly not the only factor since a cross-sectional analysis of lean men and women cross country skiers still shows a rise in cholesterol levels with age.[34] In men, the rise of cholesterol with age is most prominent between age 20 and 50, thereafter being stable for the remainder of life. In women, the rise of cholesterol with age is less steep between age 20 and 50, with abrupt and continuous rise after the menopause and continued rise throughout the remainder of a woman's life span.



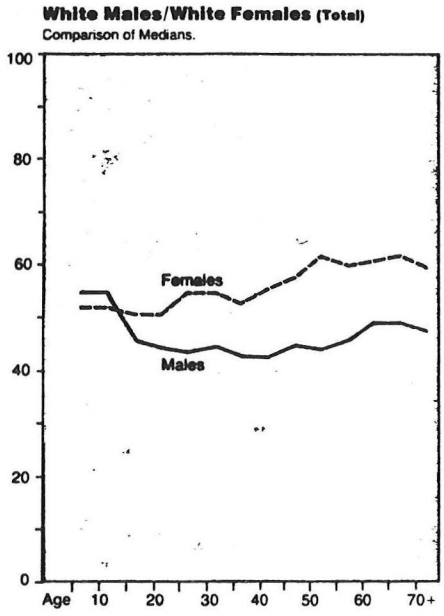
TRIGLYCERIDES: According to LRCPS, triglyceride levels also rise with age approximately 60 mg/dl. It is unclear how much of this rise is a result of aging itself, or a result of the increase in body mass with age.[35]



LDL CHOLESTEROL: The rise of LDL cholesterol with age parallels that of total cholesterol. This rise is not explained by dietary habits. Only part of this rise can be explained by increasing body weight.[36]



HDL CHOLESTEROL: The most striking sex difference in lipoprotein levels is the difference in HDL cholesterol. The sex difference in HDL cholesterol levels begins at the time of puberty. Before puberty, boys and girls have similar HDL cholesterol levels. At the time of puberty, boys' HDL cholesterol levels fall 10-15 mg/dl and remain relatively constant throughout age span. There appears to be a gradual rise of HDL cholesterol levels in women with age.



LIPOPROTEINS AS THE CAUSE OF GENDER DIFFERENCES IN CHD RATES

Why women, at any age, have lower prevalence rates of CHD remains a mystery. One popular adage is that there is some "female protective advantage" that prevents CHD in women. A likely candidate for this factor is estrogens. In fact, this hypothesis was so attractive that the Coronary Drug Project administered conjugated estrogens 2.5 mg/day or 5.0 mg/day to men with documented coronary disease to see if CHD rates could be reduced.[37] The trial ended abruptly after estrogen therapy in men was shown to paradoxically increase morbidity and mortality. The increases in morbidity were related to thrombotic events. Many subsequent studies have evaluated sex hormone levels in men and women and have tried to relate hormone levels with CHD risk. A clear relationship has not been found.[38] [39] In fact, although high estradiol levels in women may protect against CHD, men with high levels of estradiol have increased risk for CHD.[40] This may be because high levels of estrodiol in men reflect either the untoward effects of obesity at increasing peripheral conversion of adrenal androgens to estradiol[41] or an untoward effect of cigarette smoking.[42]

Since lipoprotein levels are different between men and women, emphasis on gender differences in CHD rates has shifted towards lipoproteins.[43] As discussed above, women have lower rates of CHD than men at a time when they have lower LDL cholesterol levels. In addition, HDL cholesterol levels are higher in women and have consistently been shown in multiple studies to be a strong inverse predictor of CHD risk.[44] It would follow then, that having lower LDL and higher HDL levels, women would naturally have lower CHD rates.

These sex specific differences in lipoprotein levels are not present in all cultures.[43] For example, in countries with low rates of coronary disease, there is little gender difference in HDL levels, that is, women have lower HDL levels. The cause of lower HDL levels in low CHD incidence societies is not firmly established, but is felt to be dietary or cultural in origin since studies of migrating populations show typical gender associated differences in HDL. The dietary cause of lower HDL levels in women appears to be multifactorial and may be related to three dietary components: 1) a low fat, low saturated fat diet (low dietary fat intakes are associated with lower HDL levels)[45], 2) a high fiber diet (high fiber diets lower circulating estrogen levels by interrupting biliary estrogen reabsorption; lower estrogen levels may lead to lower HDL levels)[46] and 3) caloric intake (hypocaloric diets in both men and women lowers HDL levels;[47] little data, however, is available on the chronic effect of such dietary habits). Despite this diet x culture x gender effect on lipoprotein levels, the hypothesis that lipoproteins play a key role in CHD incidence remains intact.

