Primary Prevention of Heart Disease in Women: Aspirin, LDL Reduction, and Estrogen Replacement Therapy

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Interests:

Noninvasive cardiac imaging
Valvular heart disease
Heart disease in women
Pregnancy and heart disease
Heart Failure

In the last 2 decades it has been recognized that heart disease is a prominent cause of cardiovascular morbidity and mortality in women. Approximately 2.5 million women are hospitalized annually for cardiovascular problems with 500,000 deaths from cardiovascular diseases. About 50% of these deaths are due to coronary artery disease. The age-adjusted death rates for heart disease demonstrate slightly higher death rates for men than for women and for black as opposed to white populations (Figure 1)[1]. Cardiovascular disease is the leading cause of death of white, black, and Hispanic women, representing more deaths than all types of cancer combined [1]. Cardiovascular disease in women manifests itself at an older age than in men. This 10-15 year lag in the development of coronary artery disease is believed to be related to the effect of endogenous estrogen. Endogenous estrogen has a beneficial effect on plasma lipids and is associated with improved endothelial function. Cardiovascular disease becomes most apparent in older woman (> 65 years old) and increases with age. Given the prevalence of cardiovascular disease in women, it is rational to identify strategies to prevent or delay the occurrence of this process.

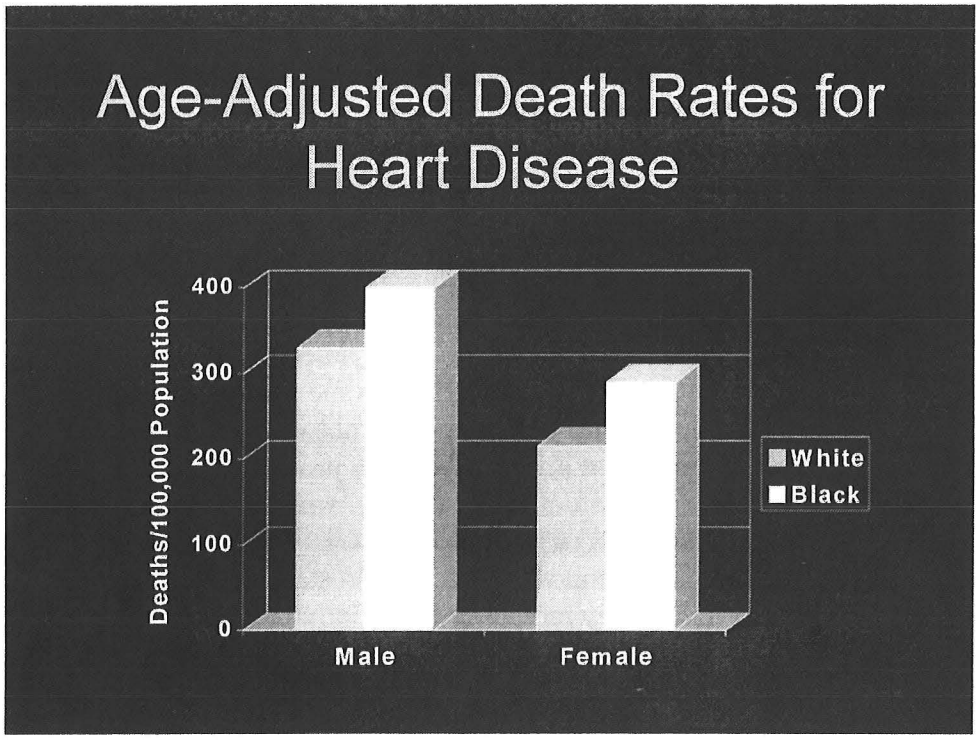

Figure 1. Age-adjusted death rates from cardiac disease are shown according to 1998 data [1]. Death rates are slightly higher in men than in women and in blacks than in whites.

Prevention of cardiovascular disease in women involves several components including patient recognition that heart disease poses an important health risk and the institution of lifestyle modifications. This discussion will focus on an additional aspect of prevention---the role of pharmacologic therapy in preventing coronary artery disease.

Specifically, the role of aspirin, statins, and estrogen replacement therapy on the development of coronary artery disease in women will be examined.

In order for a therapy to be useful in the prevention of cardiovascular disease, three criteria must be met. First, a therapy must be effective in reducing cardiac events. Ideally such an agent would reduce myocardial infarction and cardiovascular death, two "hard" endpoints. Effectiveness in reducing "soft" endpoints such as hospitalization and revascularization provides additional evidence supporting the use of an agent in prevention. Second, a therapy must have a favorable safety profile, i.e. an agent that is effective in reducing cardiovascular death but leads to increased cerebrovascular mortality would not be an appropriate preventative strategy. Lastly, preventative therapies must be cost effective.

Aspirin in the Prevention of Coronary Artery Disease

Analgesic properties were found in willow bark in the era of Hippocrates (400 B.C.). This analgesic effect was due to the presence of salicin within the bark and was either used on the skin or chewed. Salicin is toxic when ingested and is useful only as a topical agent, so efforts were undertaken to create an effective analgesic that could be ingested. Acetyl salicylic acid was synthesized in 1897 by Felix Hofmann, a German chemist. Licensed by Bayer, it has become the leading analgesic prescribed worldwide. The first reports of the use of aspirin in cardiac disorders date to the 1940's when Dr. Craven, a California physician, treated many patients with aspirin (Aspergum) following myocardial infarction, noting that these patients were unlikely to develop recurrent cardiac events [2].

The mechanism of action of aspirin is due to inhibition of prostaglandin synthesis[3, 4]. Aspirin irreversibly inhibits acetylation of the amino acid serine at position 529 of cyclooxygenase-1, thereby preventing the conversion of arachidonic acid to PGH2 [5]. PGH2 is converted to thromboxane A2 (TXA2) by thromboxane synthetase. If PGH2 is not available as a substrate for thromboxane synthetase, thromboxane A2 will not be formed. Thromboxane is extremely important in amplifying the process of platelet activation and release of a multitude of mediators stored in the platelet (Table 1). These mediators influence growth and inflammation as well as hemostasis. PGH2 is also required for the synthesis of prostacyclin in endothelial cells. Prostacyclin formation is blocked by aspirin use. This inhibition is only temporary as endothelial cells recover their ability to synthesize prostacyclin after a short time.

Once aspirin is administered and blocks cyclooxygenase activity on a platelet, that platelet will have abnormal function for its lifespan (8-10 days). Three hundred mg of aspirin is sufficient to acutely inhibit thromboxane synthesis by more than 99% [6]. Daily doses less than a baby aspirin (30-40 mg) are sufficient to chronically suppress thromboxane production.

Table 1. Examples of mediators released from the platelet

Hemostatic	Mitogenic	Inflammatory
Thromboxane A2	Vascular Endothelial Growth Factor	Nitric Oxide
ADP	Endothelial Cell Growth Factor	Platelet Factor 4
Calcium	Transforming Growth Factor-B	P-Selectin
Epinephrine	Platelet-Derived Growth Factor	Inflammatory Protein-1
Fibrinogen		CD40 Ligand
Factor V, XI, Von Willebrand Factor		

Large clinical studies have demonstrated the efficacy of aspirin in the treatment of patients with unstable angina and following myocardial infarction. Interest in the use of aspirin in the primary prevention of coronary events developed in the 1980's. The British male doctor study enrolled 5139 healthy male physicians and randomized them to aspirin (500mg/day) versus no aspirin [7]. Study subjects completed a health survey every 6 months and endpoints were confirmed by medical records. The length of follow-up was 6 years. Medical compliance was a major issue in this study with 19% of patients stopping aspirin in the first year of therapy (frequently due to gastrointestinal side effects) and another 5% discontinuing therapy annually thereafter. In addition, some doctors in the control group began taking aspirin. There was no definitive benefit of aspirin therapy in the prevention of myocardial infarction or cardiac death (Figure 2). Transient ischemic attacks were reduced in subjects taking aspirin (Figure 2). Patients treated with aspirin had an improvement in migraines, and musculoskeletal disorders while experiencing an increase in the incidence of peptic ulcer disease [7].

The Physicians Health Study was performed concurrently in the United States [8]. This trial was a randomized, double-blind, placebo-controlled trial of aspirin and beta carotene therapy. The goal of the aspirin arm was to assess whether low dose aspirin prevented cardiovascular mortality. These 22,071 male doctors greater than 40 years old were followed for 60.2 months and took a dose of 325mg of aspirin every other day. The trial was stopped prematurely due to the observed effect of aspirin on myocardial infarction. There was a 44% reduction in the risk of myocardial infarction, decreasing the rate of myocardial infarction from 4.4/1000 patient years to 2.5/1000 patient years (Figure 3) [8]. The event rate in the placebo arm was essentially the same as the event rate in the control group of the British male doctor study. There was a trend for an increase in stroke in the patients treated with aspirin, primarily in those with hemorrhagic stroke. No impact of aspirin on total cardiovascular mortality was noted.

