BEHAVIORAL ISSUES IN THE EFFICACY VERSUS EFFECTIVENESS OF PHARMACOLOGIC AGENTS IN THE PREVENTION OF CARDIOVASCULAR DISEASE

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ABSTRACT

A number of pharmacologic interventions are now recommended for the prevention of cardiovascular disease, based on the results of randomized controlled trials. These include antihypertensive drugs, lipid-lowering agents, antiplatelet and anticoagulant drugs, estrogen replacement therapy, beta-blockers, and angiotensin converting enzyme (ACE) inhibitors. It is likely that additional pharmacologic interactions will soon be proven efficacious. Despite the strength of this evidence and the development of clinical guidelines incorporating their use, a surprisingly low proportion of patients are actively treated with these agents. There may be a variety of explanations for this, including barriers at the level of the patient, health care provider, and health care institution. Finally, a number of questions remain as to the optimal combination of interventions, both behavioral and pharmacologic, which will yield maximal reduction in risk. The description of factors which reduce the effectiveness of pharmacologic interventions below the efficacy demonstrated in randomized clinical trials should be a fertile area for epidemiologic and behavioral research.

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OVERVIEW OF DRUG THERAPIES FOR THE PREVENTION OF CARDIOVASCULAR DISEASES

A large number of pharmacologic agents have been used in the acute and chronic management of cardiovascular disease (CVD), but the number of agents proven to be efficacious in the prevention of CVD is much smaller. However, recent guidelines for the comprehensive reduction of risk in patients with vascular disease have identified a number of pharmacologic interventions which should be included in a program of optimal care, along with a number of behavioral modifications (1). Since the behavioral issues regarding side effects, costs, and compliance are distinctly different for agents used for prevention rather than for treatment of acute or recurrent symptoms, this article will limit its discussion to those pharmacologic interventions with proven efficacy in either primary or secondary prevention. First, the evidence supporting the estimated efficacy of these agents will be presented. Second, estimates of efficacy will be compared with estimates of the extent to which these agents are currently used in actual practice. As documented in Table 1 for drugs used in the secondary prevention of coronary artery disease, the level of efficacy as shown in randomized clinical trials and other studies bears little relationship to the extent to which the agents are used in practice. Possible reasons for these apparent deficiencies in care, likely due to a variety of behavioral factors at the levels of the patient, physician, and health care system (4), will be presented. Third, the discussion will focus on issues related to the implementation of these pharmacologic interventions into a comprehensive program of cardiovascular risk reduction.

PHARMACOLOGIC AGENTS WITH PROVEN EFFICACY FOR CVD PREVENTION

Antihypertensive Agents

A number of interventions, both behavioral and pharmacologic, have been developed to lower blood pressure with the hope that they will prevent the anatomic sequelae of hypertension, such as left ventricular hypertrophy (LVH), and clinical sequelae, such as coronary, cerebral, and renal vascular disease (Table 2). Several different classes of drugs are currently in widespread use as antihypertensive agents (Table 2) (5).

Numerous randomized clinical trials have demonstrated that pharmacologic treatment of hypertension reduces cardiovascular events (6,7). The risk reduction for stroke has consistently been greater than for coronary events. In a meta-analysis of 14 studies, an average 5–6 mm reduction in diastolic blood pressure was associated with approximately a 40% reduction in stroke risk but only a 15% reduction in coronary heart disease risk (6). Recent studies have demonstrated the benefits of lowering blood pressure in older adults and in those with only systolic hypertension (8–10). In the Systolic Hypertension in the Elderly Program (SHEP), reduction of isolated systolic hypertension in older individuals was associated with a 36% risk reduction for stroke with no significant increase in side effects, dementia, or depression (8).

The relative benefits of various antihypertensive agents have not been extensively studied. The evidence for reduction in coronary heart disease and stroke comes primarily from studies using diuretics and/or beta-blockers (6,9). No strong evidence exists for differences in efficacy between these agents (9). Efficacy of newer agents such as calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors has not been demonstrated in large-scale trials, although the degree of blood pressure reduction that these produce is similar to older agents. There is also no clear advantage in terms of tolerance or compliance for any specific antihypertensive agent, although differences exist in individual patients and in certain clinical subgroups. Recent reviews have therefore concluded that diuretics or beta-blockers should be the first-line agents (9,11). In specific patients, clinical considerations may make other drugs more appropriate.

Antihypertensive treatment has been found to be cost-effective in several analyses (12,13), but the cost per quality-

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TABLE 1

Pharmacologic Agents Used to Prevent Recurrence and Death in Patients Surviving Acute Myocardial Infarction: Efficacy and Estimated Frequency of Use

Pharmacologic Agent	Estimated Reduction in Risk (%)*	Estimated Frequency of Use**
Aspirin	25	70%
Beta-blocker	22	40%
Calcium channel blocker	0	60%
Cholesterol-lowering drug	25–40	30%
ACE inhibitor (for LVEF <40%)	40	60%
Estrogen replacement therapy (in postmenopausal women)	30–70	20%

* Reference 2.
** Reference 3.

TABLE 2

Responses to Therapy in Hypertensive Subjects*

	Morbid Events	Blood Pressure	LVH
Weight loss	?	↓	?
Salt restriction	?	↓	?
Exercise	?	↓	?↑
Diuretic drugs	↓	↓	↓
Beta-blockers	↓	↓	↓
ACE inhibitors	?	↓	↓
Calcium antagonists	?	↓	↓
Alpha-blockers	?	↓	?

Note: ACE = angiotensin-converting enzyme; LVH = left ventricular hypertrophy; ↓ = decrease; ↑ = increase.
* Reference 5.

adjusted life year varies depending on the model assumptions and the drugs used. The cost-effectiveness ratio is favorable at all ages, but particularly for older adults. In 1990, Littenberg and colleagues (13) found that screening for hypertension is also cost-effective, with the cost-effectiveness ratio again most favorable in older individuals. In a recent update to that analysis, Littenberg took into account the increased costs of antihypertensive treatment since the original report. He concluded that screening for hypertension remains cost-effective for adults over age 45. The cost-effectiveness was strongly influenced by the cost of the drug used to treat hypertension, and he endorsed recommendations to start with diuretics or beta-blockers in most cases (14).

