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Primary and secondary prevention of coronary heart disease

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Cardiovascular disease (CVD) remains the number one cause of death in the US, accounting for nearly half of all deaths among both men and women. Despite major successes in the past 30 years, unfavorable trends in some coronary risk factors may have contributed to a slowing of the rate of decline in age-adjusted CVD mortality. Furthermore, given the aging of the population, CVD will remain a major public health concern well into the next century even if age-adjusted death rates continue to decline. Indeed, early in the next century, CVD will be the number one killer world wide.[1] Consequently, the public health importance of the both primary and secondary prevention of myocardial infarction (MI) is indisputable. During the past several decades, researchers have made great strides in identifying lifestyle, biochemical, and genetic factors affecting risk of developing coronary heart diseases (CHD). However, the process of disease prevention involves not only understanding disease mechanisms and identifying risk factors, but also establishing intervention strategies that will reduce risk. Weighing the benefits of any given intervention against the risks and costs has lead to the establishment of guidelines for health providers and the general public. Implementing these guidelines remains a difficult task. Current evidence strongly supports a role of risk factor modification for both primary and secondary prevention of CHD. This review summarizes data on the strength of the association with CHD and the size of the effect for major modifiable risk factors, as well as, where available data permit, estimates of reduction in risk attributable to the respective interventions.

Absolute risk in primary vs secondary prevention

While most factors that predict a first CHD event also predict subsequent events among those with known CHD, the relative importance of an intervention for primary compared to secondary prevention varies. In secondary prevention, there tends to be more trial data and interventions tend to be more cost-effective. Since absolute risk among those with known disease is higher, it is necessary to treat fewer higher risk individuals than lower risk individuals to save one life, even if the relative risk reduction (RRR) is identical. For example, assume an intervention reduces the chance of dying by 25% in relative terms in both primary and secondary prevention. Further,assume that a low-risk individual has a 1% chance of death from CVD over the next 10 years compared to a high-risk individual with CHD who has a 20% chance of death over the same time period. To save a life,one would only have to treat 20 high-risk patients (4 of whom are destined to die) for 10 years so that a 25% RRR would result in one life saved (3 instead of 4 deaths). On the other hand,one would have to treat 400 low-risk patients (4 of whom are also destined to die) so that same 25% RRR would yield 3 instead of 4 deaths. Thus, the total cost per lives saved is considerably lower amongst those at higher risk; this is the basis for more aggressive intervention strategies among those at higher risk.

Investigators at the Framingham Heart Study have developed a useful tool to assess the risk of a primary event based on age, gender, total or LDL cholesterol, HDL cholesterol, systolic and diastolic blood pressure, history of diabetes, and cigarette smoking.[4] Preventive guidelines in a number of countries have adopted various tools based on this strategy. The European Society of Cardiology (ESC) in conjunction with several other European medical societies recently released recommendations that stratify preventive interventions based on classification of patients as high-, intermediate-, or low-risk.[5] Those patients with known CHD constitute the highest risk category because most have a >20% chance of subsequent events over the next 10 years. Patients without known CHD are assessed for risk

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Table 1: Class I risk factors and interventions in the prevention of cardiovascular disease

FACTOR	Effect	Intervention	Comment
Primary and Secondary Prevention Risk Factors			
Smoking	2-3 fold increased risk	Smoking cessation with behavior and pharmacologic intervention	Smoking cessation results in a 60% reduction of CHD risk by 3 years and about half of that benefit occurs in the first 3-6 months after quitting.Interventions are cost effective in both primary and secondary prevention.
Hypercholesterolemia	10% increase in serum cholesterol increases risk of CVD by 20-30%	Dietary changes, lipid-lowering medications	Reduction of serum cholesterol by 10% reduces CVD death by 10% and CVD events by 18%. Treatment for more than five years reduces CVD events by 25%. Extensive trial and cost-efficacy data support a tiered approached based on underlying risk.
Hypertension	7 mm Hg increase in BP over baseline increases risk of CVD by 27%	Lifestyle modifications, weight loss, limited alcohol intake, aerobic exercise, and medications	A 5-6 mm Hg reduction in BP results in 42% reduction in risk of stroke and a 16% reduction in risk of CVD. Extensive trial and cost-efficacy data support a tiered approached based on underlying risk.
Pharmacologic Therapies			
Aspirin in secondary prevention	Reduces CVD events by 25%	Daily low-dose aspirin	Reduces risk among those with any form of CVD.
Beta-blockers following MI	Reduces CVD events by 18%	Daily beta-blocker use	Trial data suggest that the benefit may increase with increasing dose.
ACE inhibitors among those with low EF and following MI.	Reduces CVD events by 22% in those with low EF and by 7% following MI	Daily ACE inhibitor use	Trial data suggest that the benefit may increase with increasing dose.

