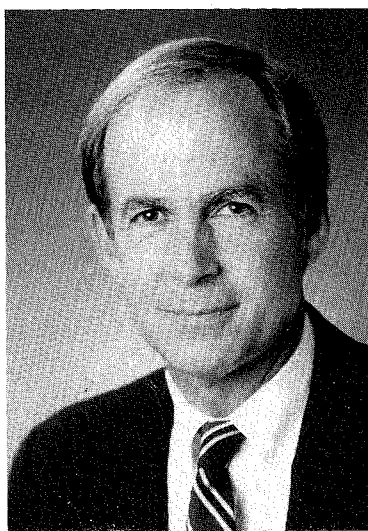


The Importance of Lipid Lowering and Other Risk Reduction Therapies for Patients with Cardiovascular Disease

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Cardiovascular diseases are the leading cause of death and disability in the United States. In 1996, nearly one million will die from heart disease and stroke, and an estimated \$150 billion will be spent to treat these patients.¹ During the past two decades, therapy for patients with coronary heart disease and other atherosclerotic vascular diseases has focused primarily on the relief of symptoms associated with

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severe vascular obstruction using medical therapy and surgical or interventional revascularization techniques. Now compelling evidence from several large randomized trials demonstrates that lipid-lowering medications and other risk reduction therapies can extend overall survival, improve quality of life, decrease the need for interventional procedures such as angioplasty and coronary bypass grafting, and reduce the incidence of subsequent myocardial infarction for patients with coronary heart disease.²⁻⁴ The widespread implementation of these therapies can substantially reduce the human toll and economic burden imposed by the atherosclerotic vascular diseases on our society.

Risk: Not Necessarily Due to Obstruction

Although treatment of atherosclerosis has been primarily directed toward relieving symptoms caused by severe obstructions, recent studies suggest risk is not necessarily related to the severity of obstruction. Coronary arteriograms obtained from patients several weeks or months before myocardial infarction reveal that in 85% of patients, the obstructions are less than 70% narrowing and in the majority less than 50% narrowing⁵ (Figure 1). Clearly, the lesions that are high risk for future events are not necessarily those that contribute to symptoms or abnormalities noted during non-invasive testing.⁶ Thus to be fully effective, therapy must be directed toward the entire atherosclerotic process, not just the amelioration of severe obstructions.

Studies involving a variety of medical therapies and lifestyle changes in patients with atherosclerotic vascular disease indicate the disease process can be stabilized and the prognosis improved.⁷ Depending upon the intervention utilized, impressive reductions can be achieved in total mortality, ranging from 10% to 43% (Table 1).

The AHA Consensus Statement

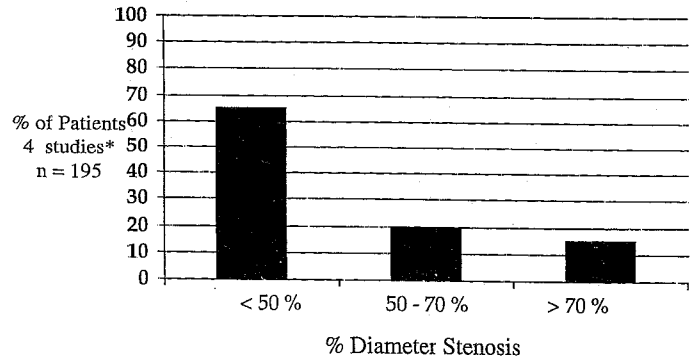
In a major effort to increase the use of lipid-lowering and other risk reduction therapies for patients with coronary heart disease, the American Heart Association (AHA) has developed a Consensus Statement² for healthcare provider use which is endorsed by the American College of Cardiology. These risk reduction strategies (Figure 2) have been the focus of a national campaign to improve outcomes for patients with coronary heart disease.

A cornerstone of the AHA risk reduction strategies has been an emphasis on the primary importance of lipid-lowering therapy. The benefits of lipid lowering include regression of disease or lack of progression in about 25% of those treated.^{8,9} However, because the actual change in severity of coronary obstructions is only in the order of 1% to 2% following lipid-lowering therapy, stabilization of high-risk (frequently nonobstructive) lesions appears to account for the dramatic improvement in outcomes for most patients (Table 2). The AHA Consensus Statement² recommends that patients with known atherosclerotic disease should have a complete lipid panel which includes determination of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Following acute myocardial infarction, the lipid profile may require 4 to 6 weeks to stabilize.