Steady improvements in the level of awareness, treatment, and control of hypertension have been demonstrated (Table 3) (11). However, if 140/90 mmHg is taken as the definition of hypertension, only half of known hypertensives are receiving treatment, and only one-fifth are controlled. The main reason for inadequate control is poor adherence to long-term treatment. Poor adherence, in turn, is the result of a number of causes due to the patient, the disease, the medication, and the health care provider. These causes include: the cost of medication, unclear instructions or instructions given in non-written form, inadequate or no patient education, lack of involvement of the patient in the treatment plan, side effects of the medication (e.g. sexual dysfunction, reduced mental acuity), inconvenient dosing, and memory deficit due to organic brain syndromes.

A variety of studies have demonstrated the ability of behavioral interventions to improve adherence to treatment with subsequent improvements in blood pressure control and reductions in

TABLE 3

Hypertension* Awareness, Treatment, and Control Rates

	1971–72†	1974–75†	1976–80‡	1988–91‡
Aware: Percentage of hypertensives told by physician	51	64	(54) 73	(65) 84
Treated: Percentage of hypertensives on medication	36	34	(33) 56	(49) 75
Controlled: Percentage of hypertensives with blood pressure <160/95 mmHg on one occasion measurement and reported currently taking antihypertensive medications	16	20	(11) 34	(21) 55

Note: Numbers in ( ) are percentage at 140/90 mmHg.
* Defined as ≥160/95 mmHg on one occasion measurement or reported currently taking antihypertensive medication.
Source: Fifth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (11).

TABLE 4

First-Line Drug Therapy for Patients with Various Lipid Abnormalities

Lipid Abnormality			First-Line Drug Therapy			
High LDL-C	Low HDL-C	High TG	BAB Resin*	Niacin	Statin**	Fibrate
+	−	−	+	+	+	−
+	+	−	−	+	+	−
+	+/−	+	−	+	+	+
−	+/−	+	−	+	−	+
−	+	−	−	?+	−	?+

* BAB Resin = Bile-Acid Binding Resin.
** Statins = HMG-CoA reductase inhibitors.

the morbidity and mortality related to elevated blood pressure (15–17). The strategies to reduce non-adherence to antihypertensive drugs include: educating the patient about hypertension and antihypertensive therapy, involving the patient in treatment decisions, individualizing the regimen to ensure it is as simple as possible with minimized side effects and costs, and providing reinforcement with feedback on levels of blood pressure and efforts to control it (11,18,19). The wide range of antihypertensive agents currently available allows the physician the opportunity to tailor the selection of the antihypertensive agent to the patient's schedule, finances, and ability to tolerate side effects.

Lipid-Modifying Agents

Several classes of drugs are in current use for the treatment of lipid disorders, with indications for use dependent on the level of low-density lipoprotein (LDL) cholesterol and number of other risk factors present (20). In practical terms, the four classes of lipid-lowering drugs [bile-acid binding resins, niacin, hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors, fibrates] differ in their usefulness depending on the lipid abnormality present (Table 4).

An extensive array of randomized clinical trials have demonstrated the efficacy of lipid-modifying agents in reducing CVD and even stopping the progression of the underlying atherosclerotic disease process. Early clinical trials of first generation lipid-modifying agents, including bile-acid binding resins, niacin, and fibric acid derivatives, demonstrated the ability of these agents to reduce coronary events, both fatal and non-fatal, in both primary

and secondary prevention (21). However, these early studies, using agents which included clofibrate, high-dose estrogens (in men), and dextrothyroxine, did not demonstrate any reduction in total mortality and, in some analyses, even showed an increase. This lack of benefit appeared to be due in large part to an excess of non-cardiovascular mortality due to agents no longer in current clinical use.

Several recent studies using ever more powerful agents, such as the HMG-CoA reductase inhibitors, have clarified the role of lipid modification. First, several studies have demonstrated that LDL cholesterol lowering results in reestablishing normal endothelial function (22–24). This is the presumed mechanism for reduced cardiac ischemia observed in patients receiving these drugs, even over relatively short time intervals (25,26). Second, studies using serial angiography have tested a variety of lipid-modifying strategies to confirm that the progression of coronary stenoses can be slowed or even reversed. These studies showed a 22% to 89% reduction in coronary events despite relatively small changes in coronary stenoses (27). These include a demonstration of ability to prevent stenoses in saphenous vein bypass grafts (28). Third, a large number of both large and small randomized trials have examined the effects of HMG-CoA reductase inhibitors in groups of patients with and without preexisting coronary disease (5). One of the largest of these was the Scandinavian Simvastatin Survival Study of 4,444 men and women with hypercholesterolemia and histories of myocardial infarction (MI) and/or angina (29). After six years, those randomized to 20–40 mg per day of simvastatin showed a 42% reduction in coronary deaths, a 34% reduction in all cardiac events, a significant (30%) reduction in stroke, and a highly significant reduction in total mortality. The Cholesterol and Recent Events Study, in which pravastatin was given to myocardial infarction survivors with total cholesterol levels <240 mg/dl (6.1 mmol/L), showed similar results, especially in those with baseline LDL cholesterol levels >125 mg/dl (30). Finally, a large primary prevention study, the West of Scotland Study, examined the benefits of pravastatin (40 mg each evening) in 6,595 men without prior infarction (31). Coronary events were significantly reduced by 31% over a six-year period with a 22% reduction in total mortality ($p = .051$). This is the first primary prevention trial to show a benefit in terms of total mortality reduction.

Finally, a number of cost-effectiveness analyses have examined lipid-modifying agents (32). In general, treatment of persons with high levels of serum LDL cholesterol has been shown to be cost-effective in high-risk patients, such as those with preexisting coronary disease. Treatment of low-risk patients with expensive therapy has not been shown to have a favorable cost–benefit ratio.

Despite the unquestioned efficacy and cost-effectiveness of lipid-modifying drugs for appropriate patients, the number of patients with apparently clear indications for treatment who are, in fact, receiving treatment is surprisingly low (33). For example, no more than 30% of myocardial infarction survivors are receiving these agents (3,34). Fewer still have achieved their goals as established by the National Cholesterol Education Program Adult Treatment Panel II (35). Therefore, lack of treatment and undertreatment have emerged as major problems in realizing the benefits documented in clinical trials.