of subsequent events using a modified Framingham risk assessment tool, a series of easy-to-use charts that allows clinicians to assess the risk of an event over the next 10 years based on age, gender, smoking status, diabetes, and level of cholesterol and blood pressure. If the risk of a primary event exceeds 20% over the next 10 years, aggressive management of various modifiable risk factors is recommended. When the risk of an event is lower, patients are prescribed a less intense and less costly approach.

Using absolute risk to gauge the level of intensity of intervention has been employed by the National Cholesterol Education Panel (NCEP) and the Sixth Joint National Committee on Hypertension Detection and Treatment (JNC VI). The NCEP Adult Treatment Panel II guidelines adjust treatment cut points and goals according to level of underlying risk.[2] Similarly the JNC VI stratifies interventions according to baseline risk.[3]

Classification of interventions for modifiable risk factors

The American College of Cardiology at its Bethesda Conferences categorized risk factors into four categories based on the likelihood that modification results in lower risk.[6] Adapting this scheme to clinical practice requires cost efficacy to be considered. This review presents a modified classification scheme for interventions for major modifiable CVD risk factors, based not only on the strength of the association and the evidence of benefit of intervention, but also on the cost efficacy of the intervention. Preventive interventions for modifiable risk factors for CVD can be divided into three main categories (Tables 1, 2, and 3). Class I interventions (Table 1) have a clear causal relation to heart disease, and good data generally from trials are available on the magnitude of benefit of intervention as well as its risks and costs. There are several instances where an intervention has proven efficacy in secondary prevention, but data are not yet available in primary prevention. Cigarette smoking,hypercholesterolemia, and hypertension are causally related to risk of CHD events, and the corresponding interventions, smoking cessation, cholesterol reduction, and blood pressure management are cost-effective both in primary and secondary prevention. For management of hypertension and hyperlipidemia, extensive trial and cost efficacy data enable a tiered approach based on baseline absolute risk. Several medications (aspirin, beta-blockers, and ACE inhibitors) are also clearly beneficial and cost-effective in secondary prevention for select groups of individuals with existing CVD.

Class II interventions (Table 2) have available data (largely basic and human observational) that strongly indicate a causal relation and that intervention is likely to reduce events, but data on the benefits, risks, and costs of intervention are limited. Class II factors that clearly increase risk of CHD include diabetes,low HDL and high triglyceride levels, obesity, physical inactivity, and menopause. Light to moderate alcohol consumption appears to reduce the risk of CHD. For several factors such as hormone replacement therapy (HRT) after menopause, trial data on interventions are forthcoming; for others, such as alcohol intake, there may never be data from large-scale randomized trials. These modifiable risk factors are useful in assessing risk, and attempts must be made to modify them in the primary and secondary prevention of heart disease; however, in the absence of trial and cost-effectiveness data, the ideal strategy to manage them remains unclear. Furthermore, while in principle it makes sense to invest more resources into modifying factors in those at highest risk, guidelines do not generally distinguish between high- and low-risk individuals.