Low HDL levels in women from low incidence CHD countries add further weight to the concept of evaluating lipoprotein levels not just by absolute levels but by evaluating ratios of LDL/HDL or total cholesterol/HDL. One might say that HDL measurements in industrialized countries is a "stress test" for lipoprotein metabolism. A healthy metabolism would be a high HDL with slightly higher LDL level on a high saturated fat diet or a low HDL in combination with an even lower LDL level on a low fat diet. A faulty metabolism would manifest as low HDL levels in the setting of high diet-induced LDL levels.

Gender differences in CHD are consistent with gender differences in lipoprotein

levels. However, it is doubtful that differences in lipoprotein levels alone explain why women have lower rates of CHD than men. Further work on the gender differences of lipoproteins and their metabolic fate is needed. In addition, gender differences in other areas of atherosclerotic plaque pathophysiology such as plaque development, clotting, etc. need investigation.

A CLINICAL APPROACH TO EVALUATING POSTMENOPAUSAL WOMEN AT RISK FOR CHD

Postmenopausal women represent the largest category of women who are at risk for CHD. The risk for CHD is not only due to the rise in lipid risk factors with age, but also because of the rise of other risk factors, most notably hypertension and diabetes with age. Therefore, the initial assessment of a postmenopausal woman in determining her risk for CHD is careful history and physical examination aimed at identifying all potential risk factors. The history should include questions concerning chest pain and exercise intolerance, smoking habits,and exercise habits. Often overlooked but an important risk factor is a family history of CHD and age of onset. A 24 hour dietary recall of dietary intake is useful.

The National Cholesterol Education Program (NCEP) guidelines[48] suggest that physicians should be more aggressive with cholesterol reduction in people with two or more risk factors for CHD. Male sex is a risk factor, and we have previously proposed that the postmenopausal state should also be a risk factor.[49] An additional risk factor that needs modification from the NCEP guidelines is age of premature death from coronary disease; for female family members, the definition of premature should be changed from age 55 to age 65[5].

Lastly and importantly for determining risk for CHD in women is the presence of diabetes. The presence of diabetes results in a two-fold increase in risk even after adjustment for age and other risk factors.[50] [51] [52] Not expressed in this statistic is that women with diabetes loose their "female protective advantage" against CHD and develop CHD at rates similar to men. In some studies diabetic women have higher CHD death rates than diabetic men.[53] Since diabetes is more common in women, diabetes is an important contributor to premature CHD deaths in women. Why diabetes in women leads to accelerated atherosclerosis is still unclear. Some researchers feel that, similar to the sex differences in lipoprotein levels and CHD incidence, the reason why diabetics have advanced CHD is in part due to changes in lipoprotein levels in diabetics that may be manifest even before the diagnosis of diabetes is made.[54] Diabetic women experience a greater increase in triglycerides, increase in LDL and decrease in HDL, despite similar glucose control when compared with diabetic men.[55] However, not all investigators agree that differences in lipoprotein levels explain entirely differences in CHD rates.[56]

As amply illustrated in the National Cholesterol Education Committee Guidelines, there is significant day to day variation in blood lipids.[48] The initial assessment, therefore, of an elderly woman should not be a single measurement of cholesterol and fasting triglycerides, but the average of 2-3 measurements.

DIETARY THERAPY

The first step in a cholesterol reduction program would be to maximize dietary therapy. The primary nutrient in the diet that raises serum cholesterol and LDL cholesterol levels is saturated fatty acids.[57] Saturated fatty acids are found mainly in animal fat, dairy fat, and hidden fats in products such as baked goods. Emphasis should probably be on saturated fat reduction rather than total fat.[58] A brief, 24 hour dietary recall as well as a questionnaire screening for high saturated fat foods would be useful in evaluating a patient in a physicians office. There is evidence that if the physician makes dietary suggestions, the patient is more likely to follow these suggestions than if they come from non-physician personnel.[59]

The second major dietary nutrient that raises total and LDL cholesterol levels is dietary cholesterol. Sources of dietary cholesterol include egg yolks and organ meats, as well as any animal product. This is a relatively simple change to make, which most patients have already made before their visit to the doctor's office.

The last major area in dietary modification for high cholesterol levels is total calories and body weight. Cross-sectional studies demonstrate that excess body weight raises total cholesterol and LDL cholesterol levels in women and in men.[60] The effects of body weight on raising total and LDL levels is seen most dramatically in young men, but is also present in older women. In addition to total cholesterol and LDL effects, excess body weight lowers HDL cholesterol levels.[61] The effects of body weight on HDL levels are seen in both sexes, and at all ages. Since HDL cholesterol levels is a significant independent predictor of CHD on both multivariate and univariate analysis, the clinical significance of excess body weight in producing low HDL levels should not be underestimated. In addition, there is evidence that peri-menopausal women are particularly susceptible to gaining weight during menopause which further compounds this problem.[62]