British Male Doctor Study

	Events/1000 man years	
	Aspirin (n=3429)	Controls (n=1710)
Nonfatal MI	4.25	4.33
Nonfatal CVA	3.24	2.85
TIA	1.59*	2.75
Bleeding, not cerebral	1.06	0.74
Death due to MI or CVA	6.32	6.23
Total death	14.35	15.95

Figure 2. Results from the British male doctor study demonstrate no significance in the incidence of myocardial infarction or death. While there was a decreased incidence of transient ischemic attacks in patients treated with aspirin, there was a trend for an increase in nonfatal strokes [7].

Physicians' Health Study

	Aspirin	Placebo	RR	p
MI				
fatal	10	26	0.34(0.17-0.75)	0.007
nonfatal	129	213	0.59(0.47-0.74)	<0.001
total	139	239	0.56(0.45-0.70)	<0.001
CVA				
fatal	9	6	1.5(.5-4.3)	0.43
nonfatal	119	98	1.2(0.9-1.6)	0.2

Figure 3. Results from the Physicians' Health Study demonstrated a beneficial effect on aspirin in the prevention of myocardial infarction [8]. There was a trend toward in increase in strokes in this population, similar to the observations of the British male doctor study.

Unfortunately, these two large trials enrolled only men. Manson and colleagues examined the relationship between aspirin consumption and cardiovascular events in the Nurses Health Study [9]. In this trial of approximately 87,000 nurses, taking 1-6 aspirin per week was associated with a 32% decrease in the incidence of first myocardial infarction[9]. Subgroup analyses suggested that those women who were older (>50 years old), had hypertension, and had lipid disorders were most likely to benefit from aspirin therapy. Although data from this trial suggests a substantial benefit from aspirin in women, individuals who took aspirin may have had fundamental differences from those not taking aspirin.

The Hypertension Optimal Treatment (HOT) trial was a randomized trial performed in Europe [10]. This trial investigated two different concepts: the impact of blood pressure lowering to different diastolic pressures (<90mmHg, <85mmHg, and <80mmHg) and the influence of low-dose aspirin on the prevention of cardiac events. The 18,790 patients were randomized to 3 different levels of blood pressure control and half of the patients in each blood pressure group were randomized to aspirin (75mg/day). Nearly half of the enrollees were women (47%), an extremely large proportion for any randomized trial within cardiology.

The primary results of the HOT trial demonstrated that diastolic blood pressure could be effectively lowered into the low 80's without increased adverse events. The lowest incidence of major cardiovascular events occurred at a diastolic blood pressure of 82.6mmHg and the lowest risk of cardiovascular mortality occurred at 86.5mmHg [10]. Further lowering of blood pressure beneath 82.6mmHg did not increase the risk of events substantially. Diabetics benefited as well as nondiabetics [10]. Aspirin use was associated with a 15% reduction in major cardiovascular events (315 vs. 368, p=0.03) and a 36% reduction in myocardial infarction (82 versus 127, p=0.002) [10].

The HOT investigators subsequently evaluated the effect of aspirin according to age and gender [11]. Intensive blood pressure lowering was associated with a greater benefit in women (decreased death, myocardial infarction, stroke) than in men. Age greater or less than 65 years old did not influence the efficacy of aspirin in the prevention of cardiovascular events. Aspirin therapy reduced myocardial infarction in men by 42% (5.0 to 2.9 infarctions/1000 patient years). There was no impact of aspirin therapy on prevention of infarction in women in this trial (1.7 events/1000 patient years on aspirin versus 2.1 events/1000 patient years on placebo)[11]. There was an increase in non-fatal major hemorrhage in men and women but no increase in fatal hemorrhage associated with aspirin therapy. The lack of increase in fatal bleeds was reassuring given the use of aspirin in this hypertensive population.

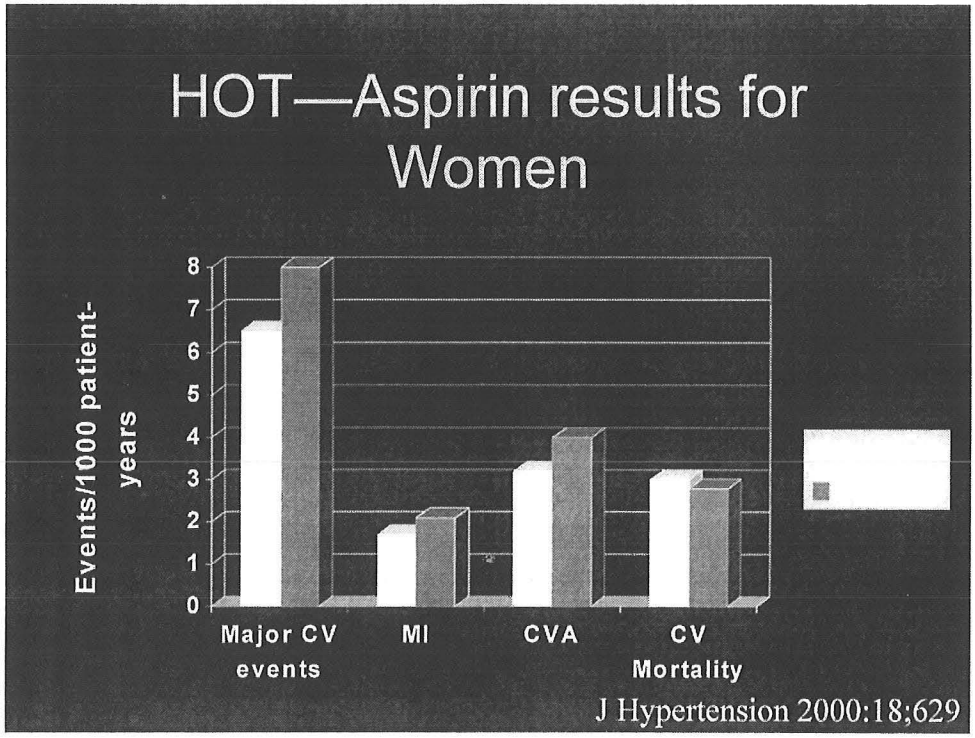

Figure 4. In the HOT trial, aspirin therapy was not associated with a significant improvement in major cardiovascular events, myocardial infarction, or stroke [11].

A comparison of the incidence of myocardial infarction in these three prospective studies is given below (Figure 5). The risk of myocardial infarction in women enrolled in HOT is substantially lower than in the other two trials despite all patients in HOT having hypertension. These women may have been at decreased risk for myocardial infarction since they were younger (mean age of 61) than the average woman with myocardial infarction.

The ongoing Women's Health Study is investigating the role of low-dose aspirin and vitamin E in the prevention of cardiovascular disease and cancer in women. This trial has enrolled 39,876 female health professionals [12]. Patients were randomized to therapy according to a 2X2 factorial design with an aspirin dose of 100mg every other day. It was anticipated that this trial would be completed this year, but the funding has recently been extended for an additional 3 years.

Prolongation of this study may imply several possible scenarios: 1) The magnitude of aspirin effect is likely less than in men. 2) While it is possible that adverse event rates (hemorrhage) are exceedingly high, this would likely lead to termination of the study. 3) It is possible that the aspirin dose selected is too low for prophylaxis of coronary disease. 4) Alternatively, patients enrolled in this trial may be somewhat healthier than the average American woman [12]. Enrolled women are younger than women who typically have myocardial infarctions. This may lead to a decreased event rate in treated and control groups.

While it is possible that there may be a different biological response to aspirin in women than in men, aspirin appears to suppress platelet-derived thromboxane concentrations completely in both men and women [13]. Platelet polymorphisms may predispose women to acute coronary events [14, 15]. Whether these polymorphisms alter the response to aspirin therapy is unknown.