Class III interventions (Table 3) are those currently under investigation. For many factors in this class, data are not complete enough to infer an independent causal relationship with CHD. For others where causal relationships are apparent,

Table 2: Class II risk factors and interventions in the prevention of cardiovascular disease

FACTOR	Effect	Intervention	Comment
Insulin-dependent diabetes	Increases risk 2-4 fold in men and 3-7 fold in women.	Maintaining normoglycemia with diet, exercise, weight management, and insulin	Trial data strongly suggest that tight control with insulin reduces risk of microvascular disease, and may reduce the risk of CVD events.
Non-insulin-dependent diabetes	Increases risk 2-4 fold in men and 3-7 fold in women.	Maintaining normoglycemia with diet, exercise, weight management, oral agents, and insulin as needed	Tight control appears to reduce microvascular disease, but data on the risk of CHD are not available. Those with NIDDM are likely to have multiple coronary risk factors which should be aggressively modified.
Elevated fasting triglyceride levels and lower HDL levels	Increases risk	Diet, exercise, and lipid-lowering therapy	HDL and triglyceride measures are useful markers of CHD risk and limited trial data suggest intervention reduces risk.
Obesity and physical inactivity	Increases risk	Diet, exercise, and weight management programs	In addition to improving other CVD risk factors, maintaining ideal body weight and a physically active lifestyle may reduce risk of MI as much as 50%, but trial data are limited.
Menopause	Increases risk	Hormone replacement therapy (HRT)	HRT in postmenopausal women may reduce risk of CVD by 40%-50%, however, risk of endometrial or breast cancer may increase.Trial data are limited.
Moderate alcohol intake (one drink per day)	Decreases risk of MI by 30-50%	Discussion of alcohol intake with all patients	The risk/benefit ratio for moderate alcohol consumption may vary widely by gender and is based on underlying risk of CHD. Recommendations must be made individually with careful regard for conditions such as HTN, diabetes, liver disease, history of alcohol abuse, risk of breast cancer, etc.
Pharmacologic therapies			
Aspirin in primary prevention	Pooled trial data in men suggest a 33% reduction in risk of first MI.	Daily or alternate day low-dose aspirin.	Prophylactic aspirin use in older men, particularly with risk factors, may reduce risk of MI.Data among women are limited but forthcoming.

interventions are not yet available or widely tested. Thus, the utility of these factors in the assessment of risk or the prevention of CHD is uncertain. These factors include various dietary practices (ie, dietary supplements), psychological factors, and novel biochemical and genetic markers.

CLASS I INTERVENTIONS

Cigarette smoking: In the US, per capita cigarette consumption rose dramatically in the first half of this century. Over 65% of men born between 1911 and 1920 were smoking by 1945;[7] however, smoking rates declined from the peak of 41% of the adult population in 1965, to 26% in 1991.[8,9] The rate of decline has been slower among women due to increasing rates among women <30 years of age. Smoking rates tend to be higher among blacks, those with lower socioeconomic status, and those with a high school education or less.

By mid-century, seminal studies linking smoking and heart disease were published by English et al,[10] Doll and Hill,[11] and Hammond and Horn.[12] The Surgeon General's Report in 1964 reaffirmed the epidemiological relationship,[13] and by 1983 firmly established cigarette smoking as a leading avoidable cause of CVD.[14] The Report in 1989 presented definitive data from observational case-control and cohort studies, largely among men, that demonstrate that smoking increases CHD mortality by 50% and doubles the incidence of CHD, and the risk increases with age.[15] Willett et al[16] and Rosenberg et al[17] have demonstrated a similar increase in relative risk for fatal and nonfatal CHD among women. The strength, consistency, and dose-responsive character of the relationship in observational epidemiology make any explanation other than a causal one extremely unlikely.

While there are virtually no large-scale randomized trial data on reduction in risk associated with smoking cessation as an isolated intervention, there are clear benefits even among those with established coronary artery disease. Half of the estimated 60% reduction in risk of MI occurs within the first few months of stopping. The vast majority who give up smoking do not use an organized cessation program. The efficacy of smoking intervention programs range from a 6% one-year success rate for physician counseling, to 18% for self-help programs, and 20% to 40% for pharmacologic interventions with nicotine gum or patch. The use of antidepressant drugs appears to increase cessation rates. Since smoking cessation programs generally cost less than continued smoking, there is little doubt of the cost-effectiveness of this intervention in primary or secondary prevention.

