

PRIMARY PREVENTION OF CORONARY ARTERY DISEASE

(Material prepared for ABIM MKSAP, 2003)

I) EPIDEMIOLOGY

Coronary Heart Disease (CAD) is the major health problem in the United States and other industrialized countries. Unfortunately, CAD is also an enormous and rapidly increasing disease in developing countries. Recent predictions estimate a steadily increasing prevalence in the developing world over the next 20 years, and in conjunction with stroke, cardiovascular disease is projected to soon become the leading cause of mortality worldwide, surpassing infections and health related mortality. It is estimated that 60 million Americans have cardiovascular disease (CVD), approximately 1/5 of the population. Over 1 million acute myocardial infarctions occur yearly, of which 1/3 are recurrent and almost 20-30% are manifest as sudden death. CVD is the largest cause of out of hospital death. The majority of CAD events occur in subjects over 65; the aging of the population in the United States and throughout the world heralds a continuing rise of CAD prevalence; although CAD mortality rates have been declining in the United States and in the Western countries over the past 30 years, the total burden of CAD is not declining due to the growth in numbers of older people. Long-term results of the Framingham Heart Study predict a lifetime risk of developing CAD at age 40 of 49% in men and 32% in women. At age 70, the lifetime risk is 35% for men and 24% for women. (REF.1).

It has been long recognized that a group of conditions or CAD risk factors increase the likelihood of CAD as well as cerebrovascular disease (Table 1-1 A). Furthermore, a number of risk factors are associated with CAD and may act as predisposing conditions. (Table 1-1 B). Many other putative risk factors have been identified (Table 1-1 C); these remain the subject of clinical investigation and ongoing epidemiologic research. Emerging important factors in the pathogenesis of atherosclerosis include inflammation, insulin resistance, and a variety of non-LDL cholesterol lipid moieties. Nevertheless, the classic CAD risk factors remain as major influences on an increased incidence and prevalence of CAD; while these do not entirely account for all clinical and fatal CAD events, prediction algorithms have repeatedly confirmed the usefulness of identifying and treating the traditional CAD risk factors. Importantly, clinical research studies have demonstrated that effective CAD factor reduction results in decreases in CAD morbidity and mortality. A recent report indicates that in young males under the age of 40, traditional CAD risk factors remain predictive of premature coronary events.

Newer concepts in primary prevention involve several developments since MKSAP 12. These include: (1) A broadening data base demonstrating that dyslipidemia is a crucial factor in CAD and that lipid lowering is beneficial in healthy subjects at increased risk for vascular disease (WESTERN SCOTLAND, AFCAPS-TEXCAPS, HEART PROTECTION STUDY). (2) Diabetes is now recognized as a lethal risk factor for both CAD and stroke; aggressive preventive therapy is mandatory for the Type II adult diabetic without overt vascular disease. (3) The use of hormone replacement to reduce atherosclerotic burden has been thrown into confusion by the negative results of secondary prevention trials of HRT in CAD and cerebrovascular disease (HERS, ERA, WEST) and with the premature cessation of the Women's Health Initiative, (July 2002), HRT is now precluded for use in primary and secondary vascular prevention (see below). (REF. 2) It is no longer appropriate to administer estrogen alone or in combination with progestins for the primary purpose of CAD prevention. (4) Antioxidant therapy with supplements of vitamin E, C, or beta carotene, has fallen into disrepute, although the oxidation hypothesis predisposing to atherosclerosis remains valid. Newer approaches utilizing different antioxidant regimens may still prove to be beneficial.

(5) Cigarette smoking remains the commonest cause of preventable illness in the United States. Approximately 25% of Americans smoke, with higher rates in women and young adults. Recent data confirms that smoking rates have decreased in high school students, from a high of 38% with 12th graders in 1997 to 30% in 2001. Eighth grade smoking is also down. Nicotine addiction and psychological dependence are the driving forces in smokers. Nicotine releases a variety of CNS components each with

neurochemical and psychological effects (eg. dopamine, norepinephrine, acetylcholine, B-endorphin, serotonin, vasopressin). Smoking induces an upregulation of nicotine receptors that do not immediately return to baseline after cessation. Passive exposure to tobacco smoke has been shown to have adverse consequences. Experts consider smoking to be a disease; effective therapy includes counseling (including “the 3 minute intervention”) and pharmacologic therapy. All physicians should routinely inquire about smoking patterns as well as initiate counseling for quitting and advising nicotine replacement therapy or bupropion (Zyban). Clinician delivered social support, staff training, and referral to a smoking cessation expert are recommended for all chronic smokers.

Increased attention is being focused on primary and secondary prevention of vascular disease. The yearly American Diabetes Association and the 2001 NCEP-ATP III guidelines have been widely publicized (Ref. 3,4). Although many pharmacologic therapies have been shown to be beneficial in preventing or slowing atherosclerosis, resulting in an enhanced commitment to prevention by physicians and healthcare professionals, far more needs to be done. Many studies indicate that patients who are candidates for specific preventive therapies are often not prescribed appropriate drugs or at the recommended dosage; furthermore, such therapy is commonly not maintained for even a year. (REF. 5,6) Furthermore, experience with cardiovascular pharmacotherapy has demonstrated a “treatment gap” among various medical specialties; for instance, cardiologists are more likely to prescribe RCT proven cardiovascular medications than internists, while family practice physician perform least well.

II) NEWER CORONARY ARTERY DISEASE RISK FACTORS

There is a long list of putative CAD risk factors that is constantly increasing. Traditional primary prevention recommendations emphasize the major established risk factors (Table 1-1 A) but this group itself may change as new evidence from basic and clinical research appears, as well as the publication of large RCT. For instance, diabetes mellitus and the metabolic syndrome are really not “new” risk factors but have recently been upgraded to a much higher level of vascular risk as more data accumulated. Table 1-1 C lists some of the newer CAD risk factor candidates. None of these have yet been conclusively proven to cause CAD or its progression, nor are they recommended at this time for routine screening approaches in a primary prevention setting.