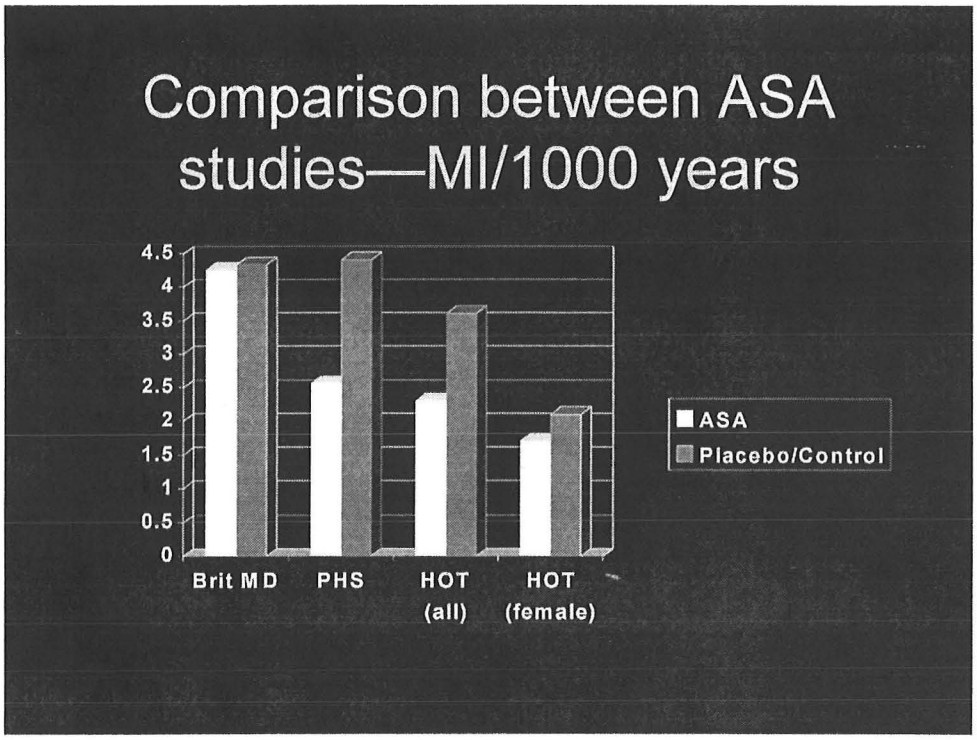

Figure 5. A comparison of the incidence of myocardial infarction per 1000 patient years is shown above. While all populations are relatively healthy, there is a reduced risk of myocardial infarction in women enrolled in these studies. Aspirin is beneficial in the Physicians' Health Study and overall in HOT but not in the British male doctor study.

Adverse effects of aspirin may be seen at virtually all doses. The most common side effect, gastric discomfort, may lead to erosions/gastritis and ultimately to significant gastrointestinal bleeding. Many physicians enrolled in the British male doctors study discontinued therapy due to gastric discomfort or ulcers. Bleeding requiring transfusion or hospital admission was more common in the aspirin treated patients in the HOT study but there was no significant difference in fatal bleeding events [11]. Aspirin is an inexpensive agent and is cost effective in the prevention of cardiovascular events in men over the age of 40.

In summary, it is probable that aspirin decreases the incidence of myocardial infarction in women, but to a lesser extent than in men. Women with cardiovascular risk factors who are at higher risk of coronary events may derive increased benefit from aspirin as compared to the female patient without definable risk factors. Use of aspirin in primary prevention of heart disease is at the discretion of the physician pending results from the Women's Health Study.

LDL Lowering in Women

Over the last few decades it has become apparent that elevated levels of cholesterol and LDL cholesterol are predictors of elevated risk of coronary events. In women, additional risk factors for coronary artery disease include reduced levels of HDL and elevated levels of triglycerides. The National Cholesterol Education Program has recently released its third set of guidelines for the detection and treatment of lipid disorders [16]. These guidelines stress the assessment of cardiovascular risk as well as the presence of coronary heart disease in determining the recommended level of treatment. The importance of low HDL and elevated triglycerides is discussed [16]. Additional attention is given to the "metabolic syndrome", a syndrome characterized by decreased insulin resistance, central obesity, hypertension, dyslipidemia (elevated triglycerides and low levels of HDL), as well as enhanced prothrombotic and proinflammatory states. Aggressive therapy of the population with this metabolic syndrome is warranted including lifestyle modification and pharmacologic therapy.

HMG-CoA reductase inhibitors were developed in the 1980's. The agents block the action of HMG-CoA reductase, an enzyme responsible for the conversion of HMG-CoA to mevalonate, an early step in the synthesis of cholesterol. The first agent of this class, compactin, is produced by the mold Penicillium citricum. It is relatively unstable and was never developed as an agent in the United States. Lovastatin, derived from Aspergillus terreus and Pravastatin derived from a Streptomyces species were two of the first agents developed in the United States for the treatment of hyperlipidemia. Pravastatin is the hydroxylated form of compactin and is more stable that the parent drug. Newer agents including fluvastatin, atorvastatin, and cerivastatin are organically synthesized. The clinical effect of statins on lipid levels is to reduce total cholesterol and LDL cholesterol while leading to a small increase in HDL cholesterol. There is variable influence of these agents on reducing triglyceride levels with most agents leading to a moderate reduction in triglyceride levels.

Agents in this class are substrates for the cytochrome P450 isoform 3A4 (all except fluvastatin) and may be influenced by intake of substances such as grapefruit juice. Ingestion of even moderate amounts of grapefruit juice is associated with increased levels of statins and their metabolites. Several drugs may interact with statins including erythromycin, immunosuppressive agents, and itraconazole. Adverse effects of statins include an elevation of liver function tests and myositis. The risk of myositis increases with concomitant use of a statin and gemfibrozil. Cerivastatin (marketed as Baycol) was recently withdrawn from the market (8/01) due to drug-associated myositis leading to death. The incidence of this complication appeared to be greater with this compound compared to other drugs in this class.

In the last 10 years, trials of lipid lowering therapy have investigated the role of HMG-CoA reductase inhibitors on the incidence of cardiac events. AFCAPS/TexCaps was a randomized comparison of lovastatin versus placebo in reducing first acute coronary events [17]. This trial enrolled 5608 men (45-73 years old) and 997 women (55-73

years old). Lipid inclusion criteria included total cholesterol (180-264 mg/dl), LDL (130-190 mg/dl); HDL ≤45 mg/dl for men and ≤47 mg/dl for women. Approximately 30% of women enrolled in the study were treated with estrogen replacement therapy. Insulin-treated diabetics and obese patients (>50% over ideal body weight) were excluded from participating.

In this trial, lovastatin was associated with a 25% reduction in LDL and a 6% increase in HDL levels. At one year of therapy there were fewer cardiac events in patients treated with lovastatin than with placebo [17]. There were significant reductions in overall coronary events, myocardial infarctions, and coronary revascularizations in patients in the active treatment arm (Figure 6). While fatal events did not significantly differ in the two arms, the reduction in myocardial infarction and revascularization represent reduced costs for society. Reduction in revascularizations may have occurred due to plaque stabilization and a reduction in the progression of coronary artery disease.

AFCAPS/TexCAPS Efficacy

Events/1000 patient-years	Placebo	Lovastatin	RR
CV Events	10.9	6.8	.63(.5-.79)
MI	5.6	3.3	.6(.43-.73)
Revascularization	9.3	6.2	.67(.52-.85)
Fatal CHD events	0.9	0.6	

Figure 6. Lovastatin resulted in a decrease in overall cardiovascular events, myocardial infarctions, and revascularization procedures in the AFCAPS/TexCAPS trial [17].

AFCAPS/TexCAPS remains the only primary prevention study to enroll women. The women were slightly older than the men. Despite being older, the incidence of cardiac events was substantially lower than in the men. The expected number of placebo events is 30 as opposed to the observed number of 13 (Figure 7)[17]. Despite the low number of total events, lovastatin therapy was associated with a reduction of events (Figure 7).