Hyperlipidemia: Based on data from several national surveys, mean age-adjusted cholesterol levels have shown a modest decline in the US since the early 1960s.[18,19] However, in 1991, one-half of all American adults aged 20-74 had cholesterol levels >200 mg/dL, and 20% had levels of ≥240 mg/dL.[20] Abundant observational evidence indicates a clear causal link between elevated serum cholesterol and CHD (ie, a 10% increase in serum cholesterol is associated with a 20% to 30% increase in CHD risk), and elevations earlier in life may be associated with higher increases. Randomized trial data clearly demonstrate a reduction in risk of CHD with treatment to lower serum cholesterol.[21] Meta-analyses of

Table 3: Class III factors and interventions in the prevention of cardiovascular disease

Category	Specific factors	Comment
Dietary Factors	Fruit and vegetable intake, type and amount of fat, type and amount of carbohydrate, fiber, trans-fatty acids, dietary antioxidants, dietary bioflavenoids, dietary folate, fish and fish oils, garlic, etc.	USDA recommends 5 servings of fruit and vegetables per day. Reduction in saturated and trans-fatty acid intake appears to be warranted.
Dietary Supplements	Multivitamins, antioxidant supplements, folate, B12, B6, fish oils, etc.	Randomized trials of antioxidant supplements have been disappointing.Randomized trial data on antioxidants and folate are forthcoming.
Psychological factors	Depression, lack of social support, stress, type A personality, etc.	Trials of antidepressants in secondary prevention are forthcoming
Novel biochemical markers	Fibrinogen, homocysteine, LP(a), t-PA, von Willebrand factor, factor VII, C-reactive protein, soluble adhesion molecules (sICAM, sVCAM), antibodies to various infectious agents, measures of oxidative stress, etc.	Additional observational data are needed to clarify the role of these factors in clinical practice.
Genetic markers	LPL receptor, Factor V Liden, ACE, etc.	Potential genetic markers and therapies are emerging at a rapid rate.

randomized trials have generally shown a reduction in risk of both fatal and nonfatal CHD in both primary and secondary prevention trials.[22-26] Treatment to lower cholesterol by 10% reduces risks of CHD death by 10%, CHD events by 18%, and treatment for >5 years yields a 25% reduction in CHD events. The recently completed large-scale primary and secondary prevention trials using statins confirm these findings and provide reassuring data that cholesterol reduction, *per se*, does not increase the risk of nonvascular mortality.[27-33]

Pharmacologic intervention to lower LDL cholesterol is clearly cost effective, and available data permit tailoring recommendations to level of baseline risk of CHD. Both the NCEP and the ESC recommend a tiered approach. The NCEP sets three LDL targets (100, 130, 160 mg/dL) according to underlying risk stratification.[2] For 30% of the US adults recommended for nonpharmacologic intervention, lifestyle modification avoids costs and potential risks associated with drug therapy. Recommendations for drug therapy have focused on those at highest risk for CHD events and approximately 7% of the adult population meet ATP II guidelines for pharmacologic intervention. The ESC uses a target of total cholesterol of 190, or LDL of 115 mg/dL, for all patients, but reserves pharmacologic intervention for those in higher risk categories.

Hypertension: Data from two national surveys suggest that 30% of US adults are hypertensive and that the prevalence of hypertension is greater in blacks *vs* whites and in men *vs* women. There is a clear increase in prevalence with older age, from 9% among those aged 19-24, to 75% of those >75;[34,35] the prevalence of this risk factor is increasing due to the aging of the population and trends toward increasing obesity. Elevation of systolic or diastolic blood pressure (BP) has consistently been associated with increased CHD risk. In a meta-analysis of nine, large, prospective observational studies among over 400,000 participants who accrued over 4,850 CHD events during follow-up, a 7 mm Hg increase in diastolic BP from baseline was associated with a 27% increase in CHD risk and a 42% increase in stroke risk.[36] For patients with malignant hypertension (defined as diastolic BP >115 mm Hg), the benefits of pharmacologic intervention are clear and uncontroversial. Beginning in the late 1960s, a number of randomized trials confirmed the protective effect of treatment of mild-to-moderate hypertension, and these data led to the establishment of treatment guidelines in the 1970s.[37,38] The most precise estimates of risk reduction are from recent meta-analyses,[39,40] reporting that lowering diastolic BP by 5 to 6 mm Hg results in a 42% reduction in risk of stroke and a 14% to 17% reduction in risk of CHD events.