INFLAMMATION AND C-REACTIVE PROTEIN (CRP):

Recent observations confirm that activation of CRP, related to systemic (and possibly localized) vascular inflammation, is related to the likelihood of future coronary events, increased morbidity and mortality in acute coronary syndromes, stroke, and carotid atherosclerosis as well as an adverse prognosis after percutaneous angioplasty. Some reports suggest that a high CRP in the absence of an elevated LDL-cholesterol is an adverse risk marker (REF 7). Other inflammatory markers, such as serum amyloid-A, fibrinogen, or interleukin-6, have an association with CAD, but current data do not support the use of these markers for screening purposes. It is quite likely that high sensitivity CRP assays will become increasingly utilized for primary prevention, especially in patients at intermediate CAD risk as a guide to determine initiation of pharmacologic therapy, e.g. a statin or ACE inhibitor in higher risk subjects. It is likely that the benefits of aspirin in prevention of CV disease are in part modulated by the drug’s anti-inflammatory activity. While, routine measurements of hs-CRP are not recommended, an expert panel has recently recommended _____. In January 2003, an expert panel recommended that determination of CRP levels are appropriate for individuals with an estimated Framingham risk score of _____. Very low risk subjects or patients at high risk (eg. diabetes, multiple risk factors) or those with established coronary, peripheral, or cerebrovascular disease, do not need CRP testing to establish targets for risk modification (Ref. 8). Support for an inflammatory component to the development and progression of atherosclerosis is robust.

LIPID MOIETIES:

It is no longer appropriate to simply measure total cholesterol, with or without an HDL-cholesterol, for CAD risk evaluation; total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides (TG) comprise the standard lipid profile. Other lipid subfractions remain the subject of considerable attention, especially Lp(a) and LDL particle size. While commercial measurements of these moieties are available, it is not recommended to routinely assess particle size or Lp(a) in the primary prevention setting. Laboratory

variation is considerable, assays are costly, and there is little to no positive randomized clinical trial data. LP(a) or lipoprotein “little a” is a lipid particle with structural similarity to plasminogen. It has long been a suspected risk factor that may enhance thrombotic activity. Niacin is the most effective drug to lower LP(a). In subjects with premature vascular disease and/or a strong family history, it may be reasonable to measure LP(a). Lowering-LDL cholesterol is the standard approach to subjects with elevated LDL-C and LP(a); niacin may be used for isolated LP(a) elevations.

LDL particle size measurements have long been a subject of controversy. Smaller LDL particles are denser, more atherogenic, and have a greater oxidation potential (Pattern B). Individuals with elevated triglycerides are most likely to have a preponderance of small LDL particles; larger, more buoyant LDL particles (pattern A), are believed to be less atherogenic. Nevertheless, although studies support an increased vascular risk with a preponderance of dense pattern B LDL cholesterol, specific therapy to alter the distribution of LDL particles are not available. Furthermore, vascular event risk reduction has not been definitively linked to a decrease in small LDL particles independent of lowering total LDL. Thus, most experts (1) do not recommend obtaining the relatively expensive LDL particle size assays, and (2) do not recommend treatment strategies directed at particle size. The goal in individuals preponderant pattern B should be to reduce total LDL cholesterol as low as possible.

Post-prandial measurements of TG, IDL and VLDL have also received attention as predictors of vascular disease, but cannot be recommended in routine clinical practice. It is generally accepted that an elevated TG is an independent risk factor and deserves treatment. However, if LDL-C is also increased, it should be the initial target of therapy (Ref. 4). The issue of hypertriglyceridemia has long been a subject of controversy; some recent studies suggest an independent increase in vascular risk in subjects with elevated TG. NCEP-ATP III has lowered the desirable range of triglyceride to <150 mg/dL and emphasizes that high TG may be a risk marker, associated with other atherogenic lipid moieties (Ref. 4).

HOMOCYSTEINE:

A large amount of epidemiologic data suggests a graded relationship between homocysteine (HC) levels and coronary vascular disease. Endothelial dysfunction and a proatherogenic state are consequences of an increased HC. Until ongoing randomized trials conclusively resolve the question of whether intervention with folic acid and B vitamins are beneficial, no definite recommendation for therapy can be made. Nevertheless, the apparent absence of an adverse effect of such therapy makes it reasonable to administer folic acid with B vitamins in selected high-risk subjects, especially those with renal disease or the elderly. Routine measurements of HC are not recommended. Preliminary data also suggests that an increased HC may be related to dementia and Alzheimer’s disease.

OTHER “NEW” RISK FACTORS

KIDNEY DISEASE:

It has recently been observed that mild renal insufficiency (creatinine >1.5 in women; > 2.0 in men) or a creatinine clearance of less than 70, are associated with increased CAD risk. Such minor abnormalities may be present in 5–10% of the population and may be associated with left ventricular hypertrophy even in the absence of hypertension. Diabetics represent 40% of this population and hypertensives approximately 30%. The HOT and HDFP studies indicate a 2-3 fold increase in cardiovascular mortality in the presence of an elevated creatinine that remains < 2.5mg/dl. An analysis of the HOPE trial indicates an increased risk of total and cardiovascular mortality, stroke, and MI in the presence of a creatinine of 1.4-2.3 mg/dl (REF 9). Furthermore, a separate analysis of HOPE data confirms that microalbuminuria is an independent risk factor for adverse CV outcomes in diabetics and non-diabetics (Ref. 10). Subjects with end stage renal disease have a 20-25% yearly CAD mortality. A recent study confirms increased mortality in acute MI patients with mild renal disease (Ref. 11). Preventive approaches include tight glycemic control in diabetics, as confirmed by the Diabetes Control and Complication trial (DCCT), and supported as suggested by many vascular biology studies. In DCCT nephropathy was reduced with more strict glycemic control, but CAD events (macro-vascular disease) were only non-significantly lowered. It remains unproven whether strict glycemic control in type II diabetics actually reduces the incidence of myocardial infarction or stroke, although a recent study is highly suggestive of this concept; thus, the UKPDS intensive

glucose control arm showed a decrease in all endpoints, including retinopathy, microalbuminuria, and a reduced loss of renal function. However, there was only a non-significant trend towards a decrease in myocardial infarction. ACE inhibitors (a) or angiotension receptor blockers have been shown to be beneficial in patients with renal abnormalities; two IR besartan trials and one losartan trial confirmed that angiotensin-II receptor antagonists lowered cardiovascular events in this population (Ref. 12-14). The role of statin therapy in this population is unclear, but is indicated in older diabetics with one other CAD risk factor (15). Aspirin seems reasonable for diabetics or subjects with 2 or more major CAD risk factors who have proteinuria or an elevated creatinine due to the significantly increased likelihood of a major CV event in these patients (Ref. 16).