In addition to physician undertreatment with lipid-modifying drugs, patient compliance appears to be a major problem. Compliance with cholestyramine or niacin at the end of twelve months has been estimated to be less than 20%. Using drugs with a better side effect profile, Andrade et al. (36) documented a 15% discontinuation rate with lovastatin and a 37% discontinuation rate with gemfibrozil. Simons et al. (37), in a study of 610 Australian adults in primary care, showed that 56% of patients prescribed HMG-CoA reductase inhibitors and 78% of patients prescribed gemfibrozil had stopped taking these agents by twelve months time.

Important factors thought to be responsible for these low rates of adherence include: common side effects [such as pruritus and flushing with niacin, constipation and bloating with bile-acid binding resins, and gastrointestinal upset with gemfibrozil (36)] and the cost of medications, although Marcelino et al. (35) and Simons et al. (37) observed low rates of adherence even in health care systems that largely paid for the medications. Simons et al. (37) identified the causes of discontinuation of lipid-modifying drugs in 309 Australian patients. The two leading causes were lack of perceived need for the therapy on the part of the patient and lack of perceived efficacy of the therapy on the part of the physician. Given the large data base proving efficacy, there appear to be behavioral issues in both patients and physicians which limit the use of these agents.

TABLE 5

Odds Reduction and Absolute Effects of Antiplatelet Agents on Vascular Events in Randomized Clinical Trials. Composite Endpoint of Myocardial Infarction, Stroke, or Vascular Death*

Type of Trial (Number of Trials)	% Odds Reduction (SD)	Events Prevented per 1,000 Patients (SD)	Months of Antiplatelet Therapy
Acute MI (9)	29 (4)	38 (5)	1
Prior MI (11)	25 (4)	36 (5)	27
Prior stroke/TIA (18)	22 (4)	37 (8)	33
Other high-risk conditions (104)	32 (4)	23 (4)	16
Primary prevention (3)	10 (6)	4 (3)	62

* Reference 38.

Antithrombotic Therapy

Anticoagulants (e.g. warfarin) and antiplatelet drugs (e.g. aspirin) have been shown to be effective in reducing the risk of myocardial infarction, stroke, or death in a variety of clinical settings. The relative benefits of these therapies and the cost-effectiveness ratio vary depending on characteristics of the population or of the individual patient.

Antiplatelet Therapy: Antiplatelet agents reduce the risk of subsequent vascular events in patients with acute myocardial infarction, unstable angina, history of myocardial infarction, stroke, transient ischemic attack (TIA), or peripheral vascular disease (38–41). Following acute myocardial infarction, antiplatelet agents reduce cardiovascular events and mortality in the short-term (40,42) and in the long-term (Table 5) (38–40). The Antiplatelet Trialists' Collaboration overview found that the relative risk reduction in vascular events (myocardial infarction, stroke, or vascular death) is similar in patients with remote prior myocardial infarction, recent acute myocardial infarction, prior stroke or TIA, and other high-risk vascular conditions. The absolute benefit of antiplatelet therapy varies somewhat because of the differing risk of these conditions (38). Importantly, the benefits of antiplatelet therapy are independent of age, gender, hypertension, or diabetes.

The optimal dose of aspirin remains controversial, especially for the prevention of stroke (Table 6) (43–46). No randomized trial has convincingly shown that higher doses of aspirin are more

TABLE 6
Minimum Dose of Aspirin Shown to be Effective in Randomized Clinical Trials*

Clinical Condition	Minimum Effective Dose (mg/day)
Stable angina	75
Unstable angina	75
Acute myocardial infarction	162.5
TIA/stroke	75
Stroke after carotid surgery	75
Atrial fibrillation	325
Prosthetic heart valves	100**

* References 43–46.
** In combination with warfarin.

effective than lower doses, and recent meta-analyses have also found no difference in efficacy (38,41,46). Gastrointestinal side effects are more common with higher doses, although serious gastrointestinal complications such as hemorrhage may not be (43,44,46). Since tolerance and compliance are improved with lower doses, most consensus panels have suggested starting with low (75–100 mg/day) or medium (160–325 mg/day) doses.

The use of antiplatelet drugs for primary prevention of cardiovascular events in patients without underlying risk factors remains controversial (40,43). Three trials (two in male physicians and one in female nurses) have examined this question. Meta-analysis suggests a significant risk reduction for fatal and non-fatal myocardial infarction, although the absolute reduction was quite small (38). The composite endpoint of myocardial infarction, stroke, or vascular death was also reduced, but the number of events prevented is only 4 per 1,000 patients treated for five years (Table 5). Vascular death and death from any cause were not reduced. In the Physicians' Health Study, there was a non-significant increase in brain hemorrhages. In view of the low absolute risk of cardiovascular events in this group, antiplatelet therapy should probably be reserved for those who have at least one major risk factor for coronary artery disease or those who develop clinical symptoms (43).

Current estimates suggest that 70% to 80% of persons surviving myocardial infarction are receiving aspirin therapy at any dosage. The reasons for the 20% to 30% deficiency are unknown, but it likely exceeds the prevalence of aspirin intolerance. Low cost and side effects also cannot be invoked as reasons for the non-adherence to this proven therapy.

Anticoagulant Therapy: Anticoagulants are effective in reducing vascular events in patients with acute myocardial infarction, valvular heart disease (rheumatic or prosthetic), atrial fibrillation, and cardioembolic stroke. Anticoagulants reduce the risk of reinfarction, stroke, and death following acute myocardial infarction (47–49). The effect is greatest in those with anterior q-wave infarction, left ventricular dysfunction, congestive heart failure, mural thrombus on 2D echocardiogram, or atrial fibrillation.

An economic analysis applying data from the ASPECT Study to medical care in the Netherlands concluded that long-term warfarin was cost-effective compared to no antithrombotic therapy (49). However, the relative benefits of warfarin versus aspirin are probably a more relevant comparison. These agents have not been directly compared in a randomized trial. In a cost-benefit analysis using data from separate trials, Cairns and Markham (39) concluded that aspirin would be cost-effective if it prevented only 0.41 as many events as oral anticoagulants. Since this is likely the case, they concluded that long-term aspirin was appropriate therapy after MI (39). Indirect efficacy comparisons suggest that patients at high risk of embolism (as noted above) should receive short-term (one to three months) anticoagulation followed by aspirin therapy (47). Patients with atrial fibrillation and myocardial infarction should probably receive warfarin indefinitely (see below).