The Benefits of Lipid-Lowering Therapy

The therapeutic benefits of lipid-lowering therapy have been demonstrated in patients with coronary heart

Figure 1. Severity of Coronary Artery Stenosis Before Myocardial Infarction



*Ambrose et al. *J Am Coll Cardiol* 1988;12:56-62 Giroud et al. *AJC* 1992;69:729-732. Little et al. *Circulation* 1988;78:1157-1166. Nobuyoshi et al. *J Am Coll Cardiol* 1991;18:904-910.

Table 1. Reduction in Cardiovascular Mortality and Total Mortality Associated with Risk Reduction Strategies*

Intervention	Event Reduction (%)	
	Cardiovascular	Total Mortality
Smoking Cessation		43
Lipid Lowering	42	30
Exercise	25	20
Aspirin	30	15
Anticoagulants	53	10
ACE Inhibitors	25	20
Beta-Blockers	26	27
Blood Pressure Control	21	12

*Patients with established cardiovascular disease

Table 2. Lipid-Lowering Trials: Stenosis Severity and Cardiac Events*

Trial	Decrease in Cholesterol (%)	Decrease in Cardiac Events (%)	Change in Stenosis (%)
FATS	23	80	1.1 ± 3.7
STARS	14	69	0.5 ± 3.6
	23	89	1.5 ± 4.0
SCRIP	16	39	0.3 ± 2.5
PLAC 1	19	74	0.69

*Trials used quantitative coronary angiography; differences in cholesterol, cardiac events, and lesion stenosis: statistically significant, control versus intervention.

disease and in those without manifest coronary heart disease but abnormal lipid levels. The Scandinavian Simvastatin Survival Study (4S)¹⁰ demonstrated the benefits of lipid-lowering therapy in 4,444 randomized patients with coronary heart disease. The results were highly significant reductions in total mortality (30%), coronary mortality (42%), revascularization procedures (37%), and hospital days (34%) (Table 3).

Table 3. Summary of Results from the Scandinavian Simvastatin Survival Study (4S)*

	Risk Reduction	
Total Mortality	30%	<i>P</i> = 0.0003
Coronary Mortality	42%	<i>P</i> = 0.00001
Revascularization	37%	<i>P</i> < 0.00001
Hospital Days	34%	<i>P</i> < 0.0001

*4,444 patients with angina or previous MI randomized 5.4 years, simvastatin vs. placebo.

The West of Scotland Coronary Prevention Study Group (WOSCOPS) randomized trial¹¹ revealed similar benefits of cholesterol lowering in 45- to 65-year-old men with no history of myocardial infarction or active coronary heart disease and mean plasma cholesterol of 272 mg/dL. Highly significant reductions occurred in total mortality (22%), all cardiovascular deaths (32%), and coronary revascularization procedures (37%). Of particular importance, the benefits of lipid lowering occurred early—within 1 to 2 years—in both of these large randomized clinical trials and did not adversely affect the risk of death from noncardiovascular causes.

Unfortunately, most patients with coronary heart disease do not receive the benefits of lipid-lowering therapy. In one recent study reviewing cardiologists' treatment of hyperlipidemia, less than 30% of candidates for therapy were treated.¹² The recommended goal for

lipid-lowering therapy in patients with coronary heart disease is to achieve LDL-C levels less than 100 mg/dL. Secondary goals include reducing triglycerides to less than 200 mg/dL and increasing HDL-C to greater than 35 mg/dL. Adherence to a Step II AHA low-fat, low-cholesterol diet is an important adjunct to pharmacologic therapy and is the foundation for these efforts. The AHA consensus panel recommends the use of statins, resins, and niacin as indicated by patient response and lipid profile.² Fibrate therapy is reserved for those with triglycerides greater than 400 mg/dL (Figure 2). In general, patient compliance with statin therapy is highest.