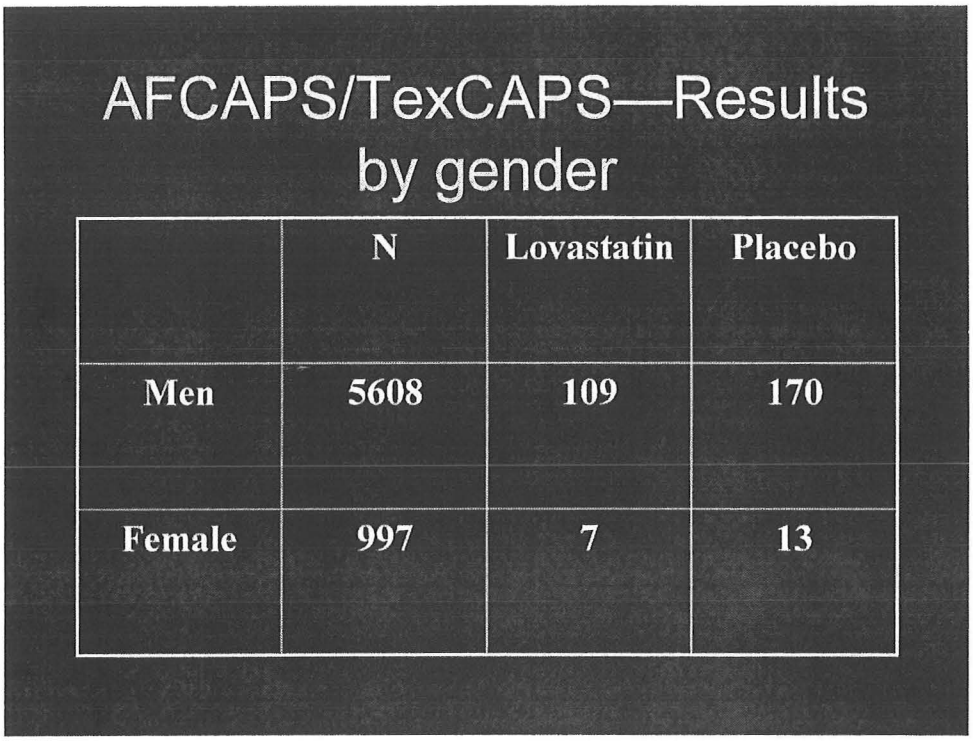

Figure 7. The incidence of cardiac events was much lower in women than in men enrolled in AFCAPS/TexCAPS [17]. Despite the decreased incidence of events in women, lovastatin was effective in reducing cardiac events.

Women have been enrolled in three large studies of statins in the secondary prevention of cardiac events [18-20]. The proportion of women enrolled in these trials is relatively small and ranges from 14-19%. Patients in the secondary prevention trials are at higher cardiovascular risk than those in AFCAPS/TexCAPS. In all four trials, there was a reduction in the number of cardiac events in those women treated with statins leading to a pooled 29% reduction in coronary events [21]. This was an extremely uniform result and mirrors the results obtained in male patients. In these trials, statins were well tolerated without severe adverse effects.

Several angiographic trials have evaluated the effect of statin therapy on coronary artery anatomy. Using quantitative angiography or intravascular ultrasound, lumen diameter has been assessed before and after statin therapy. While there is variability in these trials in terms of design and pharmacologic agent, the results are relatively uniform. Statin therapy is associated with reduced progression of baseline lesions and decreased development of new lesions [22-25]. In addition to the anatomic influence on plaque burden and stability, statins improve endothelial function and appear to reduce inflammatory activity (see below).

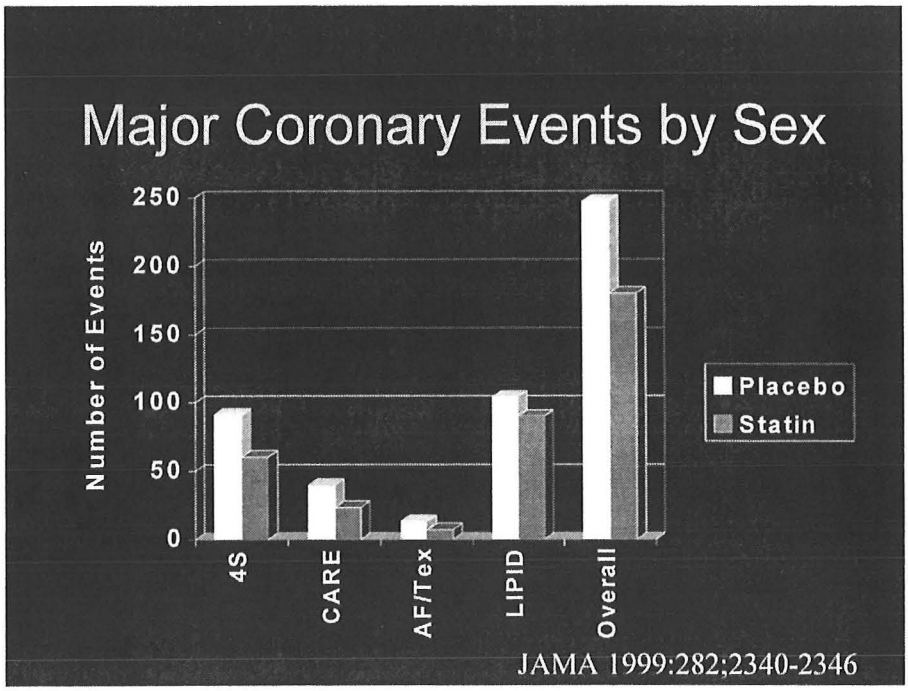

Figure 8. Major coronary events in women enrolled in the major trials of primary or secondary prevention of cardiovascular events. Statin therapy was associated with a decreased risk of events in each trial leading to a 27% reduced risk of events overall [21].

Statins have been uniformly effective in the prevention of cardiac events, but their use is associated with significant cost. The cost-effectiveness of HMG-CoA reductase inhibitors in prevent coronary artery events has been evaluated by several groups. For a 60 year old man with a cholesterol >250mg/dl the estimated cost is $4,900 per year compared to $17,000 per year if the cholesterol level is <250mg/dl [26]. Costs in women are greater than in men ($8100 per year for a 60 year old woman, cholesterol >250mg/dl; $36,000 per year for a 60 year old woman, cholesterol <250mg/dl)[26]. More recent estimates of statin therapy "costs" have decreased, probably due to decreased price of therapy and additional data demonstrating increased drug efficacy ($4,900 for a woman aged 59 with a cholesterol of 261mg/dl) [27]. As additional data become available in the elderly population, estimates of cost effectiveness are expected to decrease.

A potential strategy to improve the cost-effectiveness of statins includes prescribing therapy to patients with high-risk characteristics. The National Cholesterol Education Program guidelines do this by defining cholesterol levels and risk levels for appropriate nonpharmacologic and pharmacologic treatment [16]. A significant proportion of the population may have cholesterol levels lower than those currently recommended for pharmacologic treatment, but remain at increased risk for the development of coronary disease. Up to 50% of all patients with myocardial infarction do not have hypercholesterolemia. Identification of additional risk factors in this population is necessary in order to develop further preventative strategies.

C-reactive protein (CRP) is associated with an increased risk of coronary

events[28-30]. Women enrolled in the Women's Health Study have been evaluated for serum markers of cardiovascular risk. Women with the highest quartile of CRP levels had a 4.4 fold increase in the incidence of cardiovascular events (Figure 9)[30]. Other markers predictive of cardiac events included serum amyloid A, sICAM-1, interleukin-6, homocysteine, total cholesterol, and LDL cholesterol [30]. Levels of HDL were inversely related to cardiac events. Importantly, CRP and serum amyloid A remained predictive of events even in women with LDL levels less than 130mg/dl [30]. Statin therapy has been found to reduce CRP independently of its lipid lowering properties [31]. In AFCAPS/TexCAPS, lovastatin therapy was effective in patients with a LDL higher than the median (149 mg/dl) [32]. Therapy was equally effective in patients with a LDL lower than the median but a CRP higher than the median [32].

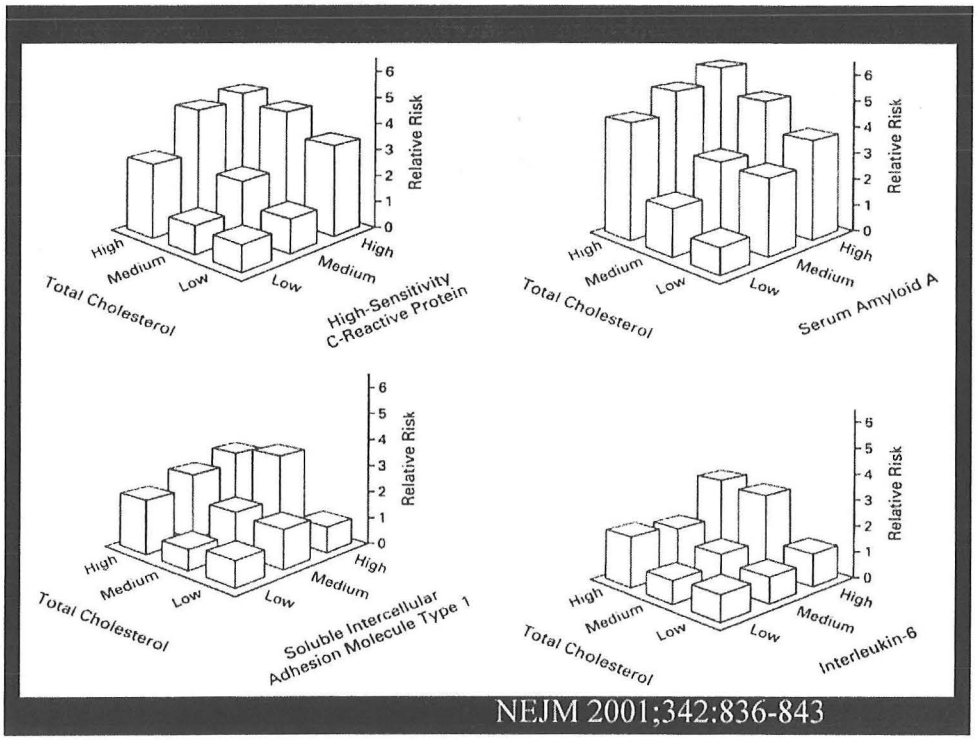

Figure 9. The relationship between cholesterol levels and CRP, serum amyloid A, soluble intercellular adhesion molecule type 1, and interleukin-6 is shown according to tertiles of data [30]. The risk rises with increasing levels of cholesterol and each marker.

