Hypertension Management in Adults With Diabetes

AMERICAN DIABETES ASSOCIATION

Hypertension (defined as a blood pressure ≥140/90 mmHg) is an extremely common comorbid condition in diabetes, affecting ~20–60% of patients with diabetes, depending on obesity, ethnicity, and age. In type 2 diabetes, hypertension is often present as part of the metabolic syndrome of insulin resistance also including central obesity and dyslipidemia. In type 1 diabetes, hypertension may reflect the onset of diabetic nephropathy. Hypertension substantially increases the risk of both macrovascular and microvascular complications, including stroke, coronary artery disease, and peripheral vascular disease, retinopathy, nephropathy, and possibly neuropathy. In recent years, adequate data from well-designed randomized clinical trials have demonstrated the effectiveness of aggressive treatment of hypertension in reducing both types of diabetes complications.

Scope

These recommendations are intended to apply to nonpregnant adults with type 1 or type 2 diabetes.

Target audience

These recommendations are intended for the use of health care professionals who care for patients with diabetes and hypertension, including specialist and primary care physicians, nurses and nurse practitioners, physicians' assistants, educators, dietitians, and others.

Method

These recommendations are based on the American Diabetes Association Technical Review "Treatment of Diabetes in Adult Patients with Hypertension." A technical review is a systematic review of the medical literature that has been peer-reviewed by the American Diabetes Association's Professional Practice Committee.

Evidence review: hypertension as a risk factor for complications of diabetes

Diabetes increases the risk of coronary events twofold in men and fourfold in women. Part of this increase is due to the frequency of associated cardiovascular risk factors such as hypertension, dyslipidemia, and clotting abnormalities. In observational studies, people with both diabetes and hypertension have approximately twice the risk of cardiovascular disease as nondiabetic people with hypertension. Hypertensive diabetic patients are also at increased risk for diabetes-specific complications including retinopathy and nephropathy. In the U.K. Prospective Diabetes Study (UKPDS) epidemiological study, each 10-mmHg decrease in mean systolic blood pressure was associated with reductions in risk of 12% for any complication related to diabetes, 15% for deaths related to diabetes, 11% for myocardial infarction, and 13% for microvascular complications. No threshold of risk was observed for any end point.

Evidence for target levels of blood pressure in patients with diabetes

The UKPDS and the Hypertension Optimal Treatment (HOT) trial both demonstrated improved outcomes, especially in preventing stroke, in patients assigned to lower blood pressure targets. Optimal outcomes in the HOT study were achieved in the group with a target diastolic blood pressure of 80 mmHg (achieved 82.6 mmHg). Randomized clinical trials demonstrate the benefit of targeting a diastolic blood pressure of ≤80 mmHg. Epidemiological analyses show that blood pressures ≥120/70 mmHg are associated with increased cardiovascular event rates and mortality in persons with diabetes. Therefore, a target blood pressure goal of <130/80 mmHg is reasonable if it can be safely achieved. There is no threshold value for blood pressure, and risk continues to decrease well into the normal range. Achieving lower levels, however, would increase the cost of care as well as drug side effects and is often difficult in practice. Whether even more aggressive treatment would further reduce the risk is an unanswered question, but may be answered by clinical trials now in progress.

Evidence for non-drug management of hypertension

Dietary management with moderate sodium restriction has been effective in reducing blood pressure in individuals with essential hypertension. Several controlled studies have looked at the relationship between weight loss and blood pressure reduction. Weight reduction can reduce blood pressure independent of sodium intake and also can improve blood glucose and lipid levels. The loss of one kilogram in body weight has resulted in decreases in mean arterial blood pressure of ~1 mmHg. The role of very low calorie diets and pharmacologic agents that induce weight loss in the management of hypertension in diabetic patients has not

The recommendations in this paper are based on the evidence reviewed in the following publication: The treatment of hypertension in adult patients with diabetes (Technical Review). *Diabetes Care* 25:134–147, 2002.

The initial draft of this position statement was prepared by Carlos Arauz-Pacheco, MD, Marian A. Parrott, MD, MPH, and Phillip Raskin, MD. The paper was peer-reviewed, modified, and approved by the Professional Practice Committee and the Executive Committee, October 2001.

Abbreviations: ACE, angiotensin-converting enzyme; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARB, angiotensin receptor blocker; DCCB, dihydropyridine calcium channel blocker; HOT, Hypertension Optimal Treatment; JNC VI, Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; UKPDS, U.K. Prospective Diabetes Study.

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been adequately studied. Some appetite suppressants may induce increases in blood pressure levels, so these must be used with care. Given the present evidence, weight reduction should be considered an effective measure in the initial management of mild-to-moderate hypertension, and these results could probably be extrapolated to the diabetic hypertensive population.

Sodium restriction has not been tested in the diabetic population in controlled clinical trials. However, results from controlled trials in essential hypertension have shown a reduction in systolic blood pressure of ~5 mmHg and diastolic blood pressure of 2–3 mmHg with moderate sodium restriction (from a daily intake of 200 mmol [4,600 mg] to 100 mmol [2,300 mg] of sodium per day). A dose response effect has been observed with sodium restriction. Even when pharmacologic agents are used, there is often a better response when there is concomitant salt restriction due to the aforementioned volume component of the hypertension that is almost always present. The efficacy of these measures in diabetic individuals is not known.

Moderately intense physical activity, such as 30–45 min of brisk walking most days of the week, has been shown to lower blood pressure and is recommended in the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI). The American Diabetes Association Consensus Development Conference on the Diagnosis of Coronary Heart Disease in People with Diabetes has recommended that diabetic patients who are 35 years of age or older and are planning to begin a vigorous exercise program should have exercise stress testing or other appropriate noninvasive testing. Stress testing is not generally necessary for asymptomatic patients beginning moderate exercise such as walking. Smoking cessation and moderation of alcohol intake are also recommended by JNC VI and are clearly appropriate for all patients with diabetes.