INFECTIONS:

Although many reports suggest a relationship between CAD prevalence and prior viral and/or bacterial infections, available data do not support the prophylactic use of antibiotics to prevent or slow down the progression of CAD. Limited trial data to date has demonstrated mixed results; several large randomized clinical trials utilizing antibiotics are underway.

OXIDATIVE STRESS:

The role of oxidation due to free radical anions within the vasculature has been extensively investigated. Many atherogenic processes are activated or enhanced in the presence of oxidative stress. Importantly, nitric oxide availability is decreased in the setting of oxidative stress. Oxidation of LDL-cholesterol is a common and important mechanism in of atherosclerotic plaque formation and development.

The oxidative hypothesis has resulted in numerous trials of anti-oxidant agents, particularly vitamin E and C. Much basic and animal research data suggests that quenching of oxidative stress should be beneficial in slowing, reversing, or even preventing athero-thrombotic processes. Unfortunately, at least 4 major trials, encompassing a total of 46,000 subjects, randomized subjects with vascular disease or at high risk for CV events to placebo or an anti-oxidative regimen including vitamin E. Unfortunately, all trials were neutral, with no difference in outcomes between the vitamin cohorts and placebo. These studies, HOPE, GISSI-P, HPS (see below), represent a wide range of subjects in a very large data base. Thus, there currently is no indication for anti-oxidants, such as vitamin E or C, or beta carotene, for primary or secondary prevention of CAD.

III) ASPIRIN AND OTHER ANTIPLATELET AGENTS

The role of aspirin in primary prevention of CAD remains still a matter of some controversy. Recent publications have recommended consideration of low dose aspirin (<100mg/day) for intermediate to high-risk subjects without overt vascular disease, i.e. those with a 10-year likelihood of a cardiovascular event of $\geq 15\%$ (Ref. 16). Thus, in individuals with multiple risk factors, diabetics, or older subjects (men over 50, women over 60), with one or more other risk factors, it may be reasonable to recommended aspirin after careful discussion with the patient about the risk benefit ratio. Minor bleeding, mostly gastrointestinal, and a non-significant increase in hemorrhagic stroke have been adverse sequelae of regular aspirin administration; therefore, low risk subjects (<1-1.5% CV event rate/year) should not necessarily be advised to take aspirin for cardiovascular prevention. Individuals with an estimated risk between 10-15% over ten years require careful patient-physician dialogue. Unresolved issues remain, including the subject of aspirin resistance, the COX-2 inhibitor risk controversy, and a possible adverse aspirin-ACE inhibitor interaction. The optimal dose of aspirin is not known, but recent studies and a meta analysis conclude that low dose ($\leq 100\text{mg/d}$) is safer and just as effective as higher dose per aspirin. Not all experts agree that widespread aspirin administration is a wise approach.

Clopidogrel is an effective anti-platelet agent that has been proven beneficial in the therapy of acute coronary syndromes as well as during and following percutaneous coronary intervention. However, this drug is not appropriate in the primary prevention setting except in aspirin resistant or aspirin intolerant high risk subjects who qualify for aspirin therapy (eg. yearly CAD event risk of $>1.5\%$).

Agents that interfere only with the cyclo-oxygenase II pathway (COX-2 inhibitors) have recently been introduced for control of musculoskeletal pain and symptoms of arthritis. There are currently three available drugs; these agents have engendered enormous popularity and sales. However, an analysis of one data base that used non-comparable controls who received naproxin suggested an increase in CAD events,

specifically myocardial infarction, with the COX-2 inhibitor rofecib, (VIGOR) (17). A major and as yet unresolved controversy about the safety of the selective COX-2 inhibitors has broken out. The inference from the VIGOR study is that these new agents may provide less potent antiplatelet protection than aspirin, thus exposing high risk patients to a lesser degree of vascular protection obtainable from aspirin, which is a non-selective COX inhibitor. Aspirin, though its inhibitory effect on thromboxane production, is the gold standard; COX-2 inhibitors do not affect thromboxane, and thus could be less protective than aspirin. Furthermore, some have postulated an over production of thromboxane when ____ may occur when another COX-2 drug is used. Not all available data confirms the VIGOR results, and this issue remains unresolved (18). It is recommended, however, to use low dose aspirin concomitantly with a COX-2 inhibitor in individuals with a high risk profile for developing CAD.

IV) NCEP-ATP III GUIDELINES

The latest recommendations from the National Cholesterol Educational Program/Adult Treatment Panel III, first released in 2001, take a more aggressive approach to CAD risk assessment and modification in primary prevention populations than in the past. (Ref. 4). In particular is the concept that CAD risk equivalents (diabetes or subjects with more than two CAD risk factors in addition to elevated LDL cholesterol) lower the target threshold for LDL cholesterol (LDL-C) by lifestyle and/or pharmacologic therapy (Table 1-2). Diabetes, recently designated as a CAD risk equivalent, imparts a $\geq 20\%$ ten year likelihood of having a coronary event, which is the highest degree of risk in the new guidelines. The presence of two or more major risk factors requires calculation of short term or ten-year CAD event risk, as defined by the Framingham Scoring System. Table 1-3 displays the new NCEP ATP III algorithm relating to LDL-C goals, and emphasizes therapeutic lifestyle change as well as lipid drug therapy. Table 1-4 displays an example of the Framingham Risk Scoring system. Lifestyle modification includes a diet low in saturated fat (less than 7% daily caloric intake), decreased cholesterol intake ($< 200\text{mg/d}$), as well as augmented use of soluble fiber, plant stanols and sterols. Weight control and regular physical activity are important for all subjects at risk (Table 1-5). Lipid modifying drug therapy is initiated if target LDL-C goals are not reached with standard lifestyle changes. Drugs that can be used to lower LDL-C include all the available agents – statins, fibrates, bile acid sequestrants, and nicotinic acid, with choice of agent to be determined by the lipid profile and the target lipid goals.

The Heart Protection Study (HPS) has suggested an even more aggressive approach to high risk subjects, with consideration of a statin in all diabetics or treated hypertensives, over 55 years, irrespective of baseline LDL-C (Ref. 15, Table 1-5A, see below). The results of HPS suggest that many to all patients with a CAD risk equivalent, such as a diabetes or peripheral/cerebrovascular disease, should be given a statin. NCEP ATP III stresses that non-coronary vascular disease or type II diabetes are CAD risk equivalents, associated with $> 20\%$ 10-year likelihood of a coronary event, irrespective of baseline LDL-C, and comparable to documented CAD patients for risk modification decisions. Individual physician judgment is essential in these high-risk “normal” individuals.