Therapy After Myocardial Infarction

Angiotensin converting enzyme (ACE) inhibitor therapy for patients after myocardial infarction with symptomatic and asymptomatic left ventricular failure is another important risk reduction therapy. In the SAVE (Survival And Ventricular Enlargement) study of 2,231 randomized patients, significant reductions were seen in total mortality (19%), cardiovascular mortality (21%), recurrent hospitalization (22%), and recurrent myocardial infarction (25%) (Table 4).¹³ These results parallel those seen with lipid-lowering therapy. In the SOLVD (Studies of Left Ventricular Dysfunction) trials involving 6,797 randomized patients with ejection fractions less than or equal to 0.35, both asymptomatic and symptomatic, the benefits of ACE inhibitor therapy on incidence of recurrent ischemic events such as myocardial infarction and unstable angina were demonstrated.¹⁴ Moreover, the SAVE study revealed a decreased (24%) need for revascularization procedures after myocardial infarction for those treated with ACE inhibitor therapy.¹⁵

Based on the results of these ACE inhibitor trials, the AHA consensus panel has recommended that ACE inhibitors be started early after acute myocardial infarction (Figure 2). Candidates

for therapy include stable high-risk patients (anterior myocardial infarction, previous myocardial infarction, Killip Class II [S3 gallop, rales, radiographic CHF]).² Therapy should be continued

indefinitely for all with left ventricular dysfunction (ejection fraction ≤ 40) or symptoms of failure. Once again, the number of patients benefiting from these risk reduction therapies has been

Figure 2. AHA Consensus Panel Risk Reduction Strategies

RISK INTERVENTION	RECOMMENDATIONS																								
Smoking: <u>Goal</u> complete cessation	Strongly encourage patient and family to stop smoking Provide counseling, nicotine replacement, and formal cessation programs as appropriate.																								
Lipid management: <u>Primary goal</u> LDL <100 mg/dL <u>Secondary goals</u> HDL >35 mg/dL; TG <200 mg/dL	<p>Start AHA Step II Diet in all patients: $\leq 30\%$ fat, $<7\%$ saturated fat, <200 mg/d cholesterol</p> <p>Assess fasting lipid profile, in post-MI patients, lipid profile may take 4 to 6 weeks to stabilize Add drug therapy according to the following guide:</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 20%; vertical-align: top;">LDL <100 mg/dL</td> <td style="width: 40%; text-align: center;">LDL 100 to 130 mg/dL</td> <td style="width: 40%; text-align: center;">LDL >130 mg/dL</td> <td style="width: 20%; vertical-align: top;">HDL <35 mg/dL</td> </tr> <tr> <td style="vertical-align: top;">No drug therapy</td> <td style="text-align: center;">Consider adding drug therapy to diet, as follows:</td> <td style="text-align: center;">Add drug therapy to diet, as follows:</td> <td rowspan="4" style="vertical-align: top;">Emphasize weight management and physical activity Advise smoking cessation If needed to achieve LDL goals, consider niacin, statin, fibrate.</td> </tr> <tr> <td colspan="2" style="text-align: center;">↙ Suggested drug therapy ↘</td> <td colspan="2"></td> </tr> <tr> <td style="text-align: center;">TG <200 mg/dL</td> <td style="text-align: center;">TG 200 to 400 mg/dL</td> <td style="text-align: center;">TG >400 mg/dL</td> <td></td> </tr> <tr> <td style="text-align: center;">Statin Resin Niacin</td> <td style="text-align: center;">Statin Niacin</td> <td style="text-align: center;">Consider combined drug therapy (niacin, fibrate, statin)</td> <td></td> </tr> <tr> <td colspan="4" style="text-align: center;">If LDL goal not achieved, consider combination therapy</td> </tr> </table>	LDL <100 mg/dL	LDL 100 to 130 mg/dL	LDL >130 mg/dL	HDL <35 mg/dL	No drug therapy	Consider adding drug therapy to diet, as follows:	Add drug therapy to diet, as follows:	Emphasize weight management and physical activity Advise smoking cessation If needed to achieve LDL goals, consider niacin, statin, fibrate.	↙ Suggested drug therapy ↘				TG <200 mg/dL	TG 200 to 400 mg/dL	TG >400 mg/dL		Statin Resin Niacin	Statin Niacin	Consider combined drug therapy (niacin, fibrate, statin)		If LDL goal not achieved, consider combination therapy			
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Physical activity: <u>Minimum goal</u> 30 minutes 3 to 4 times per week	Assess risk, preferably with exercise test, to guide prescription Encourage minimum of 30 to 60 minutes of moderate-intensity activity 3 or 4 times weekly (walking, jogging, cycling, or other aerobic activity) supplemented by an increase in daily lifestyle activities (eg, walking breaks at work, using stairs, gardening, household work) Maximum benefit 5 to 6 hours a week Advise medically supervised programs for moderate- to high-risk patients																								
Weight management:	Start intensive diet and appropriate physical activity intervention, as outlined above, in patients $>120\%$ of ideal weight for height Particularly emphasize need for weight loss in patients with hypertension, elevated triglycerides, or elevated glucose levels.																								
Antiplatelet agents/ anticoagulants:	Start aspirin 80 to 325 mg/d if not contraindicated Manage warfarin to international normalized ratio = 2 to 3.5 for post-MI patients not able to take aspirin																								
ACE inhibitors post-MI:	Start early post-MI in stable high-risk patients (anterior MI, previous MI, Killip class II (S ₃ gallop, rales, radiographic CHF) Continue indefinitely for all with LV dysfunction (ejection fraction $\leq 40\%$) or symptoms of failure Use as needed to manage blood pressure or symptoms in all other patients																								
Beta-blockers:	Start in high-risk post-MI patients (arrhythmia, LV dysfunction, inducible ischemia) at 5 to 28 days. Continue 6 months minimum. Observe usual contraindications. Use as needed to manage angina, rhythm, or blood pressure in all other patients																								
Estrogens:	Consider estrogen replacement in all postmenopausal women Individualize recommendation consistent with other health risks																								
Blood pressure control: <u>Goal</u> $\leq 140/90$ mm Hg	Initiate lifestyle modification—weight control, physical activity alcohol moderation, and moderate sodium restriction—in all patients with blood pressure >140 mm Hg systolic or 90 mm Hg diastolic Add blood pressure medication, individualized to other patient requirements and characteristics (ie, age, race, need for drugs with specific benefits) if blood pressure is not less than 140 mm Hg systolic or 90 mm Hg diastolic in 3 months or if initial blood pressure is >160 mm Hg systolic or 100 mm Hg diastolic																								