DRUG THERAPY

Unfortunately, since most of the rise of cholesterol with age is probably not dietary or weight induced, it appears likely that dietary therapy alone will be insufficient for reducing the hyperlipidemia of postmenopausal womanhood. Since the postmenopausal woman is older, more susceptible to drug-induced side effects, and in addition, probably has fewer financial resources, some have questioned the advisability of prescribing drug therapy.[63] [64] Primary prevention trials in younger men suggest that a minimum of 5-8 years of lipid lowering therapy is required before a significant reduction in CHD events can be achieved.[19] [20] Certainly all physicians can recall anectotal cases where lipid-lowering therapy is probably not in the patient's best interest. Examples would include patients with other diseases whose time course would cause a terminal event before any hope of achieving the necessary 5-8 year period needed to achieve benefit from lipid lowering therapy. For example, the presence of cancer, debilitating arthritis, dementia, and other chronic diseases would make it unlikely that the patient could have an improved quality of life in the future from an expensive lipid lowering program in present time.

Other physicians hesitate because of the adage that we should avoid drug therapy

in the elderly because of increased toxcity. Drug toxicity increases with increasing dose and polypharmacy.[65] Drug dosage should be as low as possible to achieve the desired effect. Patients who require multiple drug therapy for their other diseases may not achieve benefit from lipid lowering therapy because of the liklihood of morbidity or mortality from these diseases. As above, these patients are not good candidates because either they may not live long enough, or because they may not be capable of experiencing the improvement in quality of life that lipid lowering therapy may offer to healthier patients.

After an adequate of trial of dietary therapy, the next approach is hormonal replacement therapy (HRT). HRT has salutary effect on serum lipids, with lowering of total cholesterol and LDL cholesterol, as well as a slight increaase in HDL.[66] HRT may have other advantages besides lipid lowering, including aiding osteoporosis,[67] vaginal lubrication, symptoms of hot flashes, and urinary incontinence. Epidemiologic evidence also suggests that HRT may half the risk of CHD.[68] The lowering of LDL cholesterol levels appears to be non-linear, and on the current suggested replacement dose of 0.625 mg conjugated estrogens a day, a significant LDL reduction of 10 - 60 mg/dl is typically seen.[69] However, if the estrogen dose is increased, significant rises in serum triglyceride levels will occur without additional lowering of LDL levels.[70] It is therefore important to ensure that the dosing of estrogen therapy is kept at a standard replacement dose, since higher dosages will not lead to further improvement in blood lipid patterns. Estrogen replacement therapy is contra-indicated in women with hypertriglyceridemia.

Estrogen patch therapy, while effective in controlling symptoms of menopause, does not appear to be as effective in lowering serum lipids.[71] [72] The reduced lipid lowering effect is probably because estrogen absorbed cutaneously do not pass through the portal circulation, and hence do not undergo the "first pass effect" of the liver. If the CHD beneficial effect of HRT is due to its lipid lowering action, cutaneous estrogen replacement therapy, because its diminished effect on lipids, may not lower CHD rates. For this reason, it should be reserved for patients who have elevated triglyceride levels.

While daily estrogen replacement therapy as a single agent is appropriate for women who have undergone a hysterectomy, estrogen replacement therapy alone is contra-indicated in women with an intact uterus.[73] This is because of a two-fold increased risk of endometrial carcinoma in women with a uterus on unopposed estrogen replacement. For these women, two popular estrogen replacement therapy regimines are available: 1)cyclical replacement therapy (conjugated estrogens 0.625 mg. d 1-25 and medroxyprogesterone 10 mg. d 16-25) , and 2) continuous replacement therapy (conjugated estrogens 0.625 mg. + medroxyprogesterone 2.5 mg. QD). Both regimens include the use of medroxyprogesterone, a weak progestogen. The effects of medroxyprogesterone on serum lipids is dose-related. At the low doses suggested above, there appears to be only a small effect of raising LDL and lowering of HDL cholesterol levels.

Although estrogen replacement therapy is touted to raise HDL cholesterol levels, this may be a pharmacologic effect, and not a physiologic effect. That is, at standard replacement therapy doses, HRT only mildly increases HDL. At higher than standard dosage, an HDL raising effect is seen. As before, since these higher doses do not lead to a further lowering of LDL, there appears to be no

added benefit.

If estrogen replacement therapy does not achieve target LDL levels of less than 160 for women without risk factors, and less than 130 for women with risk factors, standard drug therapy for hyperlipidemia should be entertained. Lipid lowering therapy should considered the entire lipid profile, since triglycerides are also a strong risk factor for CHD in women.

1. Elevated total and LDL cholesterol levels with serum triglycerides under 200.

This is the easiest lipoprotein disorder to treat. If estrogen therapy alone is insufficient at lowering total and LDL cholesterol levels, or if the patient is not a candidate for estrogen therapy, a approach as listed in Table 11 could be followed. The appropriate drug regimen can be chosen based on its potency at lowering LDL cholesterol, and whether an additional HDL raising effect is desired.

