

Optimal Medical Therapy After PCI

Intensive multifactorial intervention to reduce cardiovascular risk.

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Mortality from coronary heart disease has decreased significantly in the United States during the past few decades. Nearly 50% of this decrease is due to evidence-based medical therapies, including coronary revascularization.¹ Approximately 44% of the decrease in mortality is attributed to change in risk factors, including reductions in cholesterol, blood pressure, tobacco smoking, and physical inactivity. Further reductions may have been achieved if not for increases in obesity and in the prevalence of diabetes that occurred over the same time period. The largest reductions in coronary deaths came from the use of secondary prevention medications after an acute myocardial infarction (MI) or after revascularization.

Percutaneous coronary intervention (PCI) reduces the incidence of death and recurrent MI in patients presenting with an acute coronary syndrome (ACS).² Although PCI can reduce the incidence of angina and improve quality of life in patients with stable coronary disease, it has not been shown to reduce death and MI in chronic stable patients as it has in patients with an ACS.³ A reduction in death and recurrent cardiovascular events can be achieved, however, with optimization of medical therapy that focuses on aggressive coronary heart disease (CHD) risk factor reduction. This article reviews how to optimize medical therapy for patients with chronic coronary disease after PCI treatment.

THE COURAGE TRIAL

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial was designed to study whether a management strategy of PCI with intensive pharmacological therapy and lifestyle intervention (optimal medical therapy) was superior to optimal medical therapy alone in reducing cardiovascular events in patients with stable coronary disease.⁴ The COURAGE trial investigators randomized 2,287 patients with objective evidence for myocardial ischemia and a coronary artery stenosis of at least 70% in at least one

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proximal epicardial coronary artery or at least one coronary artery stenosis of 80% and classic angina to PCI and optimal medical therapy or optimal medical therapy alone. The primary outcome was death from any cause and nonfatal MI during a follow-up period of 2.5 to 7 years. The primary event rates were not significantly different in the PCI group compared with the medical therapy group (19% vs 18.5%). Further analysis showed no significant differences in the composite of death, MI, and stroke; hospitalization for ACS; or MI alone.

The findings of the COURAGE trial can be explained by recognizing the differences in atherosclerotic plaque morphology associated with ACS and chronic coronary disease. ACS tends to occur when a vulnerable plaque (with a thin fibrous cap, a large lipid pool, and increased inflammatory cells) ruptures, allowing an acute thrombus to form. These vulnerable plaques tend not to be occlusive plaques. The majority of the plaques associated with an ACS narrow the coronary lumen with a < 50% stenosis before the acute event.⁵ In contrast, patients presenting with chronic stable angina tend to have plaques with a thick fibrous cap with more collagen, small lipid cores, and fewer inflammatory cells. These lesions are more likely to narrow the coronary lumen and are targeted by PCI to reduce angina. Optimal medical therapy is thought to reduce coronary events by reducing plaque vulnerability, making these plaques less susceptible to rupture.

LIPID-LOWERING THERAPY

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines recommend that

TABLE 1. LDL CHOLESTEROL AND NON-HDL CHOLESTEROL GOALS ACCORDING TO RISK CATEGORIES^a

Risk Category	LDL Cholesterol Goal (mg/dL)	Non-HDL Cholesterol Goal (triglycerides $\geq$ 200 mg/dL) (mg/dL)
Very high risk	< 70 optional goal	< 100 optional goal
High risk (CHD or CHD risk equivalent, 10-year risk > 20%)	< 100	< 130

^aAdapted from NCEP ATP III guidelines⁶ and the National Heart, Lung, and Blood Institute update.⁷

TABLE 2. TREATMENT GOALS IN PATIENTS WITH CARDIOMETABOLIC RISK AND LIPOPROTEIN ABNORMALITIES^{ab}

	Goals		
	LDL Cholesterol (mg/dL)	Non-HDL Cholesterol (mg/dL)	Apolipoprotein B (mg/dL)
Highest-risk patients Known CVD or diabetes plus one additional risk factor	< 70	< 100	< 80
High-risk patients No diabetes or known clinical CVD but two or more risk factors or diabetes but no other CVD risk factors	< 100	< 130	< 90