Warfarin reduces the risk of stroke in patients with non-valvular atrial fibrillation by approximately 70% (41,50–52). This benefit has been demonstrated in five primary prevention trials and one secondary prevention trial (50–52). The relative risk reduction was similar for primary and secondary prevention, but the absolute benefit was greater in the secondary prevention trial because of the greater baseline risk. Aspirin produces a much smaller risk reduction than warfarin. However, the risk of stroke is not uniform in patients with atrial fibrillation, and a remaining question is whether a low-risk group can be identified clinically for whom the risk of warfarin outweighs the benefits (50,52).

Despite the strong evidence of clinical efficacy for warfarin, patients and physicians remain reluctant to use it, particularly in the elderly (53). Reasons cited include fear of hemorrhagic complications, a perceived increased bleeding risk in older individuals, cost, need for monthly blood tests, the "hassle" factor, and being "tied" to the medical system. In patients with atrial fibrillation, the Agency for Health Care Policy and Research Stroke Patient Outcomes Research Team found that only one-quarter of patients with atrial fibrillation receive aspirin, and only half of these receive the correct dosage. They estimated that 50% to 75% of patients with atrial fibrillation should be receiving anticoagulation (54).

Hormone Replacement Therapy

In postmenopausal women, more than 30 observational studies, both case-control and prospective, have found an association between estrogen replacement therapy and a reduced risk of coronary heart disease (55,56). These associations have been strong (30% to 70% reductions in coronary disease), highly significant statistically, and extremely consistent from study to study. Adjustment for many confounding factors did not remove the association. Studies using other endpoints, such as angiographically defined coronary stenoses, have likewise documented an inverse relationship between estrogen use and coronary heart disease (57–59). A follow-up study of women with angiographically defined coronary disease also showed a striking reduction in recurrent infarction and death in women taking estrogens as compared to those not taking them, independent of the extent of coronary disease (60). Women taking estrogens had a 62% reduction in cardiovascular death or infarction after coronary angioplasty, as compared to non-users (61). These latter data suggest that estrogens may be a potent intervention in the female coronary disease patient, in addition to their promise in primary prevention.

Support for estrogen replacement as a cardioprotective agent in postmenopausal women is strengthened by the beneficial effect of estrogens on several risk factors and pathophysiological parameters. Estrogens significantly improve the lipid profile, raising high-density lipoprotein (HDL) cholesterol while lowering LDL cholesterol. In the Postmenopausal Estrogen/Progesterone Intervention study (62), five different estrogen and progesterone regimens were compared for their effects on lipids, lipoproteins, and fibrinogen. In general, all regimens improved the lipid profile versus placebo. Unopposed estrogen or estrogen plus micronized progesterone increased HDL cholesterol levels the most. Estrogen

replacement therapy also effectively reduces lipoprotein (a) levels, a risk factor increasingly recognized as important in premenopausal and postmenopausal women. Estrogens also lower plasma fibrinogen, suggesting that estrogens may not only have an antiatherosclerotic effect but an antithrombotic effect also. Finally, estrogens appear to have powerful effects on coronary vasomotion, and even acute injections of estrogen can have a vasodilatory effect. Altogether, the beneficial effects on these intermediary mechanisms support a strong protective effect of estrogens against coronary disease onset and recurrence.

Despite the observational evidence and the biologic plausibility of the associations, the use of estrogens as a way to prevent heart disease in postmenopausal women is still hotly disputed. The main argument is that observational studies contain the bias that women who take postmenopausal estrogens are inherently more healthy and at lower coronary risk than non-users. There is also concern about competing mortality due to uterine and possibly breast cancer negating any benefits from coronary disease. This is unlikely to be an issue in women with coronary disease or at high risk for its development, since the vast majority of deaths will be due to cardiovascular causes in lieu of any intervention. However, these concerns may be valid in women at low risk for coronary disease, or at high risk for uterine cancer, breast cancer, or other competing causes of mortality. Several large, randomized, placebo-controlled trials are currently being performed to clarify these issues, including the Women's Health Initiative, specifically designed to examine the role of estrogen replacement along with a low-fat diet and calcium supplementation in the primary prevention of coronary disease as well as cancer and osteoporotic fractures. Other studies, such as the Heart Estrogen Replacement Study, will examine estrogen replacement as an intervention in women with existing coronary disease.

In the setting of continuing controversy, the use of estrogen replacement continues at a relatively low level, with less than 30% of eligible postmenopausal women using it. It is estimated that fewer than 20% of women with coronary disease are receiving hormone replacement (3). In many women, this low-level use is due to the patient's reluctance to restart the menstrual cycle, as well as concerns about an increased risk of cancer. These barriers to compliance are unfortunate, since oral replacement in the usual dose used in the U.S. (Premarin, 0.625 mg/day) is relatively inexpensive and can be taken once a day. Hopefully, future clinical trials will clarify the benefits and costs of estrogen replacement so that, if warranted, compliance can be enhanced.

Beta Adrenergic Antagonistic Agents (Beta-Blockers)

As a class, beta-blockers are used for many purposes: as a first-time antihypertensive agent, as anti-ischemic therapy in patients with angina pectoris, as an antiarrhythmic agent in patients with atrial and ventricular arrhythmias, and for a variety of other indications (migraine headaches, panic attacks, etc.). This discussion will focus on their use as a cardioprotective agent used in patients following myocardial infarction for prevention against recurrent infarction and death, even in the absence of signs or symptoms of ischemia. At least 26 randomized, placebo-controlled trials involving over 24,000 patients have been subjected to meta-analyses, documenting a highly significant 23% reduction in cardiac death associated with use of these agents (63). In general, the results of these trials were markedly consistent, showing benefit in the early postinfarction period persisting until study termination. All subgroups of patients, whether defined demographically or clinically, appeared to benefit.

