Diabetes & Cardiovascular Disease Review

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AMERICAN COLLEGE of CARDIOLOGY

A Publication of the American Diabetes Association / American College of Cardiology Make the Link! Initiative

Issue 3: Diabetic Dyslipidemia

Diabetic Dyslipidemia

Cardiovascular disease (CVD) is a significant cause of illness, disability, and death among individuals with diabetes. The macrovascular complications of diabetes—CVD, cerebrovascular disease, and peripheral vascular disease—account for more than 70% of all deaths in individuals with diabetes (1). CVD events are four times more common in individuals with diabetes, occur at a younger age, and have a much greater case fatality rate (2). In fact, people with diabetes and no history of vascular disease have the same risk of having a heart attack or dying of vascular disease as nondiabetic individuals with a prior history of vascular disease (3,4). The risk of CVD conferred by diabetes is so great that the National Cholesterol Education Program (NCEP) Adult Treatment Panel III identifies diabetes as a CVD risk equivalent—a condition that requires aggressive care to prevent future vascular events in people with known vascular disease (5).

Despite the fact that dyslipidemia is a significant risk factor in the development of macrovascular complications, awareness and proper treatment of dyslipidemia are lacking. A recent American Diabetes Association/American College of Cardiology survey of individuals with diabetes reported the following:

- 60% of individuals with diabetes do not believe they are at risk for cholesterol problems.
- Only 8% of individuals with diabetes named lowering cholesterol as an important method to reduce their risk for CVD.
- 45% of individuals with diabetes reported that their healthcare provider never discussed lowering cholesterol.

The Centers for Disease Control and Prevention recently reported that 70–97% of individuals with diabetes have dyslipidemia (6). Reports from two academic medical centers document that only 35.5% of patients attending their diabetes clinics were reaching the LDL goal of <100 mg/dl (7). The letter "C" in the ABCs of diabetes reminds patients and providers of the importance of evaluating and treating "cholesterol." To decrease macrovascular complications in patients with diabetes, equal effort must be applied to controlling lipid levels and blood pressure as well as blood glucose.

Dyslipidemia of Diabetes

The characteristic pattern of lipoproteins in type 2 diabetes includes an increase in triglycerides and a decrease in HDL cholesterol. Concentrations of LDL cholesterol do not differ significantly from concentrations found in nondiabetic individuals but are predominated by the small dense form of LDL. The small dense LDL particles are more intrinsically atherogenic than the normal larger and more buoyant LDL particles. Furthermore, because of their smaller mass, a greater number of LDL particles is contained within the plasma of patients with small dense LDL, further increasing atherogenic risk. This triad of lipid abnormalities has been termed "diabetic dyslipidemia." The presence of diabetic dyslipidemia confers a CVD risk estimated to be equivalent to an LDL cholesterol concentration of 150–220 mg/dl (8).

In discussing dyslipidemia, attention has generally focused on the concentration of lipoprotein particles. To understand dyslipidemia of diabetes, it is important to appreciate the changes in the composition of the lipoproteins that enhance their atherogenicity. The Multiple Risk Factor Intervention Trial observed that CVD mortality among individuals with diabetes was four times higher than that in nondiabetic individuals with the same concentration of serum cholesterol. Further, diabetic patients in the lowest quintile for serum cholesterol had higher mortality rates than nondiabetic individuals in the highest quintile (Figure 1) (9). Glycosylation, oxidation, and triglyceride enrichment of lipoproteins contribute to the observed increase in atherogenicity.

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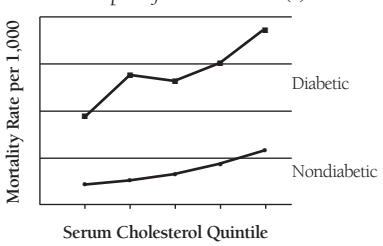
- BARI 2D Offers New Opportunity for Patients With Type 2 Diabetes

Figure 1
Multiple Risk Factor Intervention Trial (MRFIT): Mortality by quintile of total cholesterol

Adapted from Bierman (9).