^aOther risk factors beyond dyslipoproteinemia include smoking, hypertension, and family history of CAD.
^bAdapted from the consensus statement from the 2008 American Diabetes Association and the American College of Cardiology Foundation.⁸
Abbreviations: CAD, coronary artery disease CVD, cardiovascular disease.

the low-density lipoprotein (LDL) cholesterol should be the primary target of therapy for at-risk individuals.⁶ In 2004, the NCEP published an updated committee report reviewing trials published after the Adult Treatment Panel III guidelines and proposed further modification of the risk categories.⁷ High-risk individuals include patients with documented CHD or CHD risk-equivalent disease including diabetes mellitus, patients with symptomatic carotid artery disease, or peripheral vascular disease including an abdominal aortic aneurysm. Within the high-risk category, patients at very high risk can be identified. Patients considered at very high risk have established CHD plus multiple risk factors (especially diabetes mellitus), severe or poorly controlled risk factors (especially continued cigarette smoking), multiple risk factors of the metabolic syndrome including high triglycerides and a low high-density lipoprotein (HDL) cholesterol, and patients with an ACS.

LDL cholesterol treatment goals are set based on the risk category, as shown in Table 1. A therapeutic

lifestyle program and pharmacological therapy are typically begun at the same time in high-risk individuals. The LDL cholesterol level is re-evaluated after a 6-week to 3-month interval. If the goal has not been achieved, therapy can be increased to achieve the LDL goal. In general, it is desirable to lower the LDL cholesterol greater than 50% from baseline in high-risk CHD patients.

Once the LDL cholesterol goal has been achieved, additional lipid parameters should be targeted for further risk reduction. The COURAGE trial investigators attempted to increase the HDL cholesterol to 40 mg/dL or greater and to reduce triglycerides to < 150 mg/dL.⁴ The NCEP recommends non-HDL cholesterol as the secondary target for patients with fasting triglyceride levels > 200 mg/dL. Non-HDL cholesterol is simply the HDL cholesterol subtracted from the total cholesterol. Non-HDL cholesterol incorporates risk from both low HDL cholesterol and elevated triglyceride levels. The non-HDL cholesterol goals are 30 mg/dL higher than the LDL cholesterol goals.

TABLE 3. TREATMENT OF LIFESTYLE RISK FACTORS^a

Therapeutic Target/Goals of Therapy	Therapeutic Recommendations
Abdominal obesity Goal: reduce body weight by 7% during first year of therapy Goal: achieve desired weight body mass index < 25 kg/m ²	• Encourage weight maintenance/reduction with physical activity, reduced caloric intake, formal behavioral programs • Maintain/achieve waist circumference < 40 inches in men, < 35 inches in women • Initial reduction 7%–10% weight from baseline
Physical inactivity Goal: regular moderate-intensity physical activity, at least 30 min of continuous/intermittent (preferably 60 min) 5 day/week, preferably daily	• Patients with established cardiovascular disease: assess physical activity risk (history/stress test) • Encourage 30–60 min moderate-intensity aerobic activity daily supplemented by increase in daily lifestyle activities • Encourage resistance training 2 days/week • Medically supervised programs for high-risk patients
Atherogenic diet Goal: reduce saturated fat, trans fat, cholesterol	• Saturated fat < 7% total calories; reduce trans fat; dietary cholesterol < 200 mg/dL; total fat 25%–35% of total calories • Most dietary fat should be unsaturated • Simple sugars should be limited

^aAdapted from Grundy et al. *Circulation*. 2005;112:2735–2752.⁹

Patients with diabetes mellitus and the metabolic syndrome are at higher cardiovascular risk than matched patients without these conditions. Despite progress in reducing cardiovascular events with aggressive medical therapy, many patients continue to have CHD events referred to as the *residual risk*. Measuring additional lipid values may help identify which patients at the NCEP goal still have a significant residual risk. The American Diabetes Association/American College of Cardiology Foundation recommended that apolipoprotein B100 (apoB) should be considered a third treatment target for patients with cardiometabolic risk after LDL cholesterol and non-HDL cholesterol goals are achieved.⁸ Measurement of apoB, an estimate of LDL particle number, may help identify a higher-risk cohort of patients who may benefit from more intensive lipid-lowering therapy. Elevated apoB levels in patients who have achieved LDL cholesterol and non-HDL cholesterol goals indicate the presence of small dense LDL particles. These particles are more atherogenic than larger less-dense particles. It is recommended that patients with multiple cardiometabolic risk factors, but who have no clinical cardiovascular disease or diabetes, have an apoB target of < 90 mg/dL. Patients with cardiometabolic risk factors and diabetes or clinical cardiovascular disease are considered to be at very high risk and have an apoB target of < 80 mg/dL (Table 2).