In general, beta-blockers are begun early in the hospitalization for myocardial infarction and continued thereafter. Patients with bronchospasm, hypotension, severe brachycardia, or certain cardiac conduction abnormalities (atrioventricular block) are the only subgroups which should not receive these agents. Long-term compliance may also be limited by side effects such as fatigue, depression-like symptoms, and impotence. Beta-blockers are relatively inexpensive and can be taken as once-a-day therapy.

Unfortunately, the efficacy of these agents is limited by their low rate of utilization. It is estimated that only about 40% of myocardial infarction survivors are currently receiving these agents in the U.S. (3) and the United Kingdom (64). Reasons for this low rate of utilization have not been defined.

Angiotensin Converting Enzyme (ACE) Inhibitors

Another class of drugs often used in the treatment of cardiac patients is ACE inhibitors. Like the beta-blockers, they also have antihypertensive effects. This discussion will be limited to their use in patients with reduced left ventricular ejection fractions, as defined as a cardiac ejection fraction of 40% or less. In these patients with reduced systolic function of their myocardium (mostly but not entirely due to cardiac ischemia), three large randomized trials involving almost 6000 patients have consistently documented a reduction in death (63). A meta-analysis of these trials estimates a 27% reduction in death for this class of agents. Similar data are not available for patients with normal cardiac function.

ACE inhibitors are also initiated early during the hospital course in patients with evidence of left ventricular failure. Contraindications to their use include hypotension, renal failure, and renal artery stenosis. Once-a-day dosing is available. Side effects limiting long-term use include cough and angioedema.

Surveys of ACE inhibitor utilization have been performed on patients with congestive heart failure. Whereas clinical trials of this class of agents have documented improved survival and reduced hospitalization, fewer than 33% of U.S. patients hospitalized with congestive heart were receiving these agents (65). Similarly, prevalence of their use after infarction in the United Kingdom was less than 30% (64). In addition, it appears that the doses of these agents shown to be effective in randomized clinical trials are significantly higher than those often used in practice. Therefore, it appears that only a small fraction of patients with congestive heart failure are receiving ACE inhibitors at doses shown to be efficacious.

Other Agents

A variety of agents have been proposed as cardioprotective agents in the primary and secondary prevention of coronary disease. For some, clinical trials have definitely demonstrated a lack of benefit and, in some instances, actually an increase in risk. Two examples of this are calcium channel blockers and Class I antiarrhythmic agents following myocardial infarction. While calcium channel blockers enjoyed a reasonable rationale for their use, there has been no evidence of efficacy in meta-analyses of 24 clinical trials involving over 20,000 patients (63), with a suggestion that some drugs in this class actually increase the risk of death (66). Likewise, Class I antiarrhythmics used in patients with ventricular arrhythmias after infarction appear to significantly increase the risk of death (63). These scenarios reinforce the need for randomized clinical trials to demonstrate efficacy even in agents which appear to alter intermediary mechanisms beneficially.

TABLE 7
Selected Reasons for Effectiveness of Preventive Pharmacologic Interventions Differing from Efficacy as Shown in Randomized Clinical Trials

1. Differences in Patient Population
   a. "Volunteer effect": reduced risk of participants in clinical trials
   b. Selection of highly compliant patients as participants in clinical trials
2. Barriers Present in Health Care System
   a. Physician and other health care providers
   b. Health care institutions
3. Interactions of pharmacologic interventions with behavioral interventions
   a. Potential synergism of multiple risk factor reductions
   b. Deleterious effects of pharmacologic agents on programs to modify health behaviors
4. Interactions of pharmacologic interventions with other pharmacologic and surgical interventions
   a. Potential benefits of pharmacologic agents on revascularization
   b. Deleterious interactions of multiple pharmacologic agents

A variety of other agents hold promise in preventive cardiology, but efficiency has not yet been proven (5). Some of the agents likely to be tested for their preventive benefits include antidiabetic agents (especially the metformin-like agents which do not raise serum insulin levels), triglyceride-lowering and HDL-raising drugs, antiobesity drugs, folate/B12/B6 supplements to lower homocysteine, and antioxidant vitamins. The latter group is a good example of the complexity involved in identifying agents with good preventive potential. While the scientific rationale for antioxidant vitamins is becoming established as a way to prevent the oxidation of LDL particles, their efficacy in clinical trials has been mixed. Beta carotene supplements have not been shown to be efficacious in randomized trials, with subgroups of smokers possibly even having an increased risk of lung cancer (67). On the other hand, vitamin E (400–800 IU) has been shown in at least one clinical trial to reduce rates of reinfarction in patients with coronary disease (68). This reemphasizes the need to test individual compounds in carefully designed clinical trials, rather than extrapolating from one agent to the next in a single class.

EFFICACY VERSUS EFFECTIVENESS: INTEGRATION OF PHARMACOTHERAPY INTO A COMPREHENSIVE PROGRAM OF CARDIOVASCULAR DISEASE PREVENTION

Professional societies, governmental agencies, and other bodies use results of clinical trials to develop guidelines and standards of care, such as the American Heart Association/American College of Cardiology guide to comprehensive risk reduction (1). However, it must be emphasized that clinical trials test the efficacy of pharmacologic interventions, that is, the ability of these drugs to prevent disease recurrence and death when implemented in highly selected patients by specialized staffs in optimal facilities. More difficult to assess is the actual effectiveness of these agents, that is, the ability of these drugs to prevent disease recurrence and death when implemented in the average patient with cardiovascular disease by staffs with usual training in typical facilities in the community. There probably exist a number of factors which result in the effectiveness of pharmacologic agents differing, for better or worse, from their efficacy as documented in randomized, controlled trials (Table 7).

The recruitment of patients for randomized controlled trials clearly selects patients with a different risk than that of the general population of patients with the disease. This "volunteer effect" usually results in a lower risk on the part of participants. For example, cigarette smokers are frequently underrepresented in clinical trials of cardiovascular prevention. Therefore, the reduced risk of trial participants may actually underestimate the relative or absolute number of recurrent events or deaths in a higher risk population. On the other hand, many clinical trial protocols use a series of prerandomization visits or run-in periods to assess follow-up potential and adherence to protocol. The result is a level of compliance often not matched by clinical experience. For example, compliance with lipid-lowering agents in real life is far below that described for clinical trials (36).