The JNC VI recommends nonpharmacologic lifestyle modifications alone for mild hypertensives and as an adjunct to pharmacologic intervention in moderate-to-severe hypertensives.[3] The JNC VI sets a goal of 140/90 mm Hg for all patients. ESC recommends drug therapy for a BP >140/90 mm Hg among those at high risk and >160/95 for those at lower risk.

Pharmacologic intervention (aspirin, beta-blockers, ACE inhibitors): Several pharmacologic interventions have been shown to be effective in preventing second events among those with known CVD. Pharmacologic reduction of risk during, or immediately following, MI has been demonstrated for thrombolytic agents, aspirin, beta-blockers, and ACE inhibitors.[41] In longer term secondary prevention following an MI, aspirin, beta-blockers, and ACE inhibitors lower the risk of a second cardiovascular event by 22%, 18%, and 7%, respectively. Aspirin therapy among those with existing CVD reduces the risk of subsequent events by 25%.[42] ACE inhibitors clearly provide mortality and morbidity advantage for those with low ejection fraction.[41] All of the pharmacologic interventions are cost-effective and should be considered standard therapy for secondary prevention among appropriate patients with CVD; they are all recommended for secondary prevention by the ESC.

CLASS II INTERVENTIONS

Diabetes: In the US, there are approximately 14 million people who carry the diagnosis of diabetes. These estimates will increase as the American Diabetes Association recently adopted a revision of the definition of diabetes to include those with a plasma blood glucose ≥126 mg/dL. The WHO may follow with a similar recommendation. Approximately 90% of diabetics are non-insulin-dependent. Over the last decade, the prevalence of diabetes appears to be increasing, which may be a reflection of increasing body mass index.[43] CHD is a major complication of both insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) diabetes mellitus. There is little doubt that diabetes causally increases the risk of atherosclerotic disease. By age 40, CHD is the number one cause of death in both diabetic males and females.[44] Age-adjusted rates for CHD are 2 to 3 times higher among diabetic men, and 3 to 7 times higher among diabetic women than among nondiabetics.[45,46] The onset of clinically apparent CHD in those with IDDM occurs at an early age

with markedly increased risks by the third decade of life. The risk is related to the duration and not to the age of onset of diabetes.[47] In the Danish Steno Hospital Study, mortality from MI alone was 12.5% after 35 years of diabetes, regardless of the age of onset.[48] For this reason, those with diabetes, regardless of the presence or absence of other risk factors, must be considered at higher risk for CHD.

Mounting evidence would suggest that maintaining normoglycemia in IDDM and NIDDM patients may translate to reduced risks of microvascular (renal and eye) disease; however, data on the reduction of risk of CHD associated with tight glycemic control of diabetics are scant.[49] Tight control of IDDM with insulin may reduce CHD events. In the Diabetes Complications and Control Trial (DCCT), there was an apparent reduction in CHD events which did not achieve statistical significance likely owing to small numbers of events in this relatively young cohort with IDDM.[49] While oral hypoglycemic agents and insulin can improve glycemic control, their role in the reduction of risk from macrovascular complications of NIDDM remains unclear due to scant and conflicting trial data.[50] In addition, treatment of NIDDM with insulin may result in weight gain.

Diet and exercise are an integral component of the treatment strategy for any diabetic. In many NIDDM patients, glycemic control can be achieved with a modest weight loss through diet and exercise.[51] While tight control with insulin in IDDM is appropriate, its role in the prevention of CHD among those with NIDDM remains unclear. Refinement of management guidelines for both primary and secondary prevention must await more trial data. In stark contrast to well controlled IDDM, those with NIDDM are much more likely to have multiple coronary risk factors than are the general population. Thus, of paramount importance in reducing risks of CHD in the diabetic patient is the aggressive modification of associated risk factors, including treatment of hypertension, reduction of serum cholesterol, weight reduction, and increased physical activity.