Evidence for drug therapy of hypertension

There are a number of trials demonstrating the superiority of drug therapy versus placebo in reducing outcomes including cardiovascular events and microvascular complications of retinopathy and progression of nephropathy. These studies used different drug classes, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics, and β-blockers, as the initial step in therapy. All of these agents were superior to placebo; however, it must be noted that many patients required three or more drugs to achieve the specified target levels of blood pressure control. Overall there is strong evidence that pharmacologic therapy of hypertension in patients with diabetes is effective in producing substantial decreases in cardiovascular and microvascular diseases.

There are limited data from trials comparing different classes of drugs in patients with diabetes and hypertension. The UKPDS-Hypertension in Diabetes Study showed no significant difference in outcomes for treatment based on an ACE inhibitor compared with a β-blocker. There were slightly more withdrawals due to side effects and there was more weight gain in the β-blocker group. In postmyocardial infarction patients, β-blockers have been shown to reduce mortality.

There are numerous studies documenting the effectiveness of ACE inhibitors and ARBs in retarding the development and progression of diabetic nephropathy. ACE inhibitors have a favorable effect on cardiovascular outcomes, as demonstrated in the MICRO-HOPE study. This cardiovascular effect may be mediated by mechanisms other than blood pressure reduction. It is possible that other drug classes may behave similarly.

Some studies have shown an excess of selected cardiac events in patients treated with dihydropyridine calcium channel blockers (DCCBs) compared with ACE inhibitors. Ongoing trials including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study should help to resolve this issue. DCCBs in combination with ACE inhibitors, β-blockers, and diuretics, as in the HOT study and the Systolic Hypertension in Europe (Syst-Eur) Trial, did not appear to be associated with increased cardiovascular morbidity. However, ACE inhibitors and β-blockers appear to be superior to DCCBs in reducing myocardial infarction and heart failure. Therefore, DCCBs appear to be appropriate agents in addition to, but not instead of, ACE inhibitors and β-blockers. Non-DCCBs (i.e., verapamil and diltiazem) may reduce coronary events. In short-term studies, non-DCCBs have reduced albumin excretion.

There are no long-term studies of the effect of α-blockers, loop diuretics, or centrally acting adrenergic blockers on long-term complications of diabetes. The α-blocker arm of the ALLHAT study was stopped by the data and safety monitoring committee because of an increase in cases of new-onset heart failure in patients assigned to the α-blocker. While this could merely represent unmasking of heart failure in patients previously treated with an ACE inhibitor or a diuretic, it seems reasonable to use these as second-line agents when preferred classes have been ineffective or when other specific indications, such as benign prostatic hypertrophy (BPH), are present.

Summary

There is a strong epidemiological connection between hypertension in diabetes and adverse outcomes of diabetes. Clinical trials demonstrate the efficacy of drug therapy versus placebo in reducing these outcomes and in setting an aggressive blood pressure–lowering target of <130/80 mmHg. It is very clear that many people will require three or more drugs to achieve the recommended target. Achievement of the target blood pressure goal with a regimen that does not produce burdensome side effects and is at reasonable cost to the patient is probably more important than the specific drug strategy.

Because many studies demonstrate the benefits of ACE inhibitors on multiple adverse outcomes in patients with diabetes, including both macrovascular and microvascular complications, in patients with either mild or more severe hypertension and in both type 1 and type 2 diabetes, the established practice of choosing an ACE inhibitor as the first-line agent in most patients with diabetes is reasonable. In patients with microalbuminemia or clinical nephropathy, both ACE inhibitors (type 1 and type 2 patients) and ARBs (type 2 patients) are considered first-line therapy for the prevention of and progression of nephropathy. However, other strategies including diuretic and β-blocker–based therapy are also supported by evidence. Because of lingering concerns about the lower effectiveness of DCCBs (compared with ACE inhibitors, ARBs, β-blockers, or diuretics) in decreasing coronary events and heart failure and in

Table 1—*Indications for initial treatment and goals for adult hypertensive diabetic patients*

	Systolic	Diastolic
Goal (mmHg)	<130	<80
Behavioral therapy alone (maximum 3 months) then add pharmacologic treatment	130–139	80–89
Behavioral therapy + pharmacologic treatment	≥140	≥90

reducing progression of renal disease in diabetes, these agents should be used as second-line drugs for patients who cannot tolerate the other preferred classes or who require additional agents to achieve the target blood pressure. Other classes, including α-blockers, may be used under specific indications (such as symptoms of BPH for α-blockers) or other agents have failed to control the blood pressure or have unacceptable side effects. Blood pressure, orthostatic changes, renal function, and serum potassium should be monitored at appropriate intervals.

Treatment decisions should be individualized based on the clinical characteristics of the patient, including comorbidities as well as tolerability, personal preferences, and cost.

Recommendations

Refer to Table 1 for recommendations on initial treatment and goals for adult hypertensive diabetic patients.

Screening and diagnosis

- Blood pressure should be measured at every routine diabetes visit. Patients found to have systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg should have blood pressure confirmed on a separate day. (C)
- Orthostatic measurement of blood pressure should be performed when clinically indicated to assess for the presence of autonomic neuropathy. (E)

Goals

- Patients with diabetes should be treated to a systolic blood pressure <130 mmHg. (B)
- Patients with diabetes should be treated to a diastolic blood pressure <80 mmHg. (B)

Treatment

- Patients with a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg should be given lifestyle/behavioral therapy alone for a maximum of 3 months and then, if targets are not achieved, should also be treated pharmacologically with agents that block the renin-anglotensin system. (E)
- Patients with hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) should receive drug therapy in addition to lifestyle/behavioral therapy. (A)
- Multiple drug therapy (two or more agents at proper doses) is generally required to achieve blood pressure targets. (B)
- Initial drug therapy for those with a blood pressure >140/90 should be with a drug class demonstrated to reduce CVD events in patients with diabetes (ACE inhibitors, ARBs, β-blockers, diuretics, calcium channel blockers). (A)
- All patients with diabetes and hypertension should be treated with a regimen that includes either an ACE inhibitor or ARB. If one class is not tolerated, the other should be substituted. If needed to achieve blood pressure targets, a thiazide diuretic should be added. (E)
- If ACE inhibitors or ARBs are used, monitor renal function and serum potassium levels. (E)
- While there are no adequate head-to-head comparisons of ACE inhibitors and ARBs, there is clinical trial support for each of the following statements:
  - In patients with type 1 diabetes with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. (A)
  - In patients with type 2 diabetes, hypertension, and microalbuminuria, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. (A)
  - In those with type 2 diabetes, hypertension, macroalbuminuria (>300 mg/day), and renal insufficiency, an ARB should be strongly considered. (A)
- In elderly hypertensive patients, blood pressure should be lowered gradually to avoid complications. (E)
- Patients not achieving target blood pressure on three drugs, including a diuretic, and patients with a significant renal disease should be referred to a physician experienced in the care of patients with hypertension. (E)