The issue of non-compliance with recommended therapies is a challenge to behavioral science of the highest order, and is covered in considerably more detail elsewhere. Suffice it to say, it is estimated that half of the three billion prescriptions written in the U.S. each year are taken incorrectly (69). The clinical sequelae are enormous. For example, in the Beta-Blocker Heart Attack Trial, both men and women taking fewer than 75% of their prescribed beta-blockers following myocardial infarction had a 2.5- to 3-fold higher mortality than those taking more than 75% of their beta-blockers (70,71). This is likely due to a higher mortality of non-compliant patients in general, as well as loss of the cardioprotective effect of the beta-blockers. The issue of patient adherence/compliance is a complex one and deals with patient factors (knowledge, beliefs, attitudes, and values), the characteristics of the disease and its treatment, the health care setting, the provider, and the provider-patient relationship (72–74).

A variety of barriers likely exist at the levels of the physician and health care institution, as well as the patient (Table 8) (4). Physicians often use the minimum time allotted to their interaction with the patient for the addressing of acute and symptomatic problems, rather than chronic and asymptomatic ones, relegating preventive interventions to a low priority endeavor. Physicians also may not be familiar with the efficacy and administration of the pharmacotherapies described here. Finally, specialists may be confused about their role as initiators of preventive regimens, assuming (often incorrectly) that the primary care provider will institute this care. The specialist often neglects to include preventive interventions in a care plan or the discharge summary sent after hospitalization to the primary care provider. This is easily misconstrued as the specialist's opinion that such interventions are not warranted or effective. Similar problems exist at the health care institution level, in which the priority to provide acute care overwhelms the institution's ability to initiate preventive care. Lack of policies, standards, organization, and committed resources all take away the institution's incentive in developing systems to assure the initiation of pharmacologic interventions with proven preventive efficacy.

Pharmacologic interventions may also interact with behavioral interventions not included in clinical trials, with at least the potential for a synergistic effect. Risk factors have been known to have interactive effects which serve to increase risk (75). The benefits of the pharmacologic treatment of a risk factor may be greatly expanded by behavioral interventions to reduce other risk factors. The converse may also be true. There is continued concern that the prescription of a pharmacologic agent such as a lipid-lowering agent will cripple the patient's motivation for non-pharmacologic measures such as diet, exercise, and weight loss. In reality, the two should work together (i.e. the diet, exercise, and

TABLE 8
Barriers to Implementation of Preventive Services*

Patient
Lack of knowledge and motivation
Lack of access to care
Cultural factors
Social factors
Physician
Problem-based focus
Feedback on prevention is negative or neutral
Time constraints
Lack of incentives, including reimbursement
Lack of training
Poor knowledge of benefits
Perceived ineffectiveness
Lack of skills
Lack of specialist–generalist communication
Lack of perceived legitimacy
Health care settings (hospitals, practices, etc.)
Acute care priority
Lack of resources and facilities
Lack of systems for preventive services
Time and economic constraints
Poor communications between specialty and primary care providers
Lack of policies and standards
Community/society
Lack of policies and standards
Lack of reimbursement

* Reference 4.

weight control should allow minimalization of cost and side effects of drugs by requiring a lower dose of the cholesterol-lowering drug).

Finally, pharmacologic interventions may also interact with other pharmacologic or surgical interventions in heart disease patients who were not included in randomized trials. For example, it appears that aggressive cholesterol-lowering should improve the results of saphenous vein bypass graft surgery through prevention of graft atherosclerosis and occlusion (28). An interesting question is: How many pharmacologic interventions are required to minimize cardiovascular risk? Do all patients need to receive lipid-lowering agents, aspirin, beta-blockers, ACE inhibitors, and, if female, estrogens? Almost all clinical trials have examined one, or at most two, interventions. The additional benefits of adding a third or fourth pharmacologic agent have not been studied. At the same time, the use of pharmacologic interventions, such as antihypertensive therapy or estrogens, has been suggested as a way to avoid the use of other pharmacologic agents, such as lipid-lowering drugs (76). The rationale here is the risk reduction from these other drugs makes lipid-lowering drugs cost-ineffective in these patients with newly reduced risk. The empiric demonstration of this has not been presented.

REFERENCES

(1) Smith SC, Blair SN, Criqui MH, et al: Preventing heart attack and death in patients with coronary disease. *Circulation.* 1995, *92:*2–4.

(2) Pearson TA, Marx HJ: Reduction of risk in the patient with cardiovascular disease. In Pearson TA, Criqui MH, Luepker RV, Oberman A, Winston M (eds), *Primer in Preventive Cardiology.* Dallas, TX: American Heart Association, 1994, 235–237.

(3) Vogel RA: Risk factor intervention and coronary artery disease: Clinical strategies. *Coronary Artery Disease.* 1995, *6:*466–471.

(4) Pearson TA, McBride PE, Houston-Miller N, Smith SC: Organization of preventive cardiology service. *Journal of the American College of Cardiology.* 1996, *27:*1039–1047.

(5) Forrester JF, Merz NB, Bush TL, et al: Task Force 4. Efficacy of risk factor management. *Journal of the American College of Cardiology.* 1996, *27:*991–1006.

(6) Collins R, Peto R, McMahon S, et al: Blood pressure, stroke, and coronary heart disease. Part 2. Short-term reductions in blood pressure: Overview of randomized drug trials in their epidemiological context. *The Lancet.* 1990, *335:*827–839.

(7) McMahon S, Peto R, Cutler J, et al: Blood pressure, stroke, and coronary heart disease. Part 1. Prolonged differences in blood pressure: Prospective studies corrected for regression dilution bias. *The Lancet.* 1990, *335:*765–774.

(8) SHEP Cooperative Research Group: Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. *Journal of the American Medical Association.* 1991, *265:*3255–3264.

(9) McMahon S, Rodgers A: Blood pressure, antihypertensive treatment, and stroke risk. *Journal of Hypertension.* 1994, *12*(Suppl. 10):S5–S14.

(10) Hebert PR, Moser M, Mayer J, Hennekens CH: Recent evidence on drug therapy of mild to moderate hypertension and decreased risk of coronary artery disease. *Archives of Internal Medicine.* 1993, *153:*578–581.