HDL and triglycerides: In addition to total and LDL cholesterol, other lipoprotein measures may have clinical utility in primary and secondary prevention, including HDL cholesterol, LDL/HDL cholesterol ratio, and triglycerides. HDL cholesterol has emerged as an important independent predictor of CHD. Researchers with the Framingham Heart Study found that for every 1 mg/dL decrease in HDL cholesterol, there is a 3 to 4% increase in coronary artery disease.[52] An emerging body of evidence now indicates that the ratio of total or LDL/HDL cholesterol may be an important predictor of the risk of CHD. Data from the Physicians' Health Study suggest that a one unit decrease in this ratio (which is achievable with statin drugs) reduces risk of MI by 53%.[53] Imprecision in triglyceride measurements within-individual variability, as well as complex interactions between triglycerides and other lipid parameters,may obscure the impact of triglycerides in the development of CHD. However, fasting triglyceride levels appear to represent a useful marker for risk of CHD, particularly when HDL levels are considered.[54] Trial data testing interventional strategies specifically targeted at those with low HDL or elevated triglycerides in the setting of normal LDL levels, are limited. Investigators from the HDL Intervention Trial (HIT) recently reported a 22% reduction in combined cardiovascular events among those with low HDL (<40 mg/dL), many of whom had elevated triglycerides in the setting of normal LDL (mean of 111 mg/dL) who were treated with gemfibrozil.[55] While awaiting more large scale trial data on the treatment of those with high triglycerides or low HDL, these lipid measures represent a valuable means of assessing risk of CHD events. Further, HDL and triglyceride levels enable tailoring of lipid-lowering therapy among those with high LDL levels.

Physical inactivity: Despite widespread interest in exercise in the US, data on the level of activity are limited. The National Health Interview Survey estimated that 40% of adults exercise regularly (43% males, 38% females, and 23% of those >65), but only 4% to 8% of adults engage in vigorous exercise for ≥20 minutes ≥3 or more time per week.[56,57] The number of adults considered sedentary declined from over 40% in the early 1970s, to 27% by 1985.

Since Morris et al[58] first reported in the mid-1950s that CHD rates were lower among bus conductors and mail carriers compared to sedentary coworkers (bus drivers and postal supervisors), a number of observational studies have reported a similar inverse association between activity level and CHD.[59] Morris et al[60] subsequently developed questionnaires to incorporate estimates of leisure-time activity in their analysis. In this study among civil servants with sedentary jobs, those who engaged in vigorous sports were half as likely to suffer MI than those who did not. This relationship between activity of any kind and lower risk of CHD has been confirmed in a number of primary prevention studies. While data on the benefits of exercise in secondary prevention are considerably more limited, a recent report suggests that vigorous activity confers similar benefits after MI.[61] In a recent meta-analysis of 27 observational cohort studies of leisure-time and occupational activity, the risk of CHD events was almost twice that compared to inactive individuals after controlling for other coronary risk factors.[59]

While there are no large-scale, randomized primary prevention trials that determine the benefit of exercise intervention in terms of CHD reduction, cessation of activity appears to increase risk of CHD. There are clear benefits of physical activity in terms of other cardiovascular risk factors. A physically active lifestyle may increase the level of HDL, reduce LDL and triglycerides, increase insulin sensitivity, and reduce resting BP.[62,63] In secondary prevention, cardiac rehabilitation programs with an exercise component are beneficial in reducing subsequent events. Data on the optimal means of intervening to achieve modification of this risk factor are lacking.

Obesity: Over 20% of the US population is obese (defined as 20% over the desirable level),[64] a problem that seems to be more prevalent among women than men. Despite growing awareness of the ill health effects of obesity, the proportion of the US population that is overweight has increased steadily over the past two decades among both men and women, and the rate of increase is accelerating.[65,66] While there are little data that would dispute the association of obesity with CHD, there remains controversy on the independent status of this risk factor. Reports on the association of obesity with CHD have been understandably conflicting due to the use of various measures of obesity. Further, the impact of obesity on CHD risk may be mediated, at least partly by other coronary risk factors such as hypertension, dyslipidemias, and glucose intolerance.[67] Hubert[68] summarized prospective data largely among men and found an independent effect of obesity after controlling for other risk factors. Similar findings are available among women.[69] Whether or not there is residual increased risk associated with obesity after controlling for hypertension, serum lipoprotein levels, and diabetes remains unclear at this time; however, obesity is

clearly associated with CHD and is an important and easily assessed marker of risk.