Statin therapy is associated with a reduction in cardiovascular events in both men and women, with a similar magnitude of effect. This effect is seen in studies of primary prevention as well as secondary prevention. The cost of these agents prohibits their use in all individuals, so it is important to target their use to those individuals at higher risk. Women at higher risk include those with elevated LDL, elevated triglycerides as well as low HDL. Women with other cardiovascular risk factors (diabetes mellitus, hypertension, metabolic syndrome) should be treated according to NCEP III guidelines [16]. As other "risks" for cardiovascular disease are identified (such as CRP), the role of these risk factors in targeting statin therapy will be determined.

The Role of Hormone Replacement Therapy in Women to Reduce the Risk of Coronary Artery Disease

The role of estrogen in preventing coronary disease arose from the prevalence of heart disease according to age (Figure 10). Acute myocardial infarction or angina is uncommon in the premenopausal female except in those with major risks for coronary disease. Following menopause there is an increase in coronary artery disease in women that establishes a 10-15 year delay between men and women, i.e. a 70 year old woman has a similar likelihood to develop myocardial infarction as a 55 year old man. Women who have early menopause (natural or surgical) have a higher risk of coronary artery disease. In evaluating this epidemiologic information, the most likely etiology for the delay in coronary artery disease in women is a protective effect of estrogen. The hypothesis was generated that use of estrogen replacement therapy might further delay or prevent the development of coronary disease.

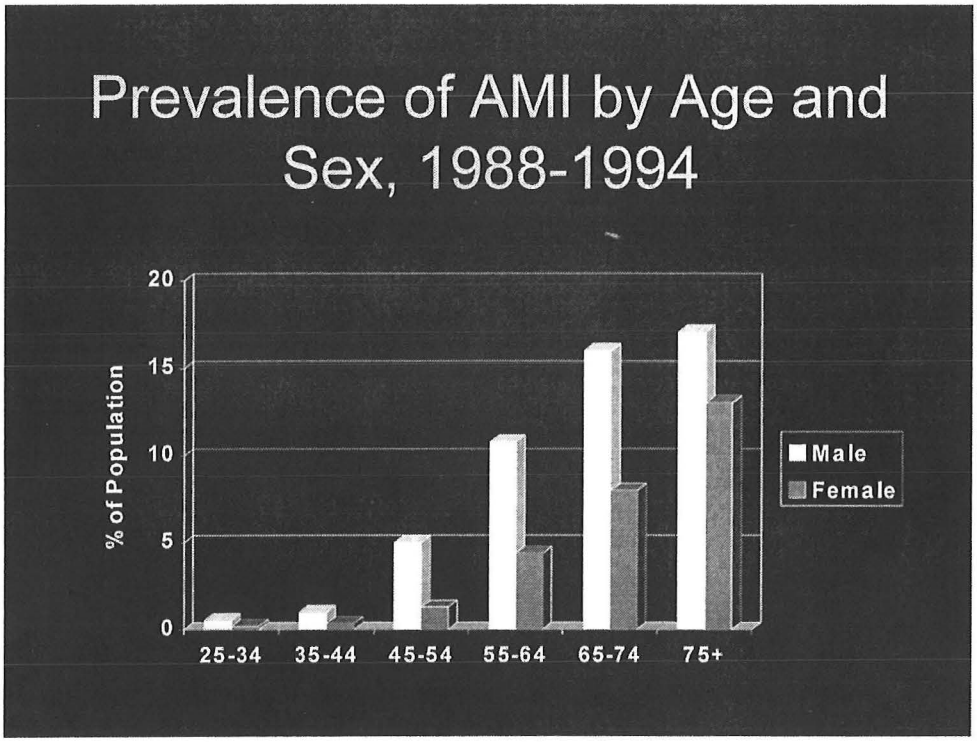

Figure 10. The incidence of acute myocardial infarction is shown for men and women according to age. More men than women suffer from acute myocardial infarction at all ages but the difference in prevalence decreases as women get older.

Estrogen has many different biologic effects, some of which are favorable and some of which are unfavorable for the development of coronary artery disease. Exogenous estrogen results in an increase in HDL and apolipoprotein A1 and a lower LDL, apolipoprotein B-100 and Lp(a) [33, 34]. Unopposed estrogen administration results in an increase in the incidence of endometrial cancers so estrogen administration is generally accompanied by progestin administration in women with an intact uterus.

Progestins, however, result in an increase in LDL and a decrease in HDL, changes would could potentially negate the effects of estrogen on cholesterol levels.

In the Postmenopausal Estrogen/Progestin Interventions Trial combined estrogen/progestin therapy was administered [34]. The combination of these agents did not interfere with the cholesterol-lowering effect of the estrogen but did prevent endometrial hyperplasia [34]. In this trial, 875 women were randomized to several different regimens: placebo, conjugated equine estrogen 0.625mg/day, conjugated equine estrogen plus cyclic medroxyprogesterone acetate (10mg/day for 12d/month), continuous estrogen and medroxyprogersone acetate, or estrogen plus cyclic micronized progesterone (200mg/day for 12 days/month). HDL cholesterol increased over time in those women treated with estrogen alone or estrogen plus cyclic medroxyprogesterone. All active treatments were associated with a reduction in LDL cholesterol (14.7-17.7mg/dl) and an increase in triglyceride levels (11.4-13.7mg/dl)[34].

In addition to the effects of estrogen on lipid metabolism, the biologic effects of estrogen are mediated by at least two estrogen receptors, alpha and beta, that are steroid hormone receptors. These receptors are wide spread and may be found in reproductive tissues, bone, liver, brain, and the vasculature [35]. These receptors function as transcription factors altering gene expression and can be activated by growth factors in the absence of estrogen. The beta-receptor appears to be particularly important in vascular injury [35]. Through these receptors, estrogen decreases the oxidation of LDL and decreases the incorporation of cholesterol into the vessel wall. Data from the Atherosclerosis Risk on Communities Study, however, suggests that the effect of estrogen is not due to a change in atherosclerotic burden [36].

Estrogen is a direct vasodilator and decreases the endothelium-dependent coronary vasoconstrictive response to increasing doses of acetylcholine [37]. Estrogen is involved in the regulation of a number of vascular and hemostasis related genes (Table 2) that result in a decrease in thrombotic potential, improved fibrinolysis, and reduced serum angiotensin converting enzyme activity. Estrogen results in an increase in C-reactive protein levels, suggesting an "inflammatory" effect of these hormones [38].

Much of the clinical evidence supporting the use of estrogen replacement therapy for the prevention of coronary artery disease comes from epidemiologic trials in which estrogen was used primarily to decrease menopausal symptoms and prevent osteoporosis. The most compelling data come from the Nurses Health Study, a study of 70,533 postmenopausal women begun in 1976 [39]. Biennial questionnaires were used to assess details of hormone use and various endpoints. Nonfatal and fatal coronary artery disease occurred in 1258 individuals (1.8% of total) during 20 years of follow-up. The incidence of coronary artery disease in this population suggests that the population is healthier than the American public given the incidence of coronary disease in subjects who did not use estrogen of 3.1/1000. Study participants were classified according to hormonal use into nonusers, current users and past users. Current use of hormone replacement therapy was associated with a 46% reduction in the risk for major coronary events (relative risk 0.54 (0.46-0.62))[39]. Because subjects who used replacement therapy were leaner and likely to

smoke less, the adjusted relative risk for hormone replacement users was RR of 0.64 (0.54-0.76). Based on these data, 21 cases of cardiovascular disease could be prevented for 100,000 years of use in postmenopausal women age 55-59 years (0.2 events/1000 years of use)[39].