Bibliography

Arauz-Pacheco C, Parrott MA, Raskin P: The treatment of hypertension in adult patients with diabetes (Technical Review). *Diabetes Care* 25:134–147, 2002

Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, Tuttle K, Douglas J, Hsueh W, Sowers J: Preserving renal function in adults with hypertension and diabetes: a consensus approach. *Am J Kid Dis* 36: 646–661, 2000

Dyslipidemia Management in Adults With Diabetes

AMERICAN DIABETES ASSOCIATION

RATIONALE FOR TREATMENT OF DYSLIPIDEMIA — The rationale for the treatment of diabetic dyslipidemia is discussed in detail in the American Diabetes Association (ADA) technical review "Management of Dyslipidemia in Adults With Diabetes" (1). Type 2 diabetes is associated with a two- to fourfold excess risk of cardiovascular disease (CVD).

PREVALENCE OF DYSLIPIDEMIA IN TYPE 2 DIABETES — The most common pattern of dyslipidemia in patients with type 2 diabetes patients is elevated triglyceride levels and decreased HDL cholesterol levels. The mean concentration of LDL cholesterol in those with type 2 diabetes is not significantly different from that in those individuals who do not have diabetes. However, qualitative changes in LDL cholesterol may be present. In particular, patients with diabetes tend to have a higher proportion of smaller and denser LDL particles, which are more susceptible to oxidation and may thereby increase the risk of cardiovascular events. Insufficient data are available to make recommendations on the measurement of particle size in clinical practice.

As in those who do not have diabetes, lipid levels may be affected by factors unrelated to glycemia or insulin resistance, such as renal disease, hypothyroidism, and frequent occurrence of genetically determined lipoprotein disorders (e.g., familial combined hyperlipidemia and familial hypertriglyceridemia). These genetic disorders may contribute to the severe hypertriglyceridemia seen in some patients with diabetes. Furthermore, use of alcohol or estrogen may also contribute to hypertriglyceridemia.

LIPOPROTEIN RISK FACTORS FOR CVD — Available prospective cohort studies suggest that lipid abnormalities are associated with increased risk of cardiovascular events in patients both with and without diabetes. Various studies have demonstrated that LDL, HDL, and triglycerides are independent predictors of CVD (2).

CLINICAL TRIALS OF LIPID LOWERING IN DIABETIC SUBJECTS — The recently completed Heart Protection Study has been the largest study to date, enrolling and randomizing 5,963 patients age >40 years with diabetes and total cholesterol >135 mg/dl. In this trial, patients with diabetes assigned to simvastatin had a 22% reduction (95% CI 13–30) in the event rate for major CVD events. This risk reduction was similar across all LDL subcategories examined, including patients with lower pretreatment LDL cholesterol levels (<116 mg/dl) and those without identified vascular disease (3). Numerous other statin trials have included much smaller numbers of patients with diabetes but have demonstrated similar reductions in CVD events.

Two outcomes studies have been conducted with the fibric acid derivative gemfibrozil. In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), gemfibrozil was associated with a 24% decrease in cardiovascular events in diabetic subjects with prior cardiovascular disease, low HDL (<40 mg/dl), and modestly elevated triglycerides (4).

MODIFICATION OF LIPOPROTEINS BY MEDICAL NUTRITION THERAPY AND PHYSICAL ACTIVITY — There is little evidence from clinical trials to determine the effect of different dietary interventions on the incidence of cardiovascular events. Observational studies suggest that patients who report healthier diets and greater physical activity have fewer cardiovascular events (5,6). The ADA has made recommendations for both medical nutrition therapy (MNT) (5) and physical activity (6). Weight loss and increased physical activity will lead to decreased triglycerides and increased HDL cholesterol levels and also to modest lowering of LDL cholesterol levels. Patients with diabetes who are overweight should be given a prescription for MNT and for increased physical activity. The proportion of saturated fat in the meal plan should be reduced. The ADA suggests an increase in either carbohydrate or monounsaturated fat to compensate for the reduction in saturated fat. Some (but not all) studies suggest that a high–monounsaturated fat diet may have better metabolic effects than a high-carbohydrate diet, although other experts have suggested that such a dietary modification may make weight loss more difficult in obese patients with diabetes.

Recommendations of the American Heart Association for patients with CVD (7) have suggested that the maximal MNT typically reduces LDL cholesterol 15–25 mg/dl (0.40–0.65 mmol/l). Lifestyle intervention may be evaluated at regular intervals, with consideration of pharmacological therapy between 3 and 6 months.

MODIFICATION OF LIPOPROTEINS BY GLUCOSE-LOWERING AGENTS — Interventions to improve glycemia usually lower triglyceride levels modestly. In general, glucose-lowering agents do not change or have only a minimal effect on HDL levels. Thiazo-

The recommendations in this paper are based on the evidence reviewed in the following publication: Management of dyslipidemia in adults with diabetes (Technical Review). *Diabetes Care* 21:160–178, 1998.

The initial draft of this paper was prepared by Steven M. Haffner, MD. This paper was peer-reviewed, modified, and approved by the Professional Practice Committee and the Executive Committee, November 1997. Most recent review/revision, 2003.

Abbreviations: ADA, American Diabetes Association; CHD, coronary heart disease: CVD, cardiovascular disease; MNT, medical nutrition therapy; NCEP, National Cholesterol Education Program.

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lidinediones may increase HDL and LDL levels, but the long-term effect of such changes is not known

TREATMENT GOALS FOR LIPOPROTEIN THERAPY — No completed clinical trials have examined the effect of implementing different lipid treatment goals, including the question of what LDL cholesterol goal should be used and whether the use of multi-drug therapy is more effective than monotherapy for patients with complex lipid abnormalities. Current trials are examining these questions.