V) LIPID RANDOMIZED CLINICAL TRIALS

A variety of large, high quality of lipid lowering RCT have appeared since the publication of 4S in 1994. These have repeatedly confirmed that statin therapy reduces adverse clinical events in dyslipidemic patients with and without coronary disease (Table 1-5). VA-HIT used a fibrate, gemfibrozil, in male patients with coronary disease, relatively normal LDL-C, low HDL-C and high triglycerides, a profile suggesting the metabolic syndrome. Primary prevention trials include Western Scotland, and TexCaps-AFCAPS, and many of the patients in the Heart Protection Study (HPS). These three statin trials enrolled a variety of healthy subjects at increased CAD risk; study results were all positive, confirming an important benefit with therapy to lower LDL-C. Western Scotland enrolled males with a markedly elevated LDL-C, whereas the Texas study involved relatively low risk subjects with decreased HDL-C and only moderate elevation of LDL-C. The Heart Protection Study utilized simvastatin in subjects with CAD or clinical atherosclerosis as well as a large number of diabetics with and without overt vascular disease. (REF 10, HPS). All patient groups, including the primary prevention cohorts, had a highly significant 24% risk reduction in major clinical endpoints, irrespective of baseline total cholesterol and LDL-C levels (Figure 1-1). Many of the patients in TexCaps and HPS did not meet the NCEP ATP III LDL-C cutpoints at baseline for drug treatment.

The new NCEP-ATP III lipid guidelines (Table 1-3) provide more restrictive LDL-C cutpoints for initiation of pharmacologic therapy than utilized in TexCaps or HPS. Thus, the clinician must make a judgment as to whom should receive pharmacologic lipid lowering in the primary prevention setting. Individuals with several CAD risk factors, diabetes (a CAD risk equivalent), or treated hypertension, who have a projected coronary event rate of greater than 2% per year, should be considered for a statin, irrespective of baseline lipid levels. HPS enrolled many subjects with baseline LDL-C < 130 mg/dl and even <100 mg/dl; these cohorts enjoyed the same relative risk reduction as those with higher LDL-C, although their actual event risk was less than those with an LDL-C > 130 mg/dL (Fig. 1-1).

VI) HYPERTENSION

High blood pressure remains one of the cardinal CAD risk factors. The majority of hypertensive Americans on treatment are not adequately controlled. Approximately 40-50 million Americans have hypertension; in the elderly, isolated systolic hypertension is ubiquitous. Three important recent concepts deserve emphasis: (1) Lower is better; (2) choice of anti-hypertensive drug class may have significant clinical implications; (3) elevated systolic pressure is now recognized as an important target for therapy, particularly in the elderly.

Blood pressure goals:

A recent observational report from the Framingham Offspring Study, as well as older randomized control trials (RCT) utilizing anti-hypertensive agents, strongly suggest that the lowest achievable blood pressure (without drug side effects) should be the treatment goal in hypertensive patients, particularly in high risk individuals with additional CAD risk factors, such as non-coronary vascular disease, diabetes, proteinuria, or evidence of LVH. The Framingham Offspring Study, a longterm followup of 6859 subjects, demonstrated that adverse clinical events are related to blood pressure cut points even within the normal range (Fig. 1-2). (Ref. 19) Thus, the lowest or optimal baseline blood pressure cohort (<120/80 mmHg) had the lowest event rate, and the highest, but still “normal” blood pressure group (high normal), had an increased incidence of coronary events over 10 years. In subjects >65 years of age, high normal blood pressure was associated with >2% per year CV event rate in men and was close to that in women. Furthermore, previous data from the HOT, SHEPS, and the UKPDS trials confirm that cohorts who achieve lower on-treatment blood pressure fare better than those with higher treated blood pressures.

The target or optimal blood pressure for healthy all individuals is <120-125/80-85 mmHg. Even lower goals are appropriate for high-risk hypertensive patients, such as diabetics and patients with overt proteinuria or an elevated creatinine, or those with documented vascular disease in the coronary, cerebral, or peripheral vascular disease. Much recent data confirms that an elevated pulse pressure or systolic pressure is more predictive of adverse outcomes than a high diastolic pressure. Blood pressure lowering in eligible individuals is mandated concomitant with therapy of all other modifiable CAD risk factors.

Lifestyle and Hypertension:

Lifestyle modifications play an important role in treatment of hypertension. Thus, weight loss (BMI > 25 and/or abdominal obesity), physical activity, moderation of alcohol intake, and reduction of sodium are critical elements of longterm blood pressure control. Maintenance of adequate potassium intake is important, particularly in subjects on diuretics. The DASH-sodium substudy confirmed the benefit of a low sodium diet plus the DASH diet of fresh fruit, vegetables, low fat dairy, whole grains, poultry, and fish (Ref. 20). Processed food, salty snack foods, and salting food at the table are the major sources of excessive sodium intake.

Choice of antihypertensive agent:

Diuretics and beta-blockers remain appropriate initial agents for the treatment of hypertension, as recommended by JNC V and VI. These recommendations are unlikely to be changed in JNC VII (not available at the time of this writing).

Important new data from the HOPE and LIFE trials suggest that an agent that interferes with the renin angiotensin system (angiotensin converting enzyme inhibitor or ACE-I; angiotensin II type 1 receptor blocker or ARB) are particularly effective in reducing clinical events in high risk subjects without overt vascular disease. The HOPE trial randomized subjects with vascular disease or diabetics over 55 years of

age with one other major CAD risk factor to ramipril or placebo (Refs. 9,10,21). There was a significant event reduction in the diabetics without clinical vascular disease, as well as in the majority of subjects in the HOPE trial who had CAD. These were not hypertensive subjects, however. The LIFE study demonstrated a lower clinical event rate over a mean of 4.8 years in hypertensive subjects with ECG-LVH who received losartan (vs. atenolol), in spite of comparable blood pressure lowering with the 2 agents (Ref. 22). (Fig. 1-3) In particular, stroke was reduced by 24% with the ARB. In the LIFE diabetic substudy, the advantages of the ARB were even more impressive (Ref. 15). Thus, it seems reasonable to include an ACE-I or ARB as part of the hypertension drug regimen in all higher risk hypertensives, such as those with diabetes, LVH, proteinuria, azotemia, or individuals with clinical or subclinical atherosclerotic vascular disease. In post-myocardial infarction patients with hypertension, congestive heart failure, or LV systolic dysfunction, an ACE-I is the preferred agent.