Glycosylation of LDL increases its half-life, causes it to be the more atherogenic small dense variety, and makes it more likely to be oxidized and taken up by macrophages to form foam cells (10). Glycosylation of HDL cholesterol shortens its half-life and causes the less protective HDL_3 to predominate over the more protective HDL_2 form of the lipoprotein (11). Triglyceride enrichment leads to increased production of the small dense form of LDL cholesterol and to depletion of HDL cholesterol. The ability of HDL to transport cholesterol from peripheral tissues back to the liver may be decreased when HDL is triglyceride enriched (12). Improvement in blood glucose control as a consequence of lifestyle change or treatment with insulin and an oral antidiabetic agent leads to decreased triglyceride levels, increased HDL levels, decreased glycosylation of lipoproteins, and decreased triglyceride enrichment of lipoproteins.

Goals of Therapy

Treatment of diabetic dyslipidemia is based on the degree of risk indicated by lipoprotein levels (Table 1). The target lipid levels for adults with diabetes are the low-risk category values. Furthermore, it is recommended that all high-risk patients receive drug therapy to manage their dyslipidemia and that drug therapy, in addition to lifestyle management, be considered even in patients with borderline values (13).

Lipoproteins should be measured at the time of diagnosis of diabetes and after initial blood glucose control is achieved. Because of the frequent changes in glycemic control in patients with diabetes and their effects on lipoprotein levels, a complete lipid profile should be performed every year in adult patients. If values fall in lower-risk levels, assessment may be repeated every 2 years. More frequent testing may be necessary to assess the response to lipid-lowering therapy and to monitor its progress. In children with diabetes, consideration should be given to measuring lipoproteins after 2 years of age, as suggested by the NCEP Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents (14).

Initial therapy should begin with medical nutrition therapy (MNT) and physical activity. Weight loss and increased physical activity will lead to decreased triglyceride levels and increased HDL cholesterol levels and also to modest lowering of LDL cholesterol levels. Diabetic patients who are overweight should be given a prescription for MNT and increase physical activity. American Heart Association recommendations for patients with CVD suggest that the maximal MNT typically reduces LDL cholesterol 15–25 mg/dl (15). Thus, if the LDL cholesterol exceeds the goal by >25 mg/dl, the physician may decide to institute pharmacological therapy at the same time as behavioral therapy for high-risk patients (i.e., diabetic patients with a prior myocardial infarction and/or other CVD risk factors, or high LDL cholesterol levels [>130 mg/dl]). In other patients, behavioral interventions may be evaluated at 6-week intervals, with consideration of pharmacological therapy between 3 and 6 months.

Table 1.
Category of Risk Based on Lipoprotein Levels in Adults With Diabetes

Risk	LDL cholesterol (mg/dl)	HDL cholesterol		Triglycerides (mg/dl)
		Men (mg/dl)	Women (mg/dl)	
High	≥130	<35	<45	≥400
Borderline	100–129	35–45	45–55	150–399
Low	<100	>45	>55	<150

Table 2.
Results of Controlled Clinical Trials of Lipid Lowering in Individuals With Diabetes

Study	LDL cholesterol	HDL cholesterol	Triglycerides	Clinical outcomes
CARE (16)	Decreased 27%	Increased 5%	Decreased 14%	25% risk reduction (P = 0.05)
4S (17,18)	Decreased 36%	Increased 8%	Decreased 10%	55% risk reduction (P = 0.002) 42% on later analysis (P = 0.001)
VA-HIT (19)	No change	Increased 6%	Decreased 31%	24% decrease in CVD death or nonfatal myocardial infarction (P = 0.05)
DAIS (20)	Decreased 10%	Increased 6%	Decreased 29%	40% reduction in progression of localized atherosclerotic lesions (P = 0.02)
AFCAPS/ TexCAPS (21)	Decreased 25%	Increased 6%	Decreased 15%	33% reduction in CVD events (NS)
HPS (22)	Decreased 29%	Increased 3%	Decreased 14%	26% reduction in first CVD event (final analysis of diabetes incomplete)

Evidence of Treatment Benefit

Randomized controlled clinical trials demonstrate that people with diabetes benefit from cholesterol-lowering therapy, with improvements in lipoprotein values and reduced CVD events (16–21) (Table 2). Lipoprotein lowering and improvement in outcomes are equivalent among diabetic and nondiabetic subjects in clinical trials. Because patients with diabetes have largely constituted a subgroup of the total population randomized in the events trials, statistical significance for mortality has not been demonstrated for these diabetes subgroups. From preliminary data presentation, it seems likely that when the final report of the diabetes subgroup of the Heart Protection Study (HPS) is complete, statistically significant effects on mortality will be demonstrated (see HPS [22]).