Because of frequent changes in glycemic control in patients with diabetes and the effects on levels of LDL, HDL, total cholesterol, and triglyceride, levels should be measured every year in adult patients. If values are at low-risk levels (LDL <100 mg/dl, triglycerides <150 mg/dl, and HDL >50 mg/dl), assessment may be repeated every 2 years.

Lipid-associated risk for CVD events is graded and continuous. Target LDL cholesterol levels for adults with diabetes are <100 mg/dl (2.60 mmol/l); HDL cholesterol levels are >40 mg/dl (1.02 mmol/l); and triglyceride levels are <150 mg/dl (1.7 mmol/l). In women, who tend to have higher HDL cholesterol levels than men, an HDL goal 10 mg/dl higher may be appropriate.

The recommendations for treatment of elevated LDL cholesterol generally follow the guidelines of both the NCEP (8) and an ADA consensus development conference (9), with the following caveats. Pharmacological therapy should be initiated after lifestyle intervention has been implemented. However, in patients with clinical cardiovascular disease and LDL >100 mg/dl, pharmacological therapy should be initiated at the same time that lifestyle intervention is started.

For patients with diabetes without preexisting CVD, the current ADA recommendations for starting pharmacological therapy are *1*) an LDL cholesterol level of ≥130 mg/dl (3.35 mmol/l) and 2) a goal of <100 mg/dl (2.60 mmol/l) for LDL cholesterol. These recommendations are based not only on the high incidence of CVD in patients with diabetes (10), but also on the higher case fatality rate of these patients once they have CVD. Since a large proportion of diabetic patients die before they reach the hospital, a preventive strategy based solely on secondary prevention would not be able to "save" large numbers of these diabetic patients. In patients with LDL between 100 mg/dl (2.60 mmol/l) and 129 mg/dl (3.30 mmol/l), a variety of treatment strategies are available, including more aggressive MNT and pharmacological treatment with a statin.

Recent findings from the Heart Protection Study (3), in people with diabetes over the age of 40 years with a total cholesterol ≥135 mg/dl, suggest that statin therapy to achieve an LDL reduction of ~30% regardless of baseline LDL levels may be appropriate.

Table 1 shows the order of priorities for treatment of dyslipidemia. Treatment of LDL cholesterol is considered the first priority for pharmacological therapy of dyslipidemia for a number of reasons (1).

Hypertriglyceridemia may be a risk factor for CVD in people with diabetes. The initial therapy for hypertriglyceridemia is lifestyle intervention with weight loss, increased physical activity, restricted intake of saturated fats, incorporation of monounsaturated fats, reduction of carbohydrate intake, and reduction of alcohol consumption. In the case of severe hypertriglyceridemia (≥1,000 mg/dl [11.3 mmol/l]), severe dietary fat restriction (<10% of calories) in addition to pharmacological therapy is necessary to reduce the risk of pancreatitis.

Improved glycemic control can be very effective for reducing triglyceride levels and should be aggressively pursued. Insulin therapy (alone or with insulin sensitizers) may also be particularly effective in lowering triglyceride levels. After the achievement of optimal glycemic control (or at least after the achievement of as much improvement as likely to be possible), the physician should consider adding a fibric acid and/or niacin.

The decision to start pharmacological therapy is dependent on the clinician's judgment between triglyceride levels of 200 mg/dl (2.30 mmol/l) and 400 mg/dl (4.50 mmol/l). Above 400 mg/dl (4.50 mmol/l), strong consideration should be given to pharmacological treatment of triglyceridemia to minimize the risk of pancreatitis. In some studies, higher-dose statins are moderately effective in reducing triglyceride levels in markedly hypertriglyceridemic subjects (triglyceride ≥300 mg/dl [3.40 mmol/l]). Gemfibrozil should not be initiated alone in diabetic patients who have undesirable levels of both triglyceride and LDL cholesterol. Fenofibrate has greater LDL-lowering effects, is arguably safer in combination with statin therapy, and may be useful in those patients with diabetes with combined hyperlipidemia.

Although HDL cholesterol is a powerful predictor of CVD in patients with diabetes, it is difficult to raise HDL cholesterol levels without pharmacological intervention. Nicotinic acid, which should be used with caution in patients with diabetes, and fibrates can effectively increase HDL cholesterol levels. Low doses of nicotinic acid (≤2 g nicotinic acid/day) may not have much of a detrimental effect of glycemic control, and any deterioration may be easily remediable by adjustment of hypoglycemic medications. Behavioral interventions (weight loss,

Table 1—*Order of priorities for treatment of diabetic dyslipidemia in adults*

I. LDL cholesterol lowering
Lifestyle interventions
Preferred
HMG CoA reductase inhibitor (statin)
Others
Bile acid binding resin (resin), cholesterol absorption inhibitor, fenofibrate or niacin
II. HDL cholesterol raising
Lifestyle interventions
Nicotinic acid or fibrates
III. Triglyceride lowering
Lifestyle interventions
Glycemic control
Fibric acid derivative (gemfibrozil, fenofibrate)
Niacin
High-dose statins (in those who also have high LDL cholesterol)
IV. Combined hyperlipidemia
First choice
Improved glycemic control plus high-dose statin
Second choice
Improved glycemic control plus statin plus fibric acid derivative
Third choice
Improved glycemic control plus statin plus nicotinic acid

Decision for treatment of high LDL before elevated triglyceride is based on clinical trial data indicating safety as well as efficacy of the available agents. The combination of statins with nicotinic acid, fenofibrate, and especially gemfibrozil may carry an increased risk of myositis. See text for recommendations for patients with triglyceride levels >400 mg/dl.

smoking cessation, increased physical activity) may increase HDL cholesterol.

In some cases, combined lipid therapy may be initiated. Several options are shown in Table 1. The combination of statins with nicotinic acid, fenofibrate, and especially gemfibrozil has been associated with increased risk of myositis, although the risk of clinical myositis (as opposed to elevated creatinine phosphokinase levels) appears to be low. However, the risk of myositis may be increased with the combination of gemfibrozil and a statin or in patients with renal disease. Combinations of statins with nicotinic acid and fibrates are extremely effective in modifying diabetic dyslipidemia.