All patients with coronary risk should be counseled about a therapeutic lifestyle program. Any pharmacologi-

cal therapy will have greater efficacy if combined with an aggressive lifestyle program. The American Heart Association/National Heart, Lung, and Blood Institute published a scientific statement (summarized in Table 3) recommending therapeutic targets and goals of a lifestyle treatment program for the long-term prevention of both cardiovascular events and diabetes for patients with the metabolic syndrome. This statement can be a useful guide for all patients with CHD.⁹

The HMG CoA reductase inhibitors (statins) are the first-line therapy for reducing LDL cholesterol. Statins work by inhibiting the enzyme that catalyzes the rate-limiting step in cholesterol synthesis, leading to clearance of LDL cholesterol particles from the circulation by the liver. In addition, statins minimally raise HDL cholesterol and lower triglycerides. Inflammatory biomarkers are also reduced by statins, suggesting that they may promote healing of vulnerable plaque.

Statins are drugs of first choice to target LDL cholesterol because of the extensive data indicating a reduction in cardiovascular events when using statins in patients with known CHD. For example, the Scandinavian Simvastatin Survival Study (4S) evaluated the effect of cholesterol lowering with simvastatin in 4,444 patients with angina or a previous MI and reported a 30% reduction in risk of death compared with the placebo group.¹⁰ This was the first major study to show a total mortality benefit with lipid-lowering therapy.

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Studies suggest that optimal therapy for high-risk individuals would need at least a 50% reduction in LDL cholesterol from baseline levels. This can be achieved with high-potency statins, such as atorvastatin and rosuvastatin. The Treating to New Targets (TNT) trial studied the efficacy of high-dose statins compared with standard-dose statins in patients with chronic coronary heart disease.¹¹ The higher-dose statin (atorvastatin 80 mg) compared with a starting-dose statin (atorvastatin 10 mg) achieved a further 22% relative risk reduction (2.2% absolute risk reduction) in coronary events, with a mean LDL cholesterol of 77 mg/dL achieved in the high-dose group.

After achieving the desired LDL cholesterol goal, non-HDL cholesterol is the second lipid target. Strategies to lower non-HDL cholesterol include further LDL lowering, raising HDL cholesterol, or lowering triglycerides, which will lower total cholesterol. The LDL cholesterol should be reduced to the greatest extent possible with the highest tolerable dose of a statin. If further LDL lowering is desired, combination therapy with an intestinal agent can be considered. An additional 20% to 25% reduction in LDL cholesterol can be achieved with the addition of a resin or ezetimibe to a statin. Outcome studies comparing combination therapy to statins alone have not been completed, so it is not known if this strategy will further reduce cardiovascular events.

Niacin therapy has the greatest efficacy in raising HDL cholesterol. Niacin as monotherapy has been shown to reduce the incidence of nonfatal MI in men with a previous MI in the Coronary Drug Project.¹² Outcome studies combining niacin to statin therapy are ongoing.

The treatment of hypertriglyceridemia consists of a combination of lifestyle modification and pharmacological therapy when lifestyle changes alone cannot achieve the desired triglyceride goal. A diet that concentrates on reducing complex carbohydrates can lower triglyceride levels. Fish oils at doses of 3 to 4 grams daily can reduce triglycerides by approximately 35%.¹³ Fibrates can also reduce triglycerides by 30% to 40%. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) compared 1,200 mg of gemfibrozil with placebo in more than 2,500 men with coronary heart disease and low HDL cholesterol levels (40 mg/dL or less).¹⁴ There was a 24% reduction in the combined endpoint of

death from coronary disease, nonfatal MI, and stroke in the gemfibrozil group. There are, however, no convincing outcome data using a combination of a statin and a fibrate. The results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which showed no reduction in cardiovascular events with the combination of simvastatin plus fenofibrate compared to simvastatin alone, raised questions about the benefit of combination therapy in diabetic patients.¹⁵