The very large ALLHAT study confirmed that a diuretic, CCB, or ACE inhibitor produced equivalent CAD event reduction; most subjects required at least 2 drugs. (Ref. 24) However, there was no special benefit with the ACE inhibitor lisinopril, even in diabetics. In the elderly subject with systolic hypertension, a diuretic, followed by a calcium channel blocker, are the preferred initial choices of therapy. ALLHAT demonstrated that the alpha-blocker doxazosin was associated with excess heart failure events than the diuretic chlorthalidone; this arm of the trial was stopped prematurely. ALLHAT also showed a somewhat lesser blood pressure lowering action, more than heart failure, and an increase in strokes in black subjects with the ACE-I lisinopril.

In summary, low dose diuretics should always be used, either as in the initiation of solo therapy in mild hypertension, or in conjunction with other anti-hypertensives, particularly beta adrenergic blockers, ACE-I and ARBS. Calcium channel blockers and/or a diuretic are the optimal agents to use in systolic hypertension of the elderly; stroke, more common than myocardial infarction in this important population, is particularly reduced by diuretics as well as dihydropyridine calcium antagonists.

Finally, physicians should anticipate that the majority of hypertensive patients will require 2-3 drugs to achieve adequate control. Once a day agents should be used whenever possible.

VII) THE METABOLIC SYNDROME

An important emerging focus of CAD risk is the individual with the metabolic syndrome (MS), usually associated with insulin resistance. MS is a variable complex of clinical and metabolic features, both lipid and non-lipid, that occurs in at least 20% of the United States population; its presence imparts an increased likelihood for CAD events. (Ref. 25, 26) In subjects over 60, the prevalence may be as high as 40%. The MS may or may not be associated with impaired glucose tolerance. Other names for the metabolic syndrome include The Deadly Quartet, The Dysmetabolic Syndrome, Reaven's Syndrome and Syndrome X. Many but not all such individuals have or will develop impaired glucose tolerance (IGT), and some will go on to overt diabetes mellitus. NCEP-ATP III has defined the metabolic syndrome and identified it as a high-risk state that warrants aggressive treatment to reduce the likelihood of subsequent CAD events (Ref. 4, Table 1-6). The metabolic syndrome is associated with a number of pathophysiologic phenomena (see Table 1-7), including an [•increased oxidative state]; [•increased free fatty acids]; [•increased glycosylation of cellular constituents]; [•insulin resistance; increased production of VLDL and triglycerides; a shift to small dense LDL and HDL particles; and elevated triglycerides and low HDL concentrations. In addition, there is often evidence of [•systemic inflammation], as indicated by increased CRP and interleukin-6 levels. An [•enhanced thrombotic state], manifest in part by elevated PAI-1 and fibrinogen levels, is common to MS.

One common hallmark of MS is the presence of visceral (male pattern) obesity, which is related to insulin resistance, increased free fatty acids, and atherogenesis. Abdominal or visceral obesity, a key marker for the metabolic syndrome, is even more predictive of this condition than an increased BMI. Elevated insulin and proinsulin levels, common in MS, are linked to subsequent CAD mortality, as well as the increased likelihood of development of type II diabetes. High CRP levels indicate a poor prognosis in MS. Certain ethnic minorities, such as Hispanics or African Americans, are particularly at risk of developing the metabolic syndrome. A recent study confirms the magnitude of enhanced CAD risk in subjects with MS using NCEP ATP III and who criteria (Ref. 26).

Therapy for the metabolic syndrome, as defined by the NCEP-ATP III, consists of initial treatment with a rigorous dietary approach (the Therapeutic Lifestyle Change Diet), as well as a substantial increase in physical activity (Table 1-4, Ref. 4). CAD risk factors in individuals with MS should be aggressively managed, including if necessary, pharmacologic therapy for dyslipidemia and hypertension if lifestyle or hygienic measures are not sufficient. Weight loss decreases insulin levels and as well as the generalized inflammatory state. Aspirin is indicated in the highest risk individuals. Many MS patients have the lipid triad of elevated triglycerides, low HDL-C, and small LDL particle size; this combination should initiate pharmacologic therapy if lifestyle changes are insufficient or unsuccessfully implemented. An elevated LDL-C, if present, should be targeted by drug therapy, usually with a statin. However, an increased LDL-C is not the commonest lipid pattern in MS. Use of the non-HDL cholesterol calculation is recommended by NCEP-AIII for those individuals with high triglycerides (>200mg/dl) with LDL-C at target level. Non-HDL cholesterol is computed by subtracting the patient's HDL-C concentration from the total cholesterol level; the treatment goal for non-HDL cholesterol is no higher than 30mg/dl greater than the individual's LDL-C goal per NCEP ATP III. Non-HDL cholesterol is considered by some as a better predictor of CAD than LDL-C. This measurement emphasizes atherogenic lipid particles over and above LDL-C, including IDL, VLDL remnants, triglycerides, and lipoprotein(a).

Pharmacologic agents that may be appropriate for patients with the metabolic syndrome include the fibrates, which are PPAR-alpha activators utilized for the MS dyslipidemia characterized by a low HDL-C and high triglycerides. The glitazones, which are PPAR-gamma activators used in diabetes, are not yet recommended for non-diabetics with MS, but may become a component of therapy in the future. Other useful agents include statins for elevated LDL-C; niacin, used with caution because of possible worsening glucose tolerance, for low HDL-high triglycerides; and an ACE inhibitor or ARB for those individuals with hypertension. These agents should be prescribed for an appropriate abnormality when a program of diet and exercise fails to induce the desired metabolic improvements. Careful and continued monitoring for the appearance of overt diabetes is indicated. Recent studies, including the Diabetes Prevention Program, indicate that weight loss and regular physical activity decrease the incidence of new diabetes (Ref. 27, Fig. 1-4).