ACE = angiotensin converting enzyme; MI = myocardial infarction; TG = triglycerides; LV = left ventricular

less than optimal. Results of the Cooperative Cardiovascular Project (CCP), a Medicare pilot study, revealed that only 59% of ideal candidates receive ACE inhibitor therapy at the time of hospital discharge following myocardial infarction.¹⁶

Antiplatelet agents and anticoagulant therapy can significantly reduce mortality and morbidity when administered chronically after myocardial infarction. Results from a large randomized trial of thrombolytic therapy for evolving myocardial infarction¹⁷ demonstrated a highly significant 23% reduction in vascular mortality at 5 weeks for those receiving aspirin therapy (160 mg/day), and these benefits persisted for 2 years afterward. In an analysis of 11 randomized trials involving aspirin or other platelet inhibitor therapy after myocardial infarction, vascular mortality was reduced (15%) as

well as nonfatal reinfarction (32%), and nonfatal stroke for both men and women (Table 5).^{18,19} Recent data from patients with known coronary heart disease demonstrate a 72% reduction in the odds ratio for myocardial infarction indicating a shift to less severe manifestations of coronary syndromes with aspirin use.²⁰ Analysis of data from the Multicenter Study of myocardial ischemia²¹ suggests an even greater reduction in long-term mortality for patients placed on aspirin therapy following thrombolytic therapy for myocardial infarction, angioplasty or therapy for unstable angina. Unfortunately, available data¹⁶ suggest only 77% of eligible Medicare patients receive aspirin therapy at the time of hospital discharge after myocardial infarction. Similarly, 20% of the Multicenter Study participants were not taking aspirin after a coronary event despite recommendations for its use.²¹

Table 4. Summary of Results from the SAVE Trial*

	Risk Reduction	
Total Mortality	19%	P = 0.019
Cardiovascular Mortality	21%	P = 0.014
Recurrent Hospitalization	22%	P = 0.019
Recurrent Myocardial Infarction	25%	P = 0.015

*2,231 patients randomized 42 months captopril vs. placebo after acute MI, with ejection fraction $\leq 40\%$ and no symptoms of angina or CHF
Pfeffer et al. *N Engl J Med* 1992;327:669-677.