LIPID-LOWERING AGENTS — The choice of statin should depend principally on the LDL reduction needed to achieve the target (<100 mg/dl [2.60 mmol/l]) and on the judgment of the treating physician.

It should also be noted that the higher doses of statins may be moderately effective at reducing triglyceride levels (though not necessarily at raising HDL levels) and thus may reduce the need for combination therapy. With the use of statins, LDL levels may be reduced to ≤50 mg/dl (1.30 mmol/l). There is no safety data at such low LDL levels. The use of very high-dose statin therapy (e.g., simvastatin 80 mg or atorvastatin 40 or 80 mg) to treat hypertriglyceridemia should be restricted to patients with both high LDL cholesterol levels and high triglyceride levels.

Changes in therapy should be based on laboratory follow-up between 4 and 12 weeks after initiating therapy. Once goals have been achieved, laboratory follow-up every 6–12 months is suggested.

CONSIDERATIONS IN THE TREATMENT OF ADULTS WITH TYPE ONE DIABETES — Patients with type 1 diabetes who are in good glycemic control tend to have normal levels of lipoproteins, unless they are overweight or obese, in which case they may get a lipid profile very similar to that seen in type 2 diabetes. Their composition of lipoproteins may be abnormal, but the effects of these compositional abnormalities in relation to CVD are unknown. There is relatively little observational data on lipoproteins and CVD, and there are no clinical trials relating lipoproteins to CVD. It seems reasonable that if patients with type 1 diabetes have LDL cholesterol levels that are above the goals recommended for those with type 2 diabetes (<100 mg/dl), they should be aggressively treated. Improved glycemic control may be even more important in those with type 1 diabetes than in those with type 2 diabetes for reduction of CVD (e.g., Wisconsin Epidemiologic Study of Diabetic Retinopathy [WESDR]).

CONCLUSIONS — Aggressive therapy of diabetic dyslipidemia will reduce the risk of CVD in patients with diabetes. Primary therapy should be directed first at lowering LDL levels. The goal is to reduce LDL concentrations to ≤100 mg/dl [2.60 mmol/l]. The initiation level for behavioral interventions is also an LDL cholesterol of ≥100 mg/dl (2.60 mmol/l). The initial pharmacological therapy should be to use statins. A cholesterol absorption inhibitor, a resin, niacin, or fenofibrate may be added if necessary to reach the LDL goal or in the case of statin intolerance. There are no outcome studies of combination lipid-lowering therapies.

In addition, if the HDL is <40 mg/dl, a fibric acid, such as fenofibrate, or niacin might be used in patients with LDL cholesterol between 100 and 129 mg/dl.

The initial therapy for hypertriglyceridemia is improved glycemic control and lifestyle intervention. Additional triglyceride lowering can be achieved with fibric acid derivatives (gemfibrozil or fenofibrate) or niacin. For subjects with both high LDL and triglyceride levels, high dose statins may be used.

RECOMMENDATIONS

Screening

- In adult patients, test for lipid disorders at least annually and more often if needed to achieve goals. In adults with low-risk lipid values (LDL <100 mg/dl, HDL >50 mg/dl, and triglycerides <150 mg/dl), repeat lipid assessments every 2 years. (E)

Treatment recommendations and goals

- Lifestyle modification focusing on the reduction of saturated fat and cholesterol intake, weight loss, increased physical activity, and smoking cessation has been shown to improve the lipid profile in patients with diabetes. (A)
- Patients who do not achieve lipid goals with lifestyle modifications require pharmacological therapy. (A)
- Lower LDL cholesterol to <100 mg/dl (2.6 mmol/l) as the primary goal of therapy for adults. (B)
- Lowering LDL cholesterol with a statin is associated with a reduction in cardiovascular events. (A)
- In people with diabetes over the age of 40 years with a total cholesterol ≥135 mg/dl, statin therapy to achieve an LDL reduction of ~30% regardless of baseline LDL levels may be appropriate. (A)
- In children and adolescents with diabetes, LDL cholesterol should be lowered to <100 mg/dl (2.60 mmol/l) using MNT and medications, based on LDL level and other cardiovascular risk factors in addition to diabetes. (E)
- Lower triglycerides to <150 mg/dl (1.7 mmol/l), and raise HDL cholesterol to >40 mg/dl (1.15 mmol/l). In women, an HDL goal 10 mg/dl higher may be appropriate. (C)
- Lowering triglycerides and increasing HDL cholesterol with a fibrate is associated with a reduction in cardiovascular events in patients with clinical CVD, low HDL, and near-normal levels of LDL. (A)
- Combination therapy using statins and fibrates or niacin may be necessary to achieve lipid targets, but has not been evaluated in outcomes studies for either event reduction or safety. (E)

References

1. Haffner SM: Management of dyslipidemia in adults with diabetes (Technical Review). *Diabetes Care* 21:160–178, 1998
2. Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR: Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus (UKPDS 23). *BMJ* 316:823–828, 1998
3. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 361: 2005–2016, 2003
4. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density li-

poprotein cholesterol: Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 341:410–418, 1999
5. American Diabetes Association: Nutrition principles and recommendations in diabetes (Position Statement). *Diabetes Care* 27 (Suppl. 1):S36–S46, 2004
6. American Diabetes Association: Physical activity/exercise and diabetes (Position Statement). *Diabetes Care* 27:S58–S62, 2004
7. Grundy SM, Balady GJ, Criqui MH, Fletcher G, Greenland P, Hiratzka LF, Houston-Miller N, Kris-Etherton P, Krumholz HM, LaRosa J, Ockene IS, Pearson TA, Reed J, Smith SC, Washington R: When to start cholesterol-lowering therapy in patients with coronary heart disease: a statement for healthcare professionals from the American Heart Association task force on risk reduction. *Circulation* 95:1683–1685, 1997
8. NCEP Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285: 2486–2497, 2001
9. American Diabetes Association: Detection and management of lipid disorders in diabetes (Consensus Statement). *Diabetes Care* 16:828–834, 1993
10. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229–234, 1998

Smoking and Diabetes

AMERICAN DIABETES ASSOCIATION

BACKGROUND — As documented in the American Diabetes Association's technical review "Smoking and Diabetes" (1), a large body of evidence from epidemiological, case-control, and cohort studies provides convincing documentation of the causal link between cigarette smoking and health risks. Cigarette smoking is the leading avoidable cause of mortality in the U.S., accounting for 400,000 deaths each year. Cigarette smoking accounts for one out of every five deaths in the U.S. and is the most important modifiable cause of premature death. Cigarettes provide the delivery system for nicotine, an addictive substance related to various pharmacological, biochemical, and psychological processes that interact to support a compulsive pattern of drug use.