Table 2. Example of genes regulated by estrogen

Vascular	**Nonvascular**
Prostacyclin	TGF-beta
Endothelin-1	Epidermal growth factor
Collagen	Platelet-derived growth factor
Matrix metalloproteinase 2	Flt-4 Tyrosine
E Selectin	Tissue Factor
Vascular adhesion molecule	Fibrinogen
Vascular endothelial growth factor	Protein S
	FactorsVII and XII
	TPA and PAI-1
	Antithrombin III

Grady and colleagues reviewed the evidence supporting the use of hormone therapy to prevent cardiovascular disease [40]. There were 32 studies published between 1970 and 1992 dealing with the issue of estrogen for prevention of cardiac events. Data have been published from a variety of trial designs ranging from case-control, cross-sectional to cohort studies. Twenty-five of these studies suggest estrogen is beneficial, while the other seven demonstrate either a neutral or detrimental effect [40]. The pooled estimate of the relative risk of coronary heart disease in these studies was 0.65 (0.59-0.71) indicating a 35% reduction in the incidence of cardiac events.

HERS (Heart and estrogen replacement study) randomized 2763 women with a previous history of heart disease to hormone replacement therapy or no therapy [41]. Conjugated equine estrogen (0.625mg) and medroxyprogesterone acetate (2.5mg) were taken daily by participants randomized to active therapy. Approximately 75% of subjects took 80% or more of the assigned pills with compliance decreasing slightly over the course of the trial. Nearly 20% of women were started on statin therapy during the trial. Institution of statin therapy did not influence the results of the trial. Overall, there was no significant benefit of hormone replacement therapy on the incidence of recurrent cardiac events: 172 in the hormone group and 176 in the placebo group over the 4.1 years of follow-up (Figure 11)[41]. During the first year of therapy there was an increased risk (52%) of a cardiac event. This increase in cardiovascular deaths in the group treated with estrogen/progestin persisted through year 4 when slightly more events occurred in the placebo group (Figure 12). Estrogen/progestin had no significant impact on the incidence of stroke or transient ischemic attack but there was a moderate increase in the incidence of deep venous thrombosis and pulmonary embolism (Figure 11) [41]. Venous thromboembolic events occurred in 34 women in the active therapy arm (6.3/1000 woman-years) and 13 in the placebo group (2.4/1000 woman-years)[41]. The risk of

thromboembolism was decreased in those individuals taking aspirin (RR 0.5(0.2-0.8)) or statins (RR 0.5 (0.2-0.9)) [42].

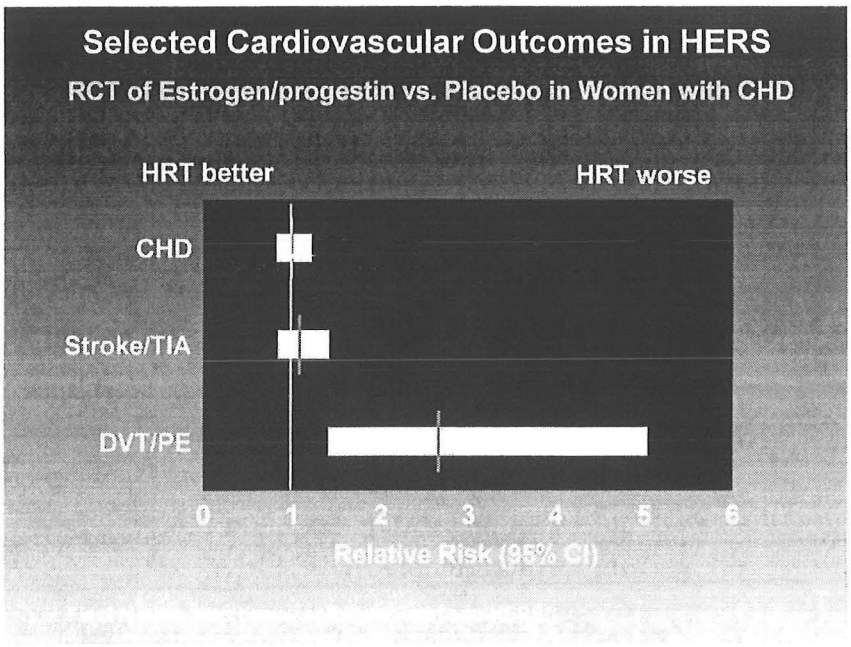

Figure 11. The relative risk of hormone replacement therapy in HERS is shown for three major outcomes—coronary heart disease (CHD), stroke or transient ischemic event (Stroke/TIA), and deep venous thrombosis/pulmonary embolism (DVT/PE) [41]. There was a significant increase in the risk of DVT/PE in patients treated with estrogen/progestin.

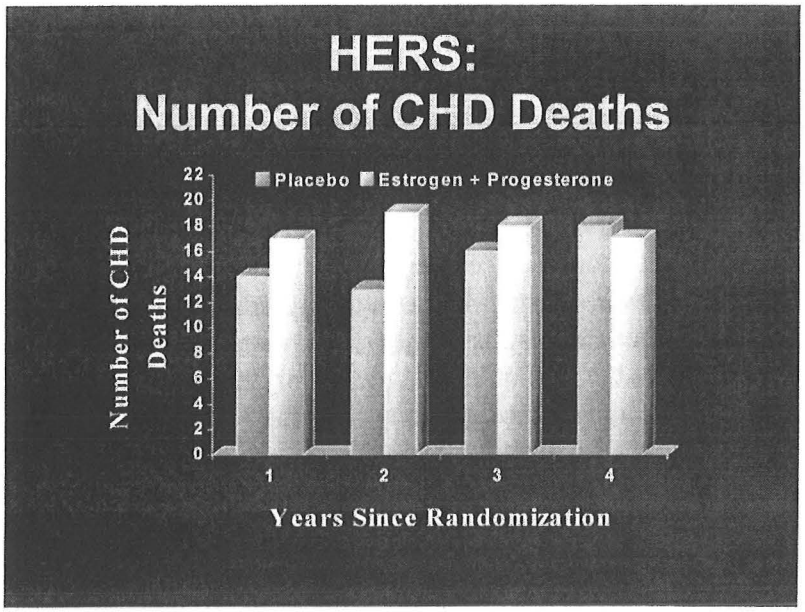

Figure 12. The number of coronary heart disease deaths is shown versus the number of years since randomization demonstrating a slight excess of deaths in the treated group until the fourth year of therapy [41].

The ongoing Women's Health Initiative is investigating the role of estrogen replacement therapy in the primary prevention of heart disease in 27,500 women [43]. Slated to be completed in 2005, the participants in this trial were notified in early 2000 of an increased risk of myocardial infarction during the first year of hormone use, suggesting that the observations made in HERS may also be true in primary prevention[44]. The trial was continued in order to increase the duration of exposure to estrogen with the hope that estrogen will have a favorable impact on events over time (greater than 1-2 years).

Recent publications have addressed the impact of estrogen replacement therapy on the progression of coronary artery disease. Three hundred nine women with documented coronary artery disease were assigned to treatment with estrogen, estrogen plus progesterone, or placebo [45]. Baseline and follow-up (3.2 ± 0.6years) quantitative angiography was performed in this population. Minimal coronary artery diameters were not significantly different at follow-up in all three groups suggesting that estrogen alone or combined estrogen/progesterone did not impact progression of disease [45]. Administration of estrogen does not impact the rate of increase in carotid intima-media thickness [46]. In the Coumadin Aspirin Reinfarction Study, women who began hormone replacement therapy following myocardial infarction had a higher incidence of cardiac events (death/myocardial infarction/angina) during follow-up than never-users of estrogen (41% versus 28%) [47]. This increase in event rates was primarily due to an increase in unstable angina [47] but was not seen in women who had been taking estrogen replacement therapy prior to the incident event and continued therapy.

Various mechanisms have been proposed for the increase in early arterial events noted in HERS. One potential mechanism is that there is an increase in thrombotic events in patients at high risk for such events (inherited thrombophilias, smoking, etc.). Psaty and colleagues studied 232 women with incident myocardial infarctions between 1995 and 1998 and compared them to 723 matched controls [48]. The women were evaluated for the presence of coagulation factor V Leiden and prothrombin 20210 G-A variants and were stratified according to hypertension. No interaction was noted between factor V Leiden and myocardial infarction. There was a marked increase in risk of myocardial infarction in those hypertensive patients taking estrogen who had the prothrombin mutation (Figure 13) [48].