VIII) ADULT ONSET TYPE II DIABETES

Diabetes has emerged as an enormous health burden in the United States and around the world over the past 10 – 20 years. It is estimated that 6 – 8% of the American population has diabetes, and millions of other individuals are prediabetic or do not know they have diabetes. Approximately 95% of all diabetics are Type II. Furthermore, it is well established that the majority of these individuals will die of cardiovascular disease (coronary artery disease, cerebrovascular disease, congestive heart failure), rather than from direct complications of diabetes itself. Based on a variety of observations, including the East-West and the Malmo Studies, it is generally accepted that the adult diabetic without overt CV disease has an equivalent risk of having a major coronary event as an individual with established CAD such as a prior MI. Furthermore, the likelihood of death or reinfarction in a diabetic with established atherosclerotic disease is 2 – 3 fold higher than that of a non-diabetic with a similar cardiovascular history. For these reasons, the American Diabetes Association, American Heart Association, and NCEP- ATP III have all categorized the Type II diabetic as a major CAD risk factor or CAD risk equivalent, i.e. treatment goals for risk factors should be at the same level as in the individual with established CV disease.

Table 1-8 highlights some of the established features associated with enhanced CAD risk in the diabetic (Ref. 29, 30). It is clear that diabetics have a greater burden of atherosclerosis and a more malignant course of vascular disease than the non-diabetic. Multiple pathophysiologic abnormalities have been identified in the diabetic, including dyslipidemia, an enhanced prothrombotic state, glycosylation of cellular components, endothelial dysfunction, and increased oxidative stress; these abnormalities should help to develop and guide therapy. Because of the aggressive nature of coronary, cerebrovascular, and peripheral vascular disease in the diabetic, management decisions must be at a heightened state in these individuals. Target treatment goals are equivalent to those in patients with established vascular disease. Older diabetics in the Cardiovascular Health Study had a high prevalence of subclinical cardiovascular disease, including an abnormal ankle-arm index; > 80% carotid intimal-medial thickness; carotid stenosis >25%; and major ECG abnormalities. These subjects had an increased all cause and CV disease mortality. (Ref. 28) Recent

data indicate that a significant gap exists between desirable or recommended diabetic therapies (glycemia, hypertension, lipids, eye, and foot examinations) and the care actually received. (Ref. 3)

MAJOR CAD RISK FACTORS IN THE DIABETIC PATIENT

Hypertension:

Approximately half of the adult diabetic population has hypertension, which is related in part to insulin resistance and obesity. Randomized clinical trials in diabetes indicate that a lower blood pressure is better; target blood pressure in diabetics is $\leq 130/80$ mmHg, or even lower (**check ADA**). Hypertension in the diabetic is often more difficult to control, and typically requires several drugs. Based on the HOPE, MICRO-HOPE, and LIFE trials as well as other data, an ACE inhibitor or angiotensin receptor blocker should be considered as a standard component of the anti-hypertensive regimen in these patients. (Ref. 10,21,23). However, in ALLHAT, the ACE inhibitor lisinopril did not preferentially benefit the large diabetic population (24). Any evidence of renal impairment, eg. microalbuminuria, proteinuria, or elevated creatine, should initiate treatment with an ACE inhibitor or an ARB. A diuretic is an alternative first choice for blood pressure lowering, and certainly should be the second drug used.

Dyslipidemia:

Lipid profiles in the diabetic are similar to those in the metabolic syndrome-insulin resistant patient: increased triglycerides, low HDL-C, and normal to moderately elevated LDL-C. Moreover, LDL-C particles are small and dense (pattern B). Post-prandial increases in VLDL and triglycerides are common, and probably contribute to the atherosclerotic burden. If LDL-C is elevated, it should be targeted first, usually with a statin. However, in patients with the more typical diabetic lipid triad a fibrate or niacin is indicated. VA-HIT confirmed a significant cardiovascular benefit with gemfibrozil in older male subjects with CAD disease (Ref. 31). Many individuals in that trial had the metabolic syndrome or diabetes mellitus. Gemfibrozil and fenofibrate work through PPAR-alpha pathways; these drugs activate nuclear transcription factors and trigger multiple intracellular mechanisms that may be beneficial in atherosclerosis and inflammation. Niaspan, a long acting niacin preparation, has been shown to be relatively safe in the diabetic, with careful initiation at low doses along with frequent blood sugar and hemoglobin A1C monitoring.

In the Heart Protection Study, 4000 diabetics were enrolled who did not have a clinical diagnosis of vascular disease (Ref. 15, Fig. 1). These individuals had a comparable relative risk reduction of major CV events with simvastatin as did subjects with vascular disease, irrespective of baseline LDL-C levels. Thus, all type II diabetes should be considered candidates for a statin.

Glycemic control:

Much data, including UKPDS report, suggest that optimal blood glucose levels in the diabetic are associated with improved outcomes. Thus, hypoglycemic agents should be aggressively used to bring HgbA1C to 7 or less. Insulin-sensitizing drugs should be included in the regimen, particularly if there is obesity and/or evidence of the metabolic syndrome.

Lifestyle:

Virtually all experts agree that lifestyle modification is the first preventive approach to the diabetic; vigorous efforts in this regard should be sustained. The recent Diabetes Prevention Program study demonstrated that weight loss and regular physical activity are instrumental in preventing the onset of new diabetes (see also sections VII and X). (Ref. 27).

High risk subjects who participated in the lifestyle-modification group goal of at least 7% weight loss and 150 minutes of physical activity per week reduced the incidence of new diabetes by 58% vs. the placebo group (Fig. 1-4). Metformin also decreased the number of new diabetics, but to a lesser degree than diet and exercise.

In a 16-year follow-up of the Nurses' Health Study, overweight or obesity at baseline was the best predictor of subsequent diabetes; a poor diet, cigarette smoking, and lack of exercise are other important factors associated with new onset diabetes (Ref. 32). Conversely a low BMI; a diet high in fiber and polyunsaturated (and low in trans fat) and glycemic load; regular exercise; no smoking; and daily alcohol

reduced the likelihood of new diabetes. The Physicians Health Study found similar results in the incidence of new diabetes related to a healthy vs. poor quality diet (Ref. 33) (see below).

A New Paradigm?