Much of the prior work documenting the impact of smoking on health did not discuss separately results on subsets of individuals with diabetes, suggesting the identified risks are at least equivalent to those found in the general population. Other studies of individuals with diabetes consistently found a heightened risk of morbidity and premature death associated with the development of macrovascular complications among smokers. The cardiovascular burden of diabetes, especially in combination with smoking, has not been effectively communicated to people with diabetes or to health care providers, and there is little evidence that this risk factor is being addressed as consistently and comprehensively as its importance requires. Smoking is also related to the premature development of microvascular complications of diabetes and may even have a role in the development of type 2 diabetes (1).

General smoking prevalence decreased substantially up until about 1990 because of extensive public health efforts, which included making the population aware of the health hazards of active and passive smoking, implementation of smoking cessation interventions, and policy changes. However, since then there has been very little further reduction, and about 25% of American adults continue to smoke, with variations reported by ethnic and sociodemographic groups. These figures mirror the prevalence of tobacco use among individuals with diabetes. It appears that adolescents may initiate smoking after being diagnosed with diabetes and that the prevalence of tobacco use decreases with disease duration (1–3).

Effectiveness of smoking cessation counseling

Smoking cessation is one of the few interventions that can safely and cost-effectively be recommended for all patients, and it has been identified as a gold standard against which other preventive behaviors should be evaluated. A number of large randomized clinical trials have demonstrated the efficacy and cost-effectiveness of certain forms of provider and behavioral counseling in changing smoking behavior of primary care and hospitalized patients. This work, combined with the more limited studies specific to individuals with diabetes, suggests that smoking cessation counseling is effective in reducing tobacco use in this high-risk group (3,4). This evidence has been summarized in the updated clinical practice guideline from the U.S. Public Health Service "Treating Tobacco Use and Dependence" (4).

Several treatment characteristics have been identified as critical to achieve cessation. These characteristics include brief counseling by multiple health care providers, use of individual or group counseling strategies, and use of pharmacotherapy (1). Effective pharmacotherapies now include nicotine replacement therapy in a variety of forms (gum, patch, inhaler, spray) and antidepressants (bupropion and nortriptyline). Although many large-scale well-controlled outcome studies have included patients with diabetes, few have reported results separately for patients with diabetes versus other participants. Special issues that affect successful abstinence have been identified in these studies and include weight management and depression. Postcessation weight gain may be an impediment to smoking cessation, especially among women or other people concerned with weight management (4). The presence of comorbid psychiatric conditions such as depression is associated with a greater prevalence of smoking and an increased risk of relapse after quitting. Though not reported separately, these issues are expected to be at least equally relevant for diabetic patients as for general patients (1).

Smoking cessation delivery systems

Despite demonstrated efficacy and cost-effectiveness, smoking cessation has not received the priority it deserves from health care providers. Only about half of smokers with diabetes have been advised to quit smoking by their health care providers (1). One important means of assuring systematic advice regarding the prevention and cessation of tobacco use is through the implementation of smoking cessation delivery systems in office practices and hospitals. These systems require organizational changes in clinics and hospitals to systematically identify all tobacco users at every visit, so that evaluation of smoking status becomes a routine vital sign (1,4). After tobacco users have been identified by staff, clinicians should provide a brief assessment of interest in quitting, advise those without current interest how important it is to quit, and connect those prepared to quit with those who can provide further information, assistance, and follow-up.

The recommendations in this paper are based on the evidence reviewed in the following publication: Smoking and diabetes (Technical Review). *Diabetes Care* 22:1887–1898, 1999.

The initial draft of this paper was prepared by Debra Haire-Joshu, PhD, Russell E. Glasgow, PhD, and Tiffany L. Tibbs, MA. The paper was peer-reviewed, modified, and approved by the Professional Practice Committee and the Executive Committee, October 2003.

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Table 1—*Recommendations regarding diabetes and smoking (E)*

Assessment of smoking status and history
- Systematic documentation of a history of tobacco use must be obtained from all adolescent and adult individuals with diabetes.

Counseling on smoking prevention and cessation
- All health care providers should advise individuals with diabetes not to initiate smoking. This advice should be consistently repeated to prevent smoking and other tobacco use among children and adolescents with diabetes under age 21 years.
- Among smokers, cessation counseling must be completed as a routine component of diabetes care.
- Every smoker should be urged to quit in a clear, strong, and personalized manner that describes the added risks of smoking and diabetes.
- Every diabetic smoker should be asked if he or she is willing to quit at this time.
  If no, initiate brief and motivational discussion regarding need to stop using tobacco, risks of continued use, and encouragement to quit as well as support when ready.
  If yes, assess preference for and initiate either minimal, brief, or intensive cessation counseling and offer pharmacological supplements as appropriate.

Effective systems for delivery of smoking cessation
- Training of all diabetes health care providers in the Public Health Service guidelines regarding smoking should be implemented.
- Follow-up procedures designed to assess and promote quitting status must be arranged for all diabetic smokers.

RECOMMENDATIONS— Substantial evidence supports inclusion of the prevention and cessation of tobacco use as an important component of state-of-the-art clinical diabetes care (4). Health care providers engaged in the care and management of individuals with diabetes should follow the approach summarized in Table 1 and address the following primary areas.

Ask

The routine assessment of current tobacco use is a critical first step toward encouraging cessation. The nurse or medical technician who prepares patients for their visit should do this. Nonsmoking adults are unlikely to start, so a sticker on their charts can prevent having to ask them at each visit.