Table 5. Secondary Prevention of Vascular Disease—Prolonged Antiplatelet Therapy

End Point	25 Trials
Nonfatal myocardial infarction	32 \pm 5
Nonfatal stroke	27 \pm 6
Impotent vascular event	25 \pm 3
Cardiovascular mortality	15 \pm 4

After Ridker and Hennekens AHA Primer in Preventive Cardiology 1994. Adapted from Antiplatelet Trialist Collaboration *BMJ* 1988;296:320-331

Aspirin and Estrogen Therapy

The AHA recommends that aspirin be given in dosages of 80 mg to 325 mg per day to patients with coronary heart disease unless contraindicated. For those patients not able to take aspirin after myocardial infarction, warfarin therapy to an international normalized ratio (INR) of 2 to 3.5 is recommended if not contraindicated.² The Norwegian Warfarin Reinfarction Study (WARIS) which randomized 1,214 patients under age 75 revealed reduced mortality (24%), reduced nonfatal myocardial infarction (34%), and reduced cerebrovascular accidents (55%) with warfarin therapy over a 3-year follow-up.²² At present, lower risk of bleeding and lower cost favor aspirin over warfarin for treatment of most patients with atherosclerotic cardiovascular disease in normal sinus rhythm and with normal left ventricular function.

Estrogen replacement therapy for postmenopausal women has favorable results reducing LDL cholesterol and increasing HDL.²³ These improvements in lipid profile in women treated

with estrogen replacement therapy are associated with normalization of the coronary endothelial response.^{24,25} In patients treated with estrogen replacement therapy, observational studies suggest reduction of recurrent cardiovascular events.²⁶ Combined therapy in animals with progestins added to estrogen to reduce negative side effects from unopposed estrogen therapy reveal reduction in atherosclerosis similar to that observed with estrogen alone. Further data regarding the benefits of estrogen replacement therapy in humans is an important goal of the Women's Health Initiative—a large nationwide trial. The AHA Consensus Panel recommends that estrogen replacement therapy be considered in all postmenopausal women with atherosclerosis. Its use should be individualized consistent with other health risks.²

Lifestyle Changes

Behavioral changes are an important adjunct to lipid-lowering and other risk reduction therapies.²⁷ An estimated 25% of the population is overweight or does not exercise regularly. A similar proportion is at risk from cigarette smoking. Adherence to a low-fat, low-cholesterol diet and regular exercise²⁸ as outlined by the AHA can improve lipid profiles; however, for most patients with established cardiovascular disease, the addition of lipid-lowering agents such as statins is necessary for maximal cardiovascular benefit. In overweight, middle-aged and older men, weight loss may have a greater impact on coronary risk factors than aerobic exercise. Weight loss may be especially efficacious in the medical management of patients with elevated triglycerides, abnormal glucose tolerance or hypertension. Prior to embarking on an exercise program, risk should be assessed with exercise treadmill testing. Medically supervised programs are advised for moderate- and high-risk patients. The new Cardiac Practice Guidelines developed by the AHCPR (Agency for Health Care Policy and Research) and the NHLBI (Na-

tional Heart, Lung, and Blood Institute) provide excellent recommendations for comprehensive programs for patients with coronary heart disease. A meta-analysis of comprehensive cardiac rehabilitation trials indicates a 25% reduction in coronary events after this intervention.³⁰

Smoking cessation is an essential behavior modification for all, especially

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those with atherosclerotic cardiovascular disease. Tobacco related illnesses claim an estimated 430,000 lives annually and represent a major health hazard for our society.³¹ For those with a long history of tobacco use, smoking cessation programs may be less than optimal. Many believe the most effective time to intervene with smoking cessation programs is at the time of a major event such as myocardial infarction or coronary bypass surgery. The Coronary Artery Surgery Study (CASS),³² a long-term follow-up of patients after coronary artery bypass surgery, demonstrated that continued cigarette smoking was a major predictor of recurrent cardiovascular events and graft failure. In fact, continued smoking ranked ahead of other important risk factors such as diabetes and hypertension. Unfortunately, as is the case with other risk reduction therapies, few patients benefit from effective smoking cessation programs. The results of the recent CCP pilot study on Medicare patients surviving acute myocardial infarction⁶ indicate that only 28% of smokers have documented smoking

cessation counseling prior to discharge from the hospital. There are numerous programs available through hospital and professional organizations to assist with counseling and nicotine replacement therapy in patients who are candidates for smoking cessation therapy.

Hypertension Therapy

Hypertension is a major risk factor for atherosclerotic disease. Lifestyle modifications including weight control, physical activity, alcohol moderation and moderate sodium restriction is recommended by the AHA Consensus Panel² for all patients with systolic blood pressure greater than 140 mm Hg and diastolic pressure greater than 90 mm Hg. Medication should be added if blood pressure is not less than 140 mm Hg systolic or 90 mm Hg diastolic within 3 months of initiating these lifestyle modification measures or, initially, if blood pressure is greater than 160 mm Hg systolic or greater than 100 mm Hg diastolic. Unfortunately, the recent National Health and Nutrition Examination Survey (NHANES III)³³ study indicates only 29% of patients with hypertension are adequately controlled by therapy. Thus, the majority of patients with hypertension in our society remain at risk for progression of cardiovascular disease due to lack of adequate treatment.