New randomized trial data suggest that an ACE inhibitor and a statin should be an imperative in the diabetic. The MICRO-HOPE study enrolled 3,577 diabetics over 55 years with at least one major risk factor, many without overt vascular disease, and demonstrated that in this cohort (as well as in diabetics with known vascular disease), ramipril resulted in a significant decrease in major events during the trial (Fig. 1-5) (Ref. 10). The LIFE trial demonstrated that losartan, an ARB, was clinically superior to a beta-blocker in hypertensive diabetics with LVH, in spite of equivalent blood pressure control. (Ref. 22) The more recent Heart Protection Study (HPS) enrolled thousands of diabetics without vascular disease and compared simvastatin to placebo (Ref. 15, Fig. 1). Baseline lipid cutpoints were not utilized for initiation of therapy. Significant benefit was found in the diabetics who received the statin. Thus, physicians should consider using these drugs in adult onset diabetics in the absence of clinical vascular disease. This is particularly true in the diabetic with additional major risk factors, such as a smoking history, hypertension, renal abnormalities, or significant dyslipidemia. Of note, however, is the finding that lisinopril demonstrated no advantage over chlorthalidone in hypertensive diabetics enrolled in ALLHAT. It is conceivable that the degree of vascular risk reduction produced by all 3 of the antihypertensive study drugs used in ALLHAT (chlorthalidone, amlodipine, lisinopril) may have masked the putative benefits suggested by the HOPE study for ACE inhibitors in the diabetic. Furthermore, lisinopril did not control the blood pressure as effectively as the diuretic or calcium antagonist. Aspirin at a dose of <100 mg/day has recently been recommended as standard therapy in higher risk diabetics in concert with careful physician counseling.

The concept that an ACE inhibitor, statin, and aspirin should be standard components of the therapeutic regimen in the diabetic represents a new and aggressive approach to perhaps the most lethal CAD risk factor.

IX) DIET AND OBESITY

The problem of society being increasingly overweight and obese has been widely popularized. It is estimated that 50-60% or more of the United States public is overweight, of whom 23% are obese. This is a particular problem in ethnic minorities, including African Americans, Native Americans, and Hispanics. Obesity and overweight are increasing rapidly in children and adolescents. Young obese men (but apparently not women), experience early atherosclerosis in proportion to their obesity status. Early childhood or adolescent overweight status predicts adult obesity. The reasons for the nation's increasing body weight is not entirely clear; it is likely related both to increased energy intake and a decrease in total energy expenditure. The specific definition of overweight is a BMI of 25-30 (weight (Kg)/height m²); obesity is diagnosed when the BMI is greater than 30. Marked obesity is a BMI of 35-40; such individuals may be candidates for gastric reduction surgery. BMI is significantly correlated with total body fat, although abdominal obesity correlates better with the metabolic syndrome than BMI. Both overweight and obese individuals are at a substantially increased risk for cardiovascular disease, including CAD, stroke, and heart failure. Recent data from the Framingham Heart Study confirms that obesity is associated with premature death and large decreases in life expectancy; obesity and smoking result in even worse survival outcomes (Ref. 34) In addition, other CAD risk factors, such as hypertension, dyslipidemia, insulin resistance, and diabetes cluster in overweight individuals, contributing to the increased cardiovascular risk.

Most experts agree that it is difficult to sustain weight loss without both lifestyle dietary changes as well as regular physical activity. It is widely accepted that in addition to a diet that results in a weight loss of approximately 1-2 lbs. per week for at least 6 months, regular physical activity should be a part of the lifestyle program for overweight individuals. Exercise duration should be a minimum of 25-30 minutes per day of moderate exertion, 5-7 days a week (See below). A reduction of total caloric intake, saturated and total fat, is indicated in overweight individuals; behavioral therapy is often utilized as well.

Weight loss has been the subject of many randomized trials and expert panels, typically, recommending both lifestyle as well as pharmacologic therapy. The aggregate results of weight loss data confirm

reductions in blood pressure, improvement in dyslipidemia, reduction in glucose and hemoglobin A1C levels, as well as decreased BMI and abdominal obesity. Abdominal circumference should be measured in all adult men and women who are overweight, in addition to calculation of BMI. NCEP-ATP III defines a waist circumference (at the iliac crest) of >40 inches in men and >35 inches in women as consistent with the metabolic syndrome; thus, this simple measurement identifies those at increased risk.

Healthy lifestyle and primary prevention:

In a recent report from the Nurses Health Study, a 16 year follow up of more than 84,000 women, five CAD risk factors were identified to predict CV disease in women who were healthy at baseline (Ref. 35). Most of these risk factors are related to lifestyle habits: type of diet, BMI, smoking, and physical activity. The other major risk factor identified in this long-term prospective observational study was alcohol consumption. At the lowest quintile of all 5 risk factor there was an 83% decrease of cardiovascular events. The authors concluded that 90% of attributable risk of subsequent CAD was related to environmental or lifestyle factors, such as diet and body weight. It is now known that the development of diabetes can be influenced by diet. Thus, in the Diabetes Prevention Program, individuals randomized to intensive lifestyle intervention over a three year period had a 80% decrease likelihood of developing diabetes compared to usual lifestyle (Ref. 27). The intensive intervention group had a goal of a 7% weight loss, produced by a low calorie, low fat diet, and a physical activity level of more than 150 minutes per week. The Physicians Health Study reported similar results (see below). (Ref. 33)

Weight reduction and physical activity are also mainstays of treatment of the metabolic syndrome; many such patients are at an increased cardiovascular risk. The present guidelines for an appropriate heart healthy diet is based on consensus panels, including NCEP-ATP III, and other sources. In the Physicians Health Study, a “prudent diet” (fruits and vegetables, fish, poultry, and whole grains) was compared to the “western pattern”, characterized by a high consumption of processed and red meat, high fat dairy, French-fries, sweets, deserts, and refined grains (Ref. 33) The prudent diet was associated with a decreased risk of the development of diabetes, compared to the western diet, which had an increased risk ratio of new diabetes of 1.6.

The NCEP ATP III Therapeutic Lifestyle Change (TLC) diet is shown in table 1-4. It emphasizes a low intake of total saturated fat, and cholesterol and trans fatty acids; total fat should range between 25-35% of total calories. The American Heart Association and other organizations emphasize a decrease in total intake of fats to less than 30% of total calories, or 70-100 grams per day, depending on body size. Very low fat diets, advocated by some, are defined by a total fat intake of less than 15% of total calories, with 70% from carbohydrates and protein. A recent overview of recommended diet programs and their components may be useful to the reader (36) Other diets that are advocated for cardiac health include a Mediterranean-type Diet, an important component of the Lyon Heart Study, which demonstrated a major improvement of cardiac survival in patients who consumed a diet high in fruit, vegetables, and omega-3 fatty acids, but low in saturated fatty acids and enriched in mono and polyunsaturated fatty acids as well as soluble fiber. Recent and older studies confirm major CAD event benefits, including a reduction in sudden death, with regular fish as well as fish oil consumption (Ref. 37).