The effect of weight reduction on the risk of CHD in both primary and secondary prevention remains uncertain due to limited trial data. However, given improvements in glucose tolerance, BP, and lipoprotein profile that have been clearly documented, there is general consensus on the role of weight reduction as part of primary and secondary prevention program.[70,71] There is little consensus on the ideal approach to weight reduction. Promoting lifestyle changes to encourage weight reduction or maintenance of an ideal body weight have been universally disappointing. While 30% to 40% of the US population report attempts at weight reduction, failure rates are exceedingly high.[72] Effective treatment strategies generally involve a multifaceted approach, including dietary counseling, behavioral modification, increased physical activity, as well as psychosocial support.[72] Without precise estimates of the benefit and with variability in the intervention strategy,it is impossible to estimate the cost/benefit ratio of this intervention.

Postmenopausal estrogen therapy: In the US, CHD is the number one cause of death among men >40 years. However, it is the number one killer among women by age 60.[73] At every age, men exhibit a higher incidence and mortality rates from CHD. After menopause the gap narrows substantially.[74] The risk of CHD rises rapidly among women both after natural menopause and following oophorectomy.[75-77] A wide range of factors may explain the postmenopausal increased risk in CHD. Endogenous estrogens appear to play a major role in reducing the risk of CHD in women; there is substantial improvement in the lipoprotein profile with a reduction in LDL and an increase in HDL following HRT.[78-80] In addition, there appears to be a protective effect on vascular function,and estrogens can protect LDL from oxidation.[81] Estrogens may also have role in maintaining normal hemostasis and improving glucose tolerance.

The effects of postmenopausal HRT on the risk of CHD have been widely studied in a number of case-control and prospective cohort studies. Recent overviews suggest that HRT reduces the risk of CHD by 44%.[82,83] There appears to be an even stronger effect among those with known CHD;[84] however, these data are limited by their observational nature. It is quite possible that those who self-select for HRT engage in other protective behaviors that confound this relationship. The strength and the consistency of the epidemiologic data would strongly argue for an overall protective effect.

Large-scale, randomized trial data in primary or secondary prevention are not yet adequate to assess fully the risks and benefits of postmenopausal HRT. Recent data from the HERS trial suggest that among women with underlying CHD, treatment with estrogen and progesterone did not result in a reduction in cardiovascular events after 4 years of treatment.[85] The ongoing Women's Health Initiative will address the risks and benefits of treatment of postmenopausal women in primary prevention with estrogen alone, as well as the use of estrogen and progestin in combination, compared to placebo.

Moderate alcohol consumption: The effects of alcohol consumption on CVD are complex. Epidemiologic data are derived almost entirely form observational studies. While heavy alcohol intake increases total[86,87] and CVD mortality,[88,89] moderate intake appears to exert a protective effect on CHD compared to no alcohol intake in both primary[90-92] and secondary prevention.[93] The evidence from both observational and experimental studies suggests that alcohol raises total HDL, and that moderate alcohol consumption appears to reduce the risk of CHD in large part by raising HDL cholesterol levels[94,95] In most studies, benefit is derived from beer, wine,and distilled beverage consumption,[96] suggesting that alcohol is the major factor responsible for the protective association.

While the association of alcohol and CHD is likely to be causal, any individual or public health recommendations must consider the complexity of alcohol's metabolic, physiologic, and psychologic effects. With alcohol,the differences between daily intake of small-to-moderate and large quantities may be the difference between preventing and causing disease. One or two drinks per day may be safe; however, counseling must be individualized. Other medical problems including other coronary risk factors (particularly hypertension and diabetes), liver disease, tendency towards excess, family history of alcoholism and possibly breast and colon cancer should be taken into account when discussing alcohol consumption.

Aspirin in primary prevention: Three large-scale studies in men assessed the benefits of prophylactic low-dose aspirin in the prevention of cardiovascular disease.[97-99] Taken together, these studies among men suggest a benefit of prophylactic aspirin in primary prevention; however, concerns over increased risk of hemorrhagic stroke have not been fully assessed. The ongoing Women's Health Study will address the risk-to-benefit ratio of treatment with aspirin in women. ESC guidelines recommend aspirin in primary prevention among high-risk men.