Beta-blockers along with ACE inhibitors have both been shown to benefit patients with atherosclerotic cardiovas-

cular disease independent of their effects on blood pressure, yet both are valuable medications in controlling hypertension. The independent effects of ACE inhibitor therapy have been discussed earlier in this article. Pooled results from several prospective randomized trials with beta-blockers have demonstrated a significant reduction in total mortality (21%), cardiac death (24%), sudden cardiac death (30%), and reinfarction after myocardial infarction (25%).³³ Beta-blocker therapy appears most efficacious in high-risk post-myocardial infarction patients (those with arrhythmia, left ventricular dysfunction, or inducible ischemia). The American Heart Association Consensus Panel recommends that beta-blockers be utilized especially in high-risk patients starting therapy at 5 to 28 days and continuing for 6 months unless usual contraindications are present (Figure 2).² The results of the CCP Pilot Study¹⁵ reveal that only 45% of eligible Medicare patients receive beta-blocker therapy at discharge from the hospital after myocardial infarction. Unfortunately, the potential benefits of lipid-lowering therapy and other risk reduction strategies remain unrecognized by the majority of patients with atherosclerotic cardiovascular disease.

Bottom Line: Patient Compliance and Funding

Although the AHA Consensus Statement on Risk Reduction is a major step forward toward enlisting participation of healthcare providers, the final success will also be dependent upon improved patient adherence to prescribed therapies and support of third-party insurers for funding of risk reduction efforts. At present, as many as 50% of patients started on lipid-lowering therapy or other risk reduction treatments for cardiovascular disease may discontinue these valuable therapies within one year.³⁵⁻³⁷ Programs that involve the development of healthcare specialist teams including nurses, nutritionists and exercise physiologists can increase

Table 6. Nurse Case Management System for Risk Modification After Acute Myocardial Infarction (MULTI-FIT)

	Usual Care (n = 292)	Nurse Managed (n = 293)	
Smoking Cessation*	53%	70%	P = 0.03
Plasma LDL*	132 ± 30	107 ± 30	P = 0.001
Functional Capacity**	8.4 ± 2.5	9.3 ± 2.4	P = 0.001
Adherence to Lipid-Lowering Rx	21%	90%	

*12 months.

**6 months

DeBusk, Houston-Miller, Superko et al. *Ann Intern Med* 1994;120:721-729.

the utilization of these therapies and improve outcomes. Many large managed care groups are actively pursuing the development of nurse case management programs in order to implement cost-effective strategies for lipid-lowering and risk reduction therapies in patient populations with cardiovascular disease.

One such example is the nurse case management program called Multiple Risk Factor Intervention in Post-Myocardial Infarction (MULTI-FIT), a management system for risk modification after acute myocardial infarction) developed at Stanford University in conjunction with Kaiser Permanente. Significant improvement in patient outcomes were seen with this nurse case management program, yet the time involvement by nurses in the MULTI-FIT program was on average 9 hours per patient per year (Table 6).³⁸

In summary, by adopting and adhering to strategies for lipid-lowering therapy and other established risk reduction treatments such as those outlined in the AHA Consensus Statement, managed care organizations can effectively improve outcomes for patients with cardiovascular disease. A significant benefit from these efforts will be a reduction in recurrent hospitalization and expensive revascularization procedures. In addition to the development of nurse case management and other healthcare provider teams, it is essential that the cardiovascular specialist and primary care physician work together to emphasize and implement risk reduction therapies for all patients with atherosclerotic cardiovascular disease. To be successful with these efforts, practice patterns must be changed to more broadly implement risk reduction therapy. This will involve new healthcare delivery teams to increase patient compliance and more active participation by both primary care and cardiovascular specialists in seeing that lipid-lowering and risk reduction therapies are implemented. Increased funding and support for these efforts is

already being discussed by many third-party insurers and managed care organizations that recognize that lipid-lowering therapy and other risk reduction strategies result in a dramatic decrease in hospitalization and revascularization procedures as well as an overall benefit to patient well-being. The beneficiaries of these enhanced efforts with lipid-lowering and risk reduction therapy will be a society with less disability and death from cardiovascular disease and stroke.

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