Assess

In those who are current tobacco users, it is important to assess their interest in quitting by asking if they are ready to quit in the next 30 days (preparation phase) or in the next 6 months (contemplation phase). Knowledge of this readiness stage allows tailoring of the intervention to each individual (1).

Advise

Health care providers should advise all smokers with diabetes how important it is for them to quit. There is a dose-response relationship between type, intensity, and duration of treatment and smoking cessation. In general, minimal interventions are defined as <3 min of counseling, whereas brief interventions are defined as 3–10 min of counseling (4). While more intense interventions are most effective in producing long-term abstinence from tobacco, few smokers are willing to participate (1,3,4).

Assist

The keys to assistance are helping the smoker to set a quit date, providing information about how to prepare for that date, and offering counseling and/or medication assistance to those who are interested. Several pharmacological agents increase smoking cessation rates when used in conjunction with behavioral interventions. These include 4–6 weeks of nicotine replacement therapy, bupropion (150 mg p.o. q.d. or b.i.d.) or nortriptyline (25–75 mg p.o. q.h.s.).

Arrange

In addition to providing support and pharmacological assistance to smokers who are ready to quit, health care providers should also make arrangements for a follow-up phone call soon after the quit date. This can be done by clinic staff. Smokers receiving pharmacotherapy should also have a return office visit arranged.

Organize your clinic

Effective systems for implementing these guidelines should be incorporated into the routine practice of diabetes care. Recording smoking status as a vital sign increases identification of current tobacco users. Organized office information systems and delegation of cessation support and follow-up to trained office staff will greatly increase tobacco cessation rates.

Advocacy for tobacco control through public policy initiatives is also an appropriate and potentially effective way to reduce the burden of excess morbidity and mortality that tobacco use confers on those with diabetes.

References

1. Haire-Joshu D, Glasgow RE, Tibbs TL: Smoking and diabetes (Technical Review). *Diabetes Care* 22:1887–1898, 1999
2. U.S. Department of Health and Human Services: *Preventing Tobacco Use Among Young People: A Report of the Surgeon General.* Atlanta, GA, U. S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1994
3. U.S. Preventive Services Task Force: Counseling to prevent tobacco use. In *Guide to Clinical Preventive Services.* 2nd ed. Baltimore, MD, Williams & Wilkins, 1996, p. 597–609
4. Fiore M, Bailey W, Cohen S: *Treating Tobacco Use and Dependence: Clinical Practice Guideline.* Rockville, MD, U.S. Department of Health and Human Services, Public Health Service, June 2000

Aspirin Therapy in Diabetes

AMERICAN DIABETES ASSOCIATION

People with diabetes have a two- to fourfold increase in the risk of dying from the complications of cardiovascular disease. Both men and women are at increased risk. Atherosclerosis and vascular thrombosis are major contributors, and it is generally accepted that platelets are contributory. Platelets from men and women with diabetes are often hypersensitive in vitro to platelet aggregating agents. A major mechanism is increased production of thromboxane, a potent vasoconstrictor and platelet aggregant. Investigators have found evidence in vivo of excess thromboxane release in type 2 diabetic patients with cardiovascular disease. Aspirin blocks thromboxane synthesis by acetylating platelet cyclooxygenase and has been used as a primary and secondary strategy to prevent cardiovascular events in nondiabetic and diabetic individuals. Meta-analyses of these studies and large-scale collaborative trials in men and women with diabetes support the view that low-dose aspirin therapy should be prescribed as a secondary prevention strategy, if no contraindications exist. Substantial evidence suggests that low-dose aspirin therapy should also be used as a primary prevention strategy in men and women with diabetes who are at high risk (over age 40 or with other CVD risk factors) for cardiovascular events (1–3). Despite its proven efficacy, aspirin therapy is underutilized in patients with diabetes. Available data suggest that less than half of eligible patients are being treated with aspirin.

EFFICACY

Secondary prevention trials

A meta-analysis of 145 prospective controlled trials of antiplatelet therapy in men and women after myocardial infarction, stroke or transient ischemic attack, or positive cardiovascular history (vascular surgery, angioplasty, angina, etc.) has been reported by the Anti-Platelet Trialists (APT) (4). Reductions in vascular events were about one-quarter in each of these categories, and diabetic subjects had risk reductions that were comparable to nondiabetic individuals. There was a trend toward increased risk reductions with doses of aspirin between 75 and 162 mg/day. It was estimated that 38 ± 12 vascular events per 1,000 diabetic patients would be prevented if they were treated with aspirin as a secondary prevention strategy. Comparable results were seen in males and females.

Primary prevention trials

Two studies have examined the effect of aspirin in primary prevention and have included patients with diabetes. The U.S. Physicians' Health Study (5) was a primary prevention trial in which a low-dose aspirin regimen (325 mg every other day) was compared with placebo in male physicians. There was a 44% risk reduction in the treated group, and subgroup analyses in the diabetic physicians revealed a reduction in myocardial infarction from 10.1% (placebo) to 4.0% (aspirin), yielding a relative risk of 0.39 for the diabetic men on aspirin therapy.

These results are supported by the Early Treatment Diabetic Retinopathy Study (ETDRS), a mixed primary and secondary prevention trial (6). This population consisted of type 1 and type 2 diabetic men and women, about 48% of whom had a history of cardiovascular disease. The study, therefore, may be viewed as a mixed primary and secondary prevention trial. The relative risk for myocardial infarction in the first 5 years in those randomized to aspirin therapy was lowered significantly to 0.72 (CI 0.55–0.95).

The Hypertension Optimal Treatment (HOT) Trial examined the effects of 75 mg/day of aspirin vs. placebo in 18,790 hypertensive patients who were randomized to achieve diastolic blood pressure goals of 90, 85, or 80 mmHg (7). Aspirin significantly reduced cardiovascular events by 15% and myocardial infarction by 36%. This study provides further evidence for the efficacy and safety of aspirin therapy in diabetic patients with systolic blood pressure less than 160 mmHg.