(11) The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Archives of Internal Medicine.* 1993, *153:*154–183.

(12) Goldman L, Garber AM, Grover SA, Hlatky MA: Task Force 6. Cost effectiveness of assessment and management of risk factors. *Journal of the American College of Cardiology.* 1996, *27*(5):1020–1030.

(13) Littenberg B, Garber AM, Sox Jr. HJ: Screening for hypertension. *Annals of Internal Medicine.* 1990, *112:*192–202.

(14) Littenberg B: A practice guideline revisited: Screening for hypertension. *Annals of Internal Medicine.* 1995, *122:*937–939.

(15) Levine DM, Green LW, Deeds SG, et al: Health education for hypertensive patients. *Journal of the American Medical Association.* 1979, *241:*1700–1703.

(16) Morisky DE, Levine DM, Green LW, et al: Five-year blood pressure control and mortality following health education for hypertensive patients. *American Journal of Public Health.* 1983, *73:*153–162.

(17) Haynes RB, Dantes R: Patient compliance and the conduct and interpretation of therapeutic trials. *Controlled Clinical Trials.* 1987, *8:*12–19.

(18) Working Group on Health Education and High Blood Pressure Control: *The Physicians Guide: Improving Adherence Among Hypertensive Patients.* Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, 1987.

(19) Levine DM, Cohen DJ, Dustan HP, et al: Behavior changes and the prevention of high blood pressure. Workshop II. AHA Prevention Conference III. Behavior change and compliance: Keys to improving cardiovascular health. *Circulation.* 1993, *88:*1387–1390.

(20) Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Journal of the American Medical Association.* 1993, *269:*3015–3033.

(21) Rossouw JE: Secondary prevention of coronary heart disease. In Rifkin BM (ed), *Lowering Cholesterol in High-Risk Individuals and Populations.* New York: Marcel Dekker, 1995, 49–67.

(22) Treasure CB, Klein JL, Weintraub WS, et al: Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. *New England Journal of Medicine.* 1995, *332:*481–487.

(23) Anderson TJ, Meredith IT, Yeung AC, et al: The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. *New England Journal of Medicine.* 1995, *332:*488–493.

(24) Egashira K, Hirooka Y, Kai H, et al: Reduction in serum cholesterol with pravastatin improves endothelium-dependent coronary vasomotion in patients with hypercholesterolemia. *Circulation.* 1994, *89:* 2519–2524.

(25) Gould KL, Martucci JP, Goldberg DI, et al: Short-term cholesterol lowering decreases size and severity of perfusion abnormalities by positron emission tomography after dipyridamole in patients with coronary artery disease. *Circulation.* 1994, *89:*1530–1538.

(26) Andrews TC, Raby K, Barry J, et al: The effect of LDL cholesterol reduction on myocardial ischemia in patients with coronary disease. *Circulation.* 1997, *95:*324–327.

(27) Brown GB, Zhao Y-Q, Sacco DE, et al: Lipid-lowering and plaque regression: New insights into prevention of plaque disruption and clinical events in coronary disease. *Circulation.* 1993, *87:*1781–1789.

(28) Post Coronary Artery Bypass Graft Trial Investigators: The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous vein coronary artery bypass grafts. *New England Journal of Medicine.* 1997, *336:*153–162.

(29) Scandinavian Simvastatin Survival Group: Randomized trial of cholesterol lowering in 4,444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *The Lancet.* 1994, *344:*1383–1389.

(30) Sacks FM, Pfeffer MA, Moye LA, et al: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *New England Journal of Medicine.* 1996, *335:* 1001–1009.

(31) Shepherd J, Cobbe SM, Ford I, et al. for the West of Scotland Coronary Prevention Study Group: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New England Journal of Medicine.* 1995, *333:*1301–1307.

(32) Goldman L, Garber AM, Grover SA, Hlatky MA: Task Force 6. Cost effectiveness of assessment and management of risk factors. *Journal of the American College of Cardiology.* 1996, *27:*1020–1030.

(33) Giles WH, Anda RF, Jones DH, et al: Recent trends in the identification and treatment of high blood cholesterol by physicians. Progress and missed opportunities. *Journal of the American Medical Association.* 1993, *269:*1133–1138.

(34) Cohen MV, Byrne M-J, Levine B, Gutowski T, Adelson R: Low rate of treatment of hypercholesterolemia by cardiologists in patients with suspected and proven coronary artery disease. *Circulation.* 1991, *83:*1294–1304.

(35) Marcelino JJ, Feingold KR: Inadequate treatment with HMG-CoA reductase inhibitors by health care providers. *American Journal of Medicine.* 1996, *100:*605–610.

(36) Andrade S, Walker D, Gottlieb L, et al: Discontinuation of antihyperlipidemia drugs—Do rates reported in clinical trials reflect rates in primary care settings? *New England Journal of Medicine.* 1995, *332:*1125–1131.

(37) Simons LA, Levis G, Simon J: Apparent discontinuation rates in patients prescribed lipid-lowering drugs. *Medical Journal of Australia.* 1996, *164:*208–211.

(38) Antiplatelet Trialists' Collaboration: Collaborative overview of randomized trials of antiplatelet therapy-I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *British Medical Journal.* 1994, *308:*81–106.

(39) Cairns JA, Markham BA: Economics and efficacy in choosing oral anticoagulants or aspirin after myocardial infarction. *New England Journal of Medicine.* 1995, *273:*965–967.

(40) Patrono C: Aspirin as an antiplatelet drug. *New England Journal of Medicine.* 1994, *330:*1287–1294.

(41) Matchar DB, McCrory DC, Barnett HJM, Feussner JR: Medical treatment for stroke prevention. *Annals of Internal Medicine.* 1994, *121:*41–53.

(42) ISIS-2 (Second International Study of Infarct Survival) Collaborative Study Group: Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *The Lancet.* 1988, *2:*349–360.

(43) Hirsh J, Dalen JE, Fuster VF, et al: Aspirin and other platelet-active drugs. The relationship among dose, effectiveness, and side effects. *Chest.* 1995, *108*(Suppl.):247S–257S.

(44) Hart RG, Harrison MJG: Aspirin wars: The optimal dose of aspirin to prevent stroke. *Stroke.* 1996, *27:*585–587.