X) PHYSICAL ACTIVITY

(see also sections VII and VIII)

Regular exercise has been shown to be of benefit in decreasing CAD risk as well as improving the CAD risk factor profile. Exercise is part of the lifestyle changes that are important in the metabolic syndrome, preventing new onset diabetes in at-risk individuals, reducing blood pressure, promoting and maintaining weight loss, with modest effects on lipid profile. Furthermore, the literature strongly suggests an inverse relationship between the degree of physical activity and all cause mortality, not only cardiovascular mortality and morbidity. The PRIME 5-year observational study in 9,800 men, demonstrated that higher levels of leisure time and physical activity are associated with decreased CAD events (Ref. 38). Sudden death is inversely related to regular moderate to vigorous exercise in many reports, including the Physician’s Health Study (Ref. 39); however, a small proportion of sudden deaths occur during vigorous exercise. Weight loss is easier to maintain with regular exercise; physical activity is an important component of reducing and maintaining desirable body weight. The

Diabetes Prevention Program trial demonstrated that the incidence of new diabetes is inversely related to regular exercise as well as weight loss (27).

While the precise amount or “dose” of physical activity that results in favorable outcomes is not completely clear, and is probably variable from subject to subject, it is generally recommended that all individuals engage in moderate exertion on a regular basis, either daily or on most days. This includes brisk walking, cycling, or swimming, as well as other activities. There is a dose response relationship between the intensity and frequency of regular exercise and the reduction in cardiovascular events as well as sudden death. Regular physical activity reduces CAD events independent from its effect on CAD risk factors; more is better, with less events occurring in more vigorous subjects. It is estimated that CAD events may be two-fold higher in sedentary individuals than in those who are active.

XI) HORMONE REPLACEMENT

Estrogen has a variety of favorable effects on the vasculature, including endothelial-dependant vasodilation; inhibition of inflammation, platelet aggregation, and smooth muscle hyperplasia; hepatic liprotein modulation; and anti-atherosclerotic effects in animal models. The presumed beneficial role of HRT in preventing or slowing the onset of clinical CAD or cerebrovascular disease had been widely accepted. The role of estrogen or the combination of estrogen and progestin (HRT) for the prevention of cardiovascular disease in women became highly questionable following the publication of the HERS (1998) and ERA (2000) trials. These two studies, carried out in older postmenopausal women with established CAD, found no benefit for hormone replacement (HRT). In fact, HERS demonstrated an adverse clinical outcome in the estrogen-progestin arm during the first two years of the trial. Thus, in spite of many large observational reports that suggested a primary prevention benefit for HRT in reducing clinical CAD or stroke, the usefulness of estrogens for vascular protection was thrown into confusion.

Until recently, there were no prospective data in a primary prevention population to confirm or exclude a benefit of HRT on future manifestations of CAD or stroke. A 2001 American Heart Association Science Advisory for Health Care Professionals concludes that “There are insufficient data to suggest that HRT should be initiated for the sole purpose of primary prevention of cardiovascular disease. Initiation and continuation ... should be based on established non-coronary benefits and risks...” (Ref. 40). Furthermore, in July 2002, the Women’s Health Initiative RCT of estrogen and progesterone was abruptly terminated due to an increased risk of invasive breast cancer and a composite index of several condition (including stroke, pulmonary embolus, total cardiovascular disease) which demonstrated an adverse risk benefit hazard ration. This study was comprised of 16,608 healthy postmenopausal women aged 50-79, followed for a mean of 5.2 years (planned duration of 8 years. (REF. 2) Thus, HRT can no longer be recommended for primary (or secondary) prevention of CAD. Hormone replacement is only appropriate for specific and bothersome post-menopausal symptoms.

MKSAP CASE

A 46 year old male requests consultation for a “high cholesterol”. Recent lab values include TC 268, LDL-C 179, HDL-C/28, Th 320. FBG is 120. He smokes 1 ½ packs per day. He is sedentary Physical exam, moderately overweight with abdominal obesity, BP is 150/95. BMI 27.

This man has a significant burden of CV risk with a Framingham 10 year risk score of 11%. He meets criteria for the metabolic syndrome; NCEP ATP III identifies his LDL-C target goal of <130 mg/dl. While an appropriate TLC diet and an exercise program is recommended, these measures may not adequately control his dyslipidemia. Pharmacotherapy is likely to be indicated. A statin will lower his LDL-C to target, but HDL may not increase. Niacin would be an appropriate choice, with or without a statin, but could precipitate overt diabetes as he has impaired glucose tolerance; a fibrate is unlikely to completely normalize the lipid profile. Consideration of aspirin therapy is appropriate. An ACE inhibitor should be considered for hypertension and vascular protection, although he does not meet the HOPE study criteria. Conversely, chlorthalidone is a low cost initial choice (ALLHAT). Vigorous effects at smoking cessation are indicated (see section I-5).

MKSAP CASE

A 53 year old post-menopausal Hispanic woman presents with recurrent RUQ discomfort, often exacerbated by meals. She does not smoke. Her examination is unremarkable except for hypertension (180/109) and being considerably overweight (180 lbs, 5'5" tall) with abdominal obesity (waist circumference 36"). Abdominal ultrasound confirms several small gallstones. Lab: BUN, creatinine normal. FBS 118 mg/dl. TC 226, LDL-C 126, HDL-C 34, TG 233.

This seemingly healthy woman is at relatively high cardiovascular risk. In addition to several individual CAD risk factors (hypertension, impaired glucose tolerance, obesity) she meets criteria for the metabolic syndrome (see table 1-6). Her calculated BMI is 30 kg/m². Her Framingham 10 year risk is 16%.

Preventive therapy must focus on her increased weight, sedentary lifestyle, elevated blood pressure, and dyslipidemia. The TLC diet and a regular walking program 5 day/week should be prescribed (Table 1-5). NCEP-ATP III guidelines indicate that her target LDL-C is <130mg/dl; for non-HDL-C it is <100 mg/d (Table 1-3). Her triglyceride goal is <150 mg/dl.

If lifestyle therapy (diet, exercise) do not result in lipid levels at the target level, drug therapy is indicated (statin, fibrate, or niacin). Careful follow-up of fasting blood glucose and HgbA1C is important if a niacin preparation is chosen. An ACE inhibitor or chlorthalidone are indicated for her hypertension regimen.