TABLE 11

TREATMENT OF
TOTAL CHOLESTEROL >240
LDL >160
WITH TG <200

DRUG CLASS	DOSE	EFFICACY
Bile Acid Sequestrants	Colestipol - 10 gm/d Cholestyramine - 8 gm/d	20-40 mg/dl LDL lowering 1-5 mg/dl HDL raising
Nicotinic Acid	2-3 gm/d	20-40 mg/dl LDL lowering 5-10 mg/dl HDL raising
Fibric Acid Derivatives	Genfibrozil - 1200 mg/d Clofibrate - 2000 mg/d	10-20 mg/dl LDL lowering 1-5 mg/dl HDL raising
Low Dose HMG CoA Reductase Inhibitors	Lovastatin - 10 mg/d	20-40 mg/dl LDL lowering 1-5 mg/dl HDL raising

2. A. Elevated total and LDL cholesterol with serum triglycerides above 250 but less than 350.

This dyslipidemia has a variety of treatments available. Bile acid resins which are the drug of first choice in the NCEP guidelines are contra-indicated, because the agents will lead to further increases in triglycerides. The drugs of first choice are listed in table 12. While fibric acid derivatives are generally effective in lowering triglycerides, they are less powerful in lowering total and

LDL cholesterol levels. Perhaps 20% of people on fibric acid derivatives will achieve adequate LDL reduction. The drug of first choice is probably HMG Co A Reductase Inhibitors either in low dose or standard dose, depending upon the degree of dyslipidemia.

2. B. Elevated total and LDL cholesterol with triglycerides over 350.

This is perhaps the most difficult dyslipidemia to treat. Bile acid sequestrants are contra-indicated. HMG Co A Reductase Inhibitors, while effective in lowering cholesterol, typically does not lower triglycerides in the normal range. Fibric acid derivatives, or a combination of fibric acid derivatives and nicotinic acid are probably the drugs of first choice for treating this disorder. (See Table 12)

TABLE 12

TREATMENT OF
TOTAL CHOLESTEROL >240
LDL >160
WITH TG >250

DRUG CLASS	DOSE	EFFICACY
Fibric Acid Derivatives	Gemfibrozil - 1200 mg/d Clofibrate - 2000 mg/d	May increase LDL while reducing TG and raising HDL. Effective at reducing all levels of TG.
Low Dose HMG CoA Reductase Inhibitors	Lovastatin - 10 mg/d	Effective at reducing mild elevations in TG under 350 mg.; less effective at reducing higher levels. Effective at lowering LDL.
Nicotinic Acid	Niacin 2-3 gm/d	Effective at lowering Chol and TG simultaneously
Combination of Fibric Acid Derivatives and Nicotinic Acid	See Above	See Above

3. Normal total and LDL cholesterol levels with elevated triglycerides over 250.

Although not specifically addressed in the NCEP guidelines, serum triglyceride levels are significant predictor of CHD risk in women. The drug of first choice

would depend on the triglyceride elevation. For serum triglycerides under 350, either fibric acid derivatives, nicotinic acid, or HMG Co A reductase inhibitors are reasonable choices. For more profound elevations in serum triglycerides, fibric acids, nicotinic acid or a combination of fibric acid derivatives and nicotinic acid is indicated.

TABLE 13

TREATMENT OF
CHOLESTEROL <200
TG >250

DRUG CLASS	DOSE	EFFICACY
Nicotinic Acid	2-3 gm/d	Variable; TG lowering typically 200 mg/dl
Fibric Acid Derivatives	Genifibrozil - 1200 mg/d Clofibrate - 2000 mg/d	Variable; TG lowering typically 200 mg/dl
Combination of Nicotinic Acid and Fibric Acid Derivatives	See Above	See Above

CONCLUSION

For a given age, women have lower rates of CHD than men, however, since there are more old women than old men, the absolute number of women affected with CHD is similar to that of men.

Coronary heart disease in women is different from that in men. Angina appears more frequently and may be associated with non-CHD diseases. CHD is difficult to diagnose with noninvasive testing because of high false positive rates. The clinical course is gender dependent: women have angina longer before myocardial infarction than men and present to the physician sooner. These differences in clinical history and course may affect interpretation of the importance of angina as a manifestation of CHD.

Of the six epidemiologic studies that relate serum cholesterol levels to CHD, five show a significant relationship between CHD and cholesterol levels. the sixth study, while not demonstrating a positive relationship between CHD and total cholesterol, shows a significant inverse relationship between HDL cholesterol levels and CHD risk.

Dyslypidemia is a significant risk factor for CHD in women. Apropriate treatment includes dietary modification, estrogen replacement therapy, and drug treatment using the same agents as commonly prescribed for men.

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