ApoB can be considered the third lipid target after LDL and non-HDL cholesterol goals are achieved. Achieving an LDL and non-HDL goal does not guarantee that apoB is optimally reduced as well. In the Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY) II trial, fewer than half of the patients who achieved LDL and non-HDL cholesterol targets were able to meet the apoB target of < 90 mg/dL.¹⁶ Clinical trials are needed to determine if targeting apoB once LDL and non-HDL cholesterol goals are achieved can bring about further reductions in risk.

BLOOD PRESSURE GOALS

Managing hypertension in patients with known coronary heart disease can both prevent cardiovascular events and reduce myocardial ischemia. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommended treating systolic and diastolic blood pressure to less than 140/90 mm Hg, except in individuals with diabetes or renal disease (in whom the recommended goal is < 130/80 mm Hg).¹⁷ An American Heart Association (AHA) Scientific Statement published in 2007 suggested a blood pressure target of less than 130/80 mm Hg for patients with demonstrated coronary artery disease.¹⁸

Some investigators have raised concern that excessive lowering of diastolic blood pressure may impair coronary artery perfusion, leading to an increase in cardiovascular events, especially in elderly patients. Epidemiological studies have shown a linear relationship between increasing diastolic blood pressure and cardiovascular risk beginning at 75 mm Hg.¹⁹ A meta-analysis of seven randomized clinical trials observed a J-shaped relationship between diastolic blood pressure and mortality in both treated and untreated subjects and therefore concluded that the increased risk seen with lower diastolic pressures was not a blood pressure treatment effect.²⁰ This suggests that patients with the lowest diastolic blood pressures or the widest pulse pressure represent a less healthy cohort.

Beta-blockers are the drugs of first choice for patients with hypertension and chronic stable angina because they are the most effective agents in reducing myocardial

ischemia. In addition, beta-blockers are indicated after an MI and for heart failure. Calcium-channel blockers (CCBs) reduce myocardial oxygen demand and vasodilate coronary arteries and are indicated in the treatment of chronic stable angina and ischemic heart disease. CCBs used in combination with beta-blockers can further reduce blood pressure or alleviate angina. Angiotensin-converting enzyme (ACE) inhibitors are indicated for patients with diabetes and heart failure and are recommended for all patients after an MI. Several studies, such as the Heart Outcomes Prevention Evaluation (HOPE) study²¹ and the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) study,²² have shown reductions in cardiovascular events in individuals with established CHD or at high risk for the development of cardiovascular disease with the use of ACE inhibitors compared with placebo.

DIABETES MELLITUS

Diabetic patients with CHD are at very high risk of developing a future cardiac event. Evidence from a number of clinical trials suggests that intensive compared with standard glycemic control significantly reduces coronary events.²³ Rapidly lowering glycated hemoglobin levels, however, may cause harm, as suggested by the increased mortality seen in the intensive therapy arm of the ACCORD study.²⁴ A more gradual reduction in glycated hemoglobin avoiding hypoglycemia may translate into long-term CHD event reduction.

There is evidence that an intensified multifactorial intervention in patients with diabetes can achieve a significant reduction in cardiovascular events. A study performed by the Steno Diabetes Center aggressively treated diabetic patients to guideline targets with tight glucose control, lipid-lowering agents, blood pressure control with ACE inhibitors, and aspirin compared with conventional treatment and showed a nearly 50% reduction in the risk of cardiovascular disease in the aggressively controlled group.²⁵ This suggests that the greatest risk reduction will be achieved only if all cardiovascular risk factors are targeted and treated to recommended goals.

CONCLUSION

PCI has achieved a substantial improvement in quality of life for patients with chronic angina. Reduction in cardiac events, however, is best achieved by aggressive optimization of known cardiovascular risk factors. The COURAGE trial demonstrated that if optimal therapy is used, medical therapy and interventional therapy have the same long-term outcomes. Future studies will help to clarify the optimal treatment targets and help guide the use of combination therapies. ■

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