Hormone replacement therapy influences a variety of hemostatic and vascular genes that may lead to different acute and chronic effects. Estrogen results in a decrease in plasminogen activator inhibitor and an increase in endogenous tissue plasminogen activator. This leads to an increase in plasmin activity and an increase in matrix metalloproteinase-9 (MMP-9). Acutely, this increase in MMP-9 may weaken the fibrous cap overlying atherosclerotic lesions leading to plaque rupture and acute myocardial infarction [49]. Thus, estrogen could have a deleterious effect on the vasculature acutely, in spite of its effects on endothelial function. Chronically this increase in MMP-9 activity could lead to altered plaque composition with reduced matrix proteins. This altered vascular wall may have improved compliance with decreased likelihood for abrupt plaque rupture (Figure 14).

Hormone Replacement Therapy, Prothrombotic Mutations and the Risk of Incident Nonfatal Myocardial Infarction in Postmenopausal Women

Prothrombin Mutation	HRT use	OR
No	No	
Yes	No	1.45(0.28-7.66)
No	Yes	0.89(0.56-1.42)
Yes	Yes	10.9(2.1-55.2)

JAMA 2001;285:906-913

Figure 13. The risk of myocardial infarction is increased in patients with underlying prothrombin mutations. The coexistence of prothrombin mutations and hormone replacement use greatly magnify the likelihood of developing a myocardial infarction [48].

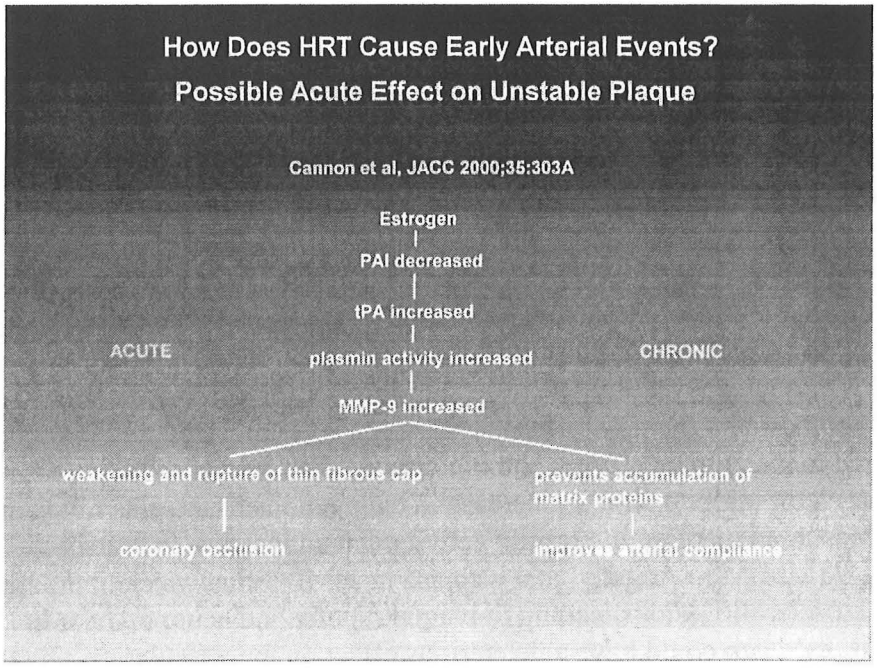

Figure 14. Following the observation of increased early arterial events in HERS, a variety of biologic explanations for the phenomenon have been developed [49].

Additional data regarding the use of estrogen replacement therapy for the prevention of heart disease will be forthcoming in the next few years. In response to the available data, the American Heart Association altered its position on the use of estrogen for cardiac indications in July 2001. A press release was issued stating that there were no current indications for initiating estrogen therapy in women with the intent of altering the occurrence of cardiac disease. While cost of estrogen replacement therapy is reasonable, concerns about effectiveness and risk of thromboembolism prohibit ERT from becoming mainstream therapy in the prevention of heart disease in women.

Prevention of Coronary Artery Disease in Women

Prevention of coronary artery disease is important as it represents a leading cause of death in women (Table 3). The first step in preventing disease is to increase awareness of the importance of heart disease in women. A recent American Heart Association Survey showed that 62% of women believe cancer is the greatest health concern and less than 10% of women identified heart disease as the greatest threat [50]. On a positive note, the knowledge of heart disease has increased from 34 to 40% since 1997 and the knowledge of stroke has increased from 28 to 35%. Additional educational efforts are needed to improve the recognition of heart disease as an important health risk. These efforts are ongoing through many venues, ranging from the internet, books, magazines, television, and programs for school and religious groups.

Table 3. Key factors in the prevention of heart disease in women

Steps in Prevention of Heart Disease in Women
Increase awareness of disease
Lifestyle modifications
Pharmacologic modifications

Lifestyle modifications are important in the prevention of cardiovascular disease. These modifications include weight control, regular exercise and smoking cessation. Each of these modifications is as important as pharmacologic therapies yet is not practiced by a significant proportion of American women. In addition to their effectiveness in preventing cardiovascular disease, these lifestyle modifications are safe and extremely cost effective. They are also associated with a reduction in respiratory illnesses and cancers (smoking cessation) and a reduction in fractures (regular exercise).

In addition to lifestyle modifications, pharmacologic modifications offer hope in the attempt to prevent or reduce cardiovascular disease in women. Demonstration of efficacy may be difficult in women due to the low incidence of cardiovascular disease in women under the age of 55. Aspirin is effective in men over the age of 40 in preventing cardiovascular events. Data from the HOT (Hypertension Optimal Treatment) trial failed to demonstrate a benefit of aspirin therapy in the prevention of coronary events. This lack of benefit in women may be due to insufficient power or related to the dose of aspirin used (75mg/day). The Women's Health Study has recently been extended for an additional 3 years as no definitive answer regarding the use of aspirin in the prevention of

cardiovascular disease in women has been reached. While aspirin may be effective in preventing cardiovascular disease in women, the impact of aspirin for this indication in women is likely less than in men.

Table 4. Overall assessment of Aspirin, Statin Therapy, and Estrogen Replacement Therapy (ERT) for primary prevention of heart disease in women.

	Aspirin	**Statin**	**ERT**
Effectiveness	+/-	++	+/-
Safety	+/-	+	--
Cost	+	--	+

Lipid lowering therapy with statins has been demonstrated to be highly effective in reducing cardiac events and death in patients with preexisting coronary artery disease. Frequently, cholesterol is not effectively reduced to treatment goal. This "compliance" needs to be improved to successfully reduce cardiovascular events. In HERS, 91% of women did not meet the cholesterol treatment goal defined by NCEP II, the guidelines in place at the time of the study [51]. Myocardial infarction and revascularizations are also reduced in patients with hyperlipidemia treated with lovastatin enrolled in the AFCAPS/TexCAPS trial. The small proportion of women enrolled in this trial benefited from statin therapy but their overall event rate was much lower than men enrolled in the trial. The benefit of statin therapy may be related to a reduction in circulating lipid levels, plaque stabilization and regression, as well as to an altered inflammatory environment.

The costs associated with long-term statin therapy may be substantial. Highly-sensitive CRP may identify patients with normal cholesterol levels who will benefit from statin therapy. Use of strategies such as CRP may decrease the costs associated with statin therapy by selecting a high-risk population. Until more data concerning strategies for lipid treatment are available, clinicians should carefully evaluate the HDL and triglyceride levels as well as the LDL of women and be familiar with the National Cholesterol Education Program (NCEP III) guidelines.

Estrogen replacement therapy is historically associated with a reduction in cardiovascular events and mortality. Although estrogen replacement therapy is associated with a positive effect on lipid profiles, recent prospective clinical studies suggest ERT may have an adverse or neutral effect on cardiovascular outcome. The American Heart Association has now changed its guidelines to state that "women who have entered menopause should not start hormone replacement for the sole purpose of preventing heart disease." The mechanism for the adverse effects of ERT may be related to prothrombotic or proinflammatory effects of this therapy. Data from the Women's Health Initiative and other prospective clinical trials of ERT for primary prevention will be forthcoming in the next few years. In the meantime additional research is needed to explore the acute and chronic effects of estrogen on the vasculature.