(45) Dyken ML, Barnett HJM, Easton JD, et al: Low-dose aspirin and stroke: "It ain't necessarily so." *Stroke.* 1992, *23:*1395–1399.

(46) Patrono C, Roth GJ: Aspirin in ischemic cerebrovascular disease. How strong is the case for a different dosing regimen? *Stroke.* 1996, *27:*756–760.

(47) Cairns JA, Lewis HD, Meade TW, Sutton GC, Thèroux P: Antithrombotic agents in coronary artery disease. *Chest.* 1995, *108*(Suppl.): 380S–400S.

(48) Smith P, Arnesen H, Holme I: The effect of warfarin on mortality and reinfarction after myocardial infarction. *New England Journal of Medicine.* 1990, *323:*147–152.

(49) Anticoagulation in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group: Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. *The Lancet.* 1994, *343:*499–503.

(50) Laupacis A, Albers GW, Dalen JE, et al: Antithrombotic therapy for atrial fibrillation. *Chest.* 1995, *108*(Suppl.):352S–359S.

(51) Atrial Fibrillation Investigators: Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: Analysis of pooled data from five randomized controlled trials. *Archives of Internal Medicine.* 1994, *154:*1449–1457.

(52) Albers GW: Atrial fibrillation and stroke. Three new studies, three remaining questions. *Archives of Internal Medicine.* 1994, *154:*1443–1448.

(53) McCrory DC, Matchar DB, Samsa G, Sanders LL, Pritchett ELC: Physician attitudes about anticoagulation for non-valvular atrial fibrillation in the elderly. *Archives of Internal Medicine.* 1995, *155:*277–281.

(54) Agency for Health Care Policy and Research: Life-saving treatments to prevent stroke underused. *Research Activities.* 1995, *187*(September):1–2.

(55) Barrett-Connor E, Bush RL: Estrogen and coronary heart disease in women. *Journal of the American Medical Association.* 1991, *265:* 1861–1867.

(56) Stampfer MH, Colditz GA: Estrogen replacement therapy and coronary heart disease: A quantitative assessment of the epidemiologic evidence. *Preventive Medicine.* 1991, *20:*47–63.

(57) Sullivan JM, Vander Zwaag R, Lemp GF, et al: Postmenopausal estrogen use and coronary atherosclerosis. *Annals of Internal Medicine.* 1988, *108:*358–363.

(58) Gruchow HW, Anderson AJ, Barboriak JJ, Sobocinski KA: Postmenopausal estrogen use of estrogen and occlusion of coronary arteries. *American Heart Journal.* 1988, *115:*954–963.

(59) McFarland KF, Boniface ME, Hornung CA, Barnhardt W, Humphries JO: Risk factors and non-contraceptive estrogen use in women with and without coronary disease. *American Heart Journal.* 1989, *117:*1209–1214.

(60) Sullivan JM, Vander Zwaag R, Hughes JP, et al: Estrogen replacement and coronary artery disease: Effects on survival in post menopausal women. *Archives of Internal Medicine.* 1990, *150:*2557–2562.

(61) O'Keefe JH, Kun SC, Hall RR, et al: Estrogen replacement therapy after coronary angioplasty. *Journal of the American College of Cardiology.* 1997, *29:*1–5.

(62) The Writing Group for the PEPI Trial: Effect of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *Journal of the American Medical Association.* 1996, *273:*199–208.

(63) Hennekens CH, Albert CM, Godfried SL, Gaziano JM, Buring JE: Adjunctive drug therapy of acute myocardial infarction. Evidence

from clinical trials. *New England Journal of Medicine.* 1996, *335:*1660–1667.

(64) ASPIRE Steering Group: A British Cardiac Society survey of the potential for the secondary prevention of coronary disease: ASPIRE (Action in Secondary Prevention through Intervention to Reduce Events. Principal Results). *Heart.* 1996, *75:*334–342.

(65) Philbin EF, Andreou C, Rocco Jr. TA, Lynch LJ, Baker SL: Patterns of angiotensin converting enzyme inhibitor use in congestive heart failure in two community hospitals. *American Journal of Cardiology.* 1996, *77:*832–838.

(66) Furberg CD, Psaty BM, Meyer JV: Nifedipine: Dose-related increase in mortality in patients with coronary heart disease. *Circulation.* 1995, *92:*1326–1331.

(67) The Alpha-Tocophenol, Beta Carotene Cancer Prevention Study Group: The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *New England Journal of Medicine.* 1994, *330:*1029–1035.

(68) Stephen NG, Parson A, Schofield PM, et al: Randomized controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *The Lancet.* 1996, *347:*781–786.

(69) Berg JS, Dischler J, Wagner DJ, Raia JJ, Palmer-Shelvin N: Medication compliance: A health care problem. *Annals of Pharmacotherapy.* 1993, *27*(Suppl.):S2–S22.

(70) Horwitz RI, Viscoli CM, Berkman L, et al: Treatment adherence and risk of death after a myocardial infarction. *The Lancet.* 1990, *336:*542–545.

(71) Gallagher EJ, Viscoli CM, Horwitz RI: The relationship of treatment adherence to the risk of death after myocardial infarction in women. *Journal of the American Medical Association.* 1993, *270:*742–744.

(72) Levine DM: Behavioral and psychosocial factors, processes, and strategies. In Pearson TA, Criqui MH, Luepker RV, et al (eds), *Primer in Preventive Cardiology.* Dallas, TX: American Heart Association, 1994, 217–226.

(73) Eraker SA, Knight JP, Becker MH: Understanding and improving patient compliance. *Annals of Internal Medicine.* 1984, *100:*258–268.

(74) Luepker RV: Patient adherence: A "risk factor" for cardiovascular disease. *Heart Disease and Stroke.* 1993, 419–421.

(75) The Pooling Project Research Group: Relationships of blood pressure, serum cholesterol, smoking habit, relative weight, and ECG abnormalities to incidence of major coronary events: Final report of the pooling project. *Journal of Chronic Diseases.* 1978, *31:*201–306.

(76) Avins AL, Browner WS: Lowering risk without lowering cholesterol: Implications for National Cholesterol Policy. *Annals of Internal Medicine.* 1996, *125:*502–506.