CLASS III FACTORS

Dietary factors: Diet represents an important aspect of any myocardial prevention program. Dietary habits greatly impact other risk factors including weight, dyslipidemia, hypertension, and diabetes. One of the most consistent findings in dietary research is that those who consume higher amounts of fresh fruits and vegetables have lower rates of heart disease, stroke, and cancer. The USDA recommends 2 to 4 servings of fresh fruit and 3 to 5 servings of fresh vegetables per day. Saturated and trans-fatty acids appear to increase risk of CHD. Low fat diets have been shown to reduce the risk of MI and even cause regression of coronary artery disease in secondary prevention. Controversy remains over the issues of the health effects of the amount and type of fat and carbohydrates. While there is a general consensus that reduction in saturated fat intake reduces the risk of CHD, whether to replace these fats with simple or complex carbohydrates or mono- or poly-unsaturated fats remains controversial.

A number of specific foods and micronutrients are currently under investigation (ie, fiber, fish and fish oils, garlic, folate, and soy protein). Observational epidemiologic studies tend to report lower rates of CHD events among those who take antioxidant vitamins and perhaps folate supplements; however, studies are not all consistent, and the effect size is generally modest. Recent randomized trials have not supported a role of antioxidant supplementation in the prevention of CHD, but there are only limited trial data on folates.

Psychological factors: The impact of psychological factors such as depression, social support, and stress appear to contribute to increasing risk of CHD. Further data are needed to confirm the relationship and to establish efficacy of interventional strategies. Therapeutic interventions, while not blinded, do suggest a role as part of a prevention program particularly for those with known CHD. Trials of antidepressants following MI are currently underway.

Novel biochemical markers: Hemostatic markers, inflammatory markers, novel lipid parameters, cellular adhesion markers, indicators of prior infection, and markers of oxida-

tive stress have been linked to steps in atherogenesis or thrombosis and/or CVD events. These include factors such as fibrinogen, homocysteine, LP(a), t-PA, von Willebrand factor, factor VII, C-reactive protein, antibodies to oxidized LDL. Many of these are promising areas for future research. Whether or not these parameters represent independent risk factors for atherosclerotic disease or are in the causal pathway for other risk factors is not entirely clear. Cigarette smoking, alcohol consumption, and dyslipidemia appear to alter the levels of various biochemical factors. Additional observational data, as well as interventional trials aimed at altering these factors, will provide valuable information on their role in the treatment and prevention of atherosclerotic disease. At this point, recommendations targeted at modifying these factors are premature.

Genetic markers: Recent advances permit exploration of a number of gene polymorphysms that are associated with coronary risk factors or directly with cardiovascular events. The role of genetic screening in primary or secondary prevention remains unclear. However, one can envision a time when genetic assays will play a role in identifying those at risk and targeting therapies to reduce the risk of subsequent events; genetic manipulation may be another option.

Conclusion

Current data strongly support a role for risk factor modification in both primary and secondary prevention of CHD. There are three risk factors for which the strength and consistency of the association with atherosclerotic disease indicate a causal relationship and the benefits of intervention are well-documented in both primary and secondary prevention: cigarette smoking, elevated serum cholesterol, and hypertension. There is little doubt that diabetes mellitus, reduced levels of HDL cholesterol, elevated levels of triglycerides, physical inactivity, obesity, and menopause increase the risk of CHD, and that light-to-moderate alcohol consumption reduces the risk, but the precise magnitude of the effect attributable to intervention in these risk factors has been difficult to document. Other potential factors include various dietary practices, biochemical and genetic markers, and psychological factors.

In summary, primary and secondary prevention have contributed substantially to the reduction in CHD mortality rates over the last several decades. In addition to developing a better understanding of mechanistic and epidemiologic determinants of atherosclerotic disease, considerably more attention must be given to effective strategies for prioritizing factors in a prevention program, implementing existing guidelines for risk factor modification, and developing low cost interventions for those factors where guidelines are not yet available. Many lifestyle changes are difficult to achieve and even harder to maintain over the long term. Interventions need to involve not only the affected individuals, but often families, work places,schools, and even whole communities. For clinicians, identification of the strategy most likely to be successful for each individual is key. Further research on the cost- and risk-benefit ratios will enable better targeting of interventions for maximal individual and societal benefit. Widespread use of multifaceted self-help and health professional directed prevention programs should help sustain the decline in CVD mortality rates in the US.

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