SAFETY — A major risk of aspirin therapy is gastric mucosal injury and gastrointestinal hemorrhage. Aspirin increases the relative risk of major gastrointestinal bleeding (relative risk 1.6), even with relatively low doses. Enteric coating does not appear to reduce such risk. Minor bleeding episodes (epistaxis, bruising, etc.) are also increased. A well-conducted meta-analysis of primary and secondary prevention trials found a moderately increased relative risk of hemorrhagic stroke in aspirin users. Absolute risk was approximately 1 event per 1,000 users over 3–5 years. Risk did not appear to differ significantly by dosage, but power to detect such differences was limited. Contraindications to aspirin therapy include allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease.

The ETDRS (6) established that aspirin therapy was not associated with an increased risk for retinal or vitreous hemorrhage. Since the primary endpoint in this trial was retinopathy and maculopathy, these serial observations by ophthalmologists, using retinal photography in a group of diabetic subjects with retinopathy, established conclusively that aspirin therapy conveyed no increase in benefit or in risk regarding progression of diabetic retinopathy and maculopathy.

Regular use of nonsteroidal anti-

The recommendations in this paper are based on the evidence reviewed in the following publication: Aspirin therapy in diabetes (Technical Review). *Diabetes Care* 20:1767–1771, 1997.

The initial draft of this paper was prepared by John A. Colwell, MD, PhD. This paper was peer-reviewed, modified, and approved by the Professional Practice Committee in May 1997 and by the Executive Committee in June 1997. Most recent review/revision, 2000.

Abbreviations: APT, Anti-Platelet Trialists; ETDRS, Early Treatment Diabetic Retinopathy Study.

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inflammatory drugs may increase the risk for chronic renal disease and may impair blood pressure control in hypertensive patients. However, a low dose of aspirin is a very weak inhibitor of renal prostaglandin synthesis and has no clinically significant effect on renal function or on blood pressure control.

DOSAGE — The platelet release reaction is exquisitely sensitive to inhibition by aspirin. In this regard, it has been shown that a dose as low as 75 mg of enteric-coated aspirin is just as effective as higher doses of either plain or enteric-coated aspirin in inhibiting thromboxane synthesis. When platelet turnover is rapid, as may be the case with diabetic vascular disease, the steady plasma aspirin concentration from enteric preparations theoretically allows for constant suppression of thromboxane synthesis.

The APT meta-analysis (4) explored the results achieved with various doses of aspirin, alone or in combination with other antiplatelet agents, including dipyridamole and sulfinpyrazone. Whereas risk reductions of 21 ± 4% were seen in cardiovascular events in 30 trials in which doses of 500–1,500 mg/day were used, a trend for greater risk reductions of 29 ± 7% was seen in 5,000 patients in whom doses of 75 mg/day were used. Comparable risk reductions of 28 ± 3% were seen in 12 trials in which doses of 160–325 mg/day were used. No evidence was found that combinations of aspirin with other antiplatelet drugs were any more effective than aspirin alone. Because low-dose aspirin (75–162 mg/day) appears to be equally or more effective, and possibly to have lower risk than higher doses, low-dose aspirin should be recommended routinely.

SPECIAL CONSIDERATIONS — The meta-analysis of the secondary prevention trials provided sample sizes that were adequate to determine aspirin's efficacy in a wide variety of patients. Separate analyses were done in males and females, patients with or without diastolic hypertension, those over or under age 65 years, and in diabetic and nondiabetic subjects. Proportional benefits of aspirin therapy were seen in all subgroups studied. Absolute benefit was greater among those at high risk (over age 65 years, diastolic hypertension, diabetes). Intervention trials in women are underway. Case-control studies have shown that the use of one to six aspirins a week is associated with a reduced risk for myocardial infarction in women. Further, the APT meta-analysis of secondary prevention trials showed no difference in responses in men and women, and the ETDRS included men and women in the trial. Diabetes appears to place women at high risk for myocardial infarction. For these reasons, recommendations in this article apply to men and women with diabetes.

Although data are limited in diabetic subjects, agents such as clopidogrel may be considered as a substitute in the case of aspirin allergy. In one large study (CAPRIE), clopidogrel (75 mg) was slightly more effective than aspirin (325 mg) in reducing the combined risk of stroke, myocardial infarction, or vascular death in diabetic and nondiabetic subjects (8). Other approaches, such as blocking a key platelet receptor (GPIIb/IIIa), are under study.

RECOMMENDATIONS

1. Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in diabetic men and women with a history of myocardial infarction, vascular bypass procedure, stroke or transient ischemic attack, peripheral vascular disease, claudication, and/or angina. (A)
2. Use aspirin therapy therapy (75–162 mg/day) as a primary prevention strategy in men and women with type 2 diabetes at increased cardiovascular risk, including those over 40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, albuminuria). (A)
3. Use aspirin therapy as a primary prevention strategy in men and women with type 1 diabetes at increased cardiovascular risk, including those over 40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, albuminuria). (C)
4. People with aspirin allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease are not candidates for aspirin therapy. Other antiplatelet agents may be a reasonable alternative for patients with high risk. (E)
5. Aspirin therapy should not be recommended for patients under the age of 21 years because of the increased risk of Reye's syndrome associated with aspirin use in this population. People under the age of 30 have generally not been studied. (E)

References

1. Colwell JA: Aspirin therapy in diabetes (Technical Review). *Diabetes Care* 20: 1767–1771, 1997
2. Hayden M, Pignone M, hillips C: Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 136:161–171, 2002
3. US Preventive Services Task Force: Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Ann Intern Med* 136:157–160, 2002
4. Collaborative overview of randomised trials of antiplatelet therapy-I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antipatelet Trialists' Collaboration. *BMJ* 308:81–106, 1994
5. Final report on the aspirin component of the ongoing Physicians' Health Study Research Group. *N Engl J Med* 321:129–135, 1989
6. The ETDRS Investigators: Aspirin effects on mortality and morbidity in patients with diabetes mellitus: Early Treatment Diabetic Retinopathy Study report 14, *JAMA* 268: 1292–1300, 1992
7. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood-pressure lowering and low dose aspirin on patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 351:1755–1762, 1998
8. CAPRIE Steering Committee: A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 348:1329–1339, 1996