Studies of pharmacologic therapy for the prevention of heart disease in women explore the impact of a single agent. A more important issue is how these agents interact

and whether or not a combination of therapies is beneficial or detrimental. No large studies have explored the issue of combination therapy yet physicians make the decision to combine them daily. Physicians will depend on the results of ongoing studies to make rational decisions on whether to use individual or combinations of these therapies.

References

1. NHLBI. Morbidity and mortality: 2000 chart book on cardiovascular, lung, and blood diseases. 2000:1-70.
2. Craven L. Experience with aspirin (acetylsalicylic acid) in the nonspecific prophylaxis of coronary thrombosis. Miss Valley Med J 1953; 75:38-44.
3. Vane J. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature New Biol 1971; 231:231-235.
4. Smith J, Willis A. Aspirin selectively inhibits prostaglandin production in human platelets. Nature New Biol 1971; 231:235-237.
5. Roth G, Stanford N, Majerus P. Acetylation of prostaglandin synthase by aspirin. Proc Natl Acad Sci 1975; 72:3073-3076.
6. Buerke M, Pittroff W, Meyer J, Darius H. Aspirin therapy: optimized platelet inhibition with different loading and maintenance doses. Am Heart J 1995; 130:465-472.
7. Peto R, Gray R, Collins R, et al. Randomized trial of prophylactic daily aspirin in British male doctors. British Medical Journal 1988; 296:317-320.
8. Steering Committee of the Physicians' Health Study Research Group. Final Report on the Aspirin Component of the Ongoing Physicians' Health Study. NEJM 1988; 321:129-135.
9. Manson J, Stampfer M, Colditz G, et al. A prospective study of aspirin use and primary prevention of cardiovascular disease in women. JAMA 1991; 266:521-527.
10. Hansson L, Zanchetti A, Carruthers S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998; 351:1755-1762.
11. Kjeldsen S, Kolloch R, Leonetti G, et al. Influence of gender and age on preventing cardiovascular disease by antihypertensive treatment and acetylsalicylic acid. The HOT study. J Hypertension 2000; 18:629-642.
12. Rexrode K, Lee I, Cook N, Hennekens C, Buring J. Baseline characteristics of participants in the Women's Health Study. J Womens Health Gend Based Med 2000; 9:19-27.
13. Feldman M, Jialal I, Devaraj S, Cryer B. Effects of low-dose aspirin on serum C-reactive protein and thromboxane B2 concentrations: A placebo-controlled study using a highly sensitive C-reaction protein assay. JACC 2001; 37:2036-2041.
14. Roest M, Banga J, Grobbee D, et al. Homozygosity for 807 T polymorphism in alpha(2) subunit of platelet alpha(2)beta(1) is associated with

increased risk of cardiovascular mortality in high-risk women. Circulation 2000; 102:1645-1650.
15. Reiner A, Schwartz S, Kuman P, et al. Platelet glycoprotein IIb polymorphism, traditional risk factors and non-fatal myocardial infarction in young women. Br J Haematol 2001; 112:632-636.
16. Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. Executive summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. JAMA 2001; 285:2486-2497.
17. Downs J, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998; 279:1615-22.
18. Scandinavian Simvastatin Survival Study (4S). Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the 4S. Lancet 1994; 344:1383-1389.
19. Sacks F, Pfeffer M, Moye L, et al. Cholesterol and Recurrent Events (CARE). The effect of pravastatin on coronary events after MI in patients with average cholesterol levels. NEJM 1996; 335:1001-1009.
20. The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. NEJM 1998; 339:1349-1357.
21. LaRosa J, He J, Vupputuri S. Effect of statins of risk of coronary disease--A meta-analysis of randomized controlled trials. JAMA 1999; 282:2340-2346.
22. Waters D, Higginson L, Gladstone P, et al. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography: The Canadian Coronary Atherosclerosis Intervention Trial. Circulation 1994; 89:959-968.
23. Pitt B, Mancini G, Ellis S, et al. Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I): Reduction in atherosclerosis progression and clinical events. JACC 1995; 26:1133-1139.
24. Blankenhorn D, Azen S, Kramsch D, et al. Coronary angiographic changes with lovastatin therapy: The Monitored Atherosclerosis Regression Study (MARS). Annals of Internal Medicine 1993; 119:969-976.
25. Herd J, Ballantyne C, Farmer J, et al. Influence of low HDL on progression of coronary artery disease and response to fluvastatin therapy. Circulation 1999; 99:736-743.
26. Goldman L, Weinstein M, Goldman P, Williams L. Cost-effectiveness of HMG-CoA reductase inhibition for primary and secondary prevention of coronary heart disease. JAMA 1991; 265:1145-1151.
27. Johannesson M, Jonsson B, Kjekshus J, Olsson A, Pedersen T, Wedel H. Cost effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. NEJM 1997; 336:332-336.

28. Ridker P, Cushman M, Stampfer M, Tracy R, Hennekens C. Inflammation, aspirin, and the risk of cardiovascular disease in apparently health men. NEJM 1997; 336:973-979.
29. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analysis. BMJ 2000; 321:199-204.
30. Ridker P, Henneken C, Buring J, Rifai N. C-reactive protein and other makers of inflammation in the prediction of cardiovascular disease in women. NEJM 2000; 342:836-842.
31. Ridker P, Rifai N, Pfeffer M, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. Circulation 1999; 100:230-235.
32. Ridker P, Ridai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. NEJM 2001; 344:1959-1965.
33. Shlipak M, Simon J, Vittinghoff E, et al. Estrogen and progestin, lipoprotein (a), and the risk of recurrent coronary heart disease events after menopause. JAMA 2000; 283:1845-52.
34. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factgors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. JAMA 1995; 273:199-207.
35. Mendelsohn M, Karas R. Mechanisms of disease: The protective effects of estrogen on the cardiovascular system. NEJM 1999; 340:1801-1811.
36. Nabulsi A, Folsom A, White A, et al. Association of hormone replacement therapy with various cardiovascular risk factors in postmenopausal women. The Atherosclerosis Risk in Communities Study Investigators. NEJM 1993; 328:1069.
37. Reis S, Gloth S, Blumenthal R, et al. Ethinyl estradiol acute attenuates abnormal coronary vasomotor responses to acetylcholine in postmenopausal women. Circulation 1994; 89:52.
38. Cushman M, Legault C, Barrett-Connor E, et al. Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. Circulation 1999; 100:717-722.
39. Grodstein F, Manson J, Colditz G, Willett W, Speizer F, Stempfer M. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Annals of Internal Medicine 2000; 133:933-41.
40. Grady D, Rubin S, Petitti D, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Annals of Internal Medicine 1992; 117:1016-1037.
41. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998; 280:605-613.
42. Grady D, Wenger N, Herrington D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and

Estrogen/progestin Replacement Study. Annals of Internal Medicine 2000; 132:689-696.
43. The Women's Health Initiative Study Group. Design of the Women's Health Initiative Clinical Trial and Observation Study. Controlled Clinical Trials 1998; 19:61-109.
44. Lenfant C. Statement from Claude Lenfant, MD, NHLBI Director, on preliminary trends in the Women's Health Initiative. NHLBI Communications Office. 2000.
45. Herrington D, Reboussin D, Brosnihan K, et al. Effects of estrogen replacement on the progression of coronary artery atherosclerosis. NEJM 2000; 343:522-529.
46. Angerer P, Stork S, Kothny W, Schmitt P, von Schacky C. Effect of oral postmenopausal hormone replacement on progression of atherosclerosis: a randomized, controlled trial. Arteriosclerosis, Thrombosis and Vascular Biology 2001; 21:262-268.
47. Alexander K, Newby L, Hellkamp A, et al. Initiation of hormone replacement therapy after acute myocardial infarction is associated with more cardiac events during follow-up. JACC 2001; 38:1-7.
48. Psaty B, Smith N, Lemaitre R, et al. Hormone replacement therapy, prothrombotic mutations, and the risk of incident non-fatal MI in postmenopausal women. JAMA 2001; 285:906-913.
49. Cannon R, Yang B, Ardans J, et al. Increased serum matrix metalloproteinase-9 expression in postmenopausal women on estrogen therapy. JACC 2000; 35:303A.
50. Robertson R. Women and cardiovascular disease: the risks of misperception and the need for action. Circulation 2001; 103:2318-2320.
51. Schrott H, Bittner V, Vittinghoff E, Herrington D, Hulley S. Adherence to National Cholesterol Education Program treatment goals in postmenopausal women with heart disease. The Heart and Estrogen/Progestin Replacement Study (HERS). The HERS Research Group. JAMA 1997; 277:1281-6.