Results of published trials support the American Diabetes Association's (ADA) recommendations that an LDL cholesterol

level <100 mg/dl is the primary target for cholesterol-lowering therapy (16–18,22). The importance of triglyceride lowering is demonstrated in the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) secondary prevention study, in which there was a 24% reduction in recurrent events using gemfibrozil (19). The improved outcomes were achieved without a significant lowering of LDL cholesterol. Priorities for the treatment of diabetic dyslipidemia are provided in Table 3 (13).

Table 3.
Order of Priorities for Treatment of Diabetic Dyslipidemia in Adults

1. **LDL cholesterol lowering***
   - *First choice:* HMG CoA reductase inhibitor (statin)
   - *Second choice:* Bile acid binding resin (resin) or fenofibrate
2. **HDL cholesterol raising**
   - Behavioral interventions such as weight loss, increased physical activity, and smoking cessation may be useful
   - Nicotinic acid, which on occasion will raise glucose significantly, or fibrates (gemfibrozil, fenofibrate)
3. **Triglyceride lowering**
   - Glycemic control is the first priority
   - Fibric acid derivative (gemfibrozil, fenofibrate)
   - High doses of statins are moderately effective in hypertriglyceridemic subjects who also have high LDL cholesterol
4. **Combined hyperlipidemia**
   - *First choice:* Improved glycemic control plus statin
   - *Second choice:* Improved glycemic control plus statin plus fibric acid derivative† (gemfibrozil, fenofibrate)
   - *Third choice:* Improved glycemic control plus resin plus fibric acid derivative (gemfibrozil, fenofibrate); Improved glycemic control plus statin plus nicotinic acid† (monitor glycemic control)

* The decision to treat high LDL levels before elevated triglycerides was based on clinical trial data indicating safety as well as efficacy of the available agents.
† The combination of statins with nicotinic acid and especially with gemfibrozil or fenofibrate may carry an increased risk of myositis.

Combination therapy. The goal of therapy for diabetic dyslipidemia is to have all lipoproteins in the desirable range. Because dyslipidemia generally affects all components of the lipid profile, treatment with a single agent often cannot address the full array of abnormal lipid parameters. Niacin is associated with improvements in all the lipid parameters—LDL cholesterol, HDL cholesterol, triglycerides, and LDL particle size. Although substantial concern previously existed regarding the potential for niacin to raise glucose levels in patients with diabetes, more recent studies suggest that niacin in moderate doses (1–2 g daily) generally has minimal effects on glycemia (23). Newer formulations of niacin that are generally well tolerated are available, leading to a renewed interest in using niacin for managing dyslipidemia in diabetes. A recent report of atorvastatin plus extended-release niacin demonstrated a 56% reduction in LDL cholesterol, a 69% reduction in triglycerides, a 42% increase in HDL cholesterol, and a 72% reduction in small dense LDL (24). Because outcomes studies in patients with diabetes treated with niacin are not available, statins and fibrates are generally the preferred agents.

Similarly, a recent study of the use of atorvastatin in combination with fenofibrate showed a 46% decrease in LDL cholesterol, a 50% decrease in triglycerides, and a 22% increase in HDL cholesterol. It was projected that lipid lowering would result in a decrease from 21.6 to 4.2% in the 10-year probability of a myocardial infarction (25).

Several studies are ongoing to test the safety and efficacy of the use of statins in combination with fibric acid derivatives and nicotinic acid; variably, the package inserts of all statin drugs have either warnings or cautions regarding these combinations. With appropriate caution and patient education regarding the signs and symptoms of myositis, these combinations can generally be used to the patient's advantage.

Patients with average to low LDL levels. The recently reported HPS included 5,963 individuals with diabetes—the largest number in a cholesterol-lowering trial (22). The study was designed to determine whether statins (simvastatin) are beneficial to individuals with average to low LDL cholesterol levels. Subjects were divided into three groups by baseline LDL levels: individuals with LDL levels <116 mg/dl, individuals with LDL levels between 116 and 135 mg/dl, and individuals with LDL levels >135 mg/dl. During the first 36 months of the trial, individuals with diabetes had on average a 46 mg/dl decrease in LDL cholesterol and a 35 mg/dl decrease in triglycerides. Overall, therapy resulted in a highly significant 25% reduction in the combination of fatal and nonfatal myocardial infarctions, stroke, and the need for revascularization procedures ($P < 0.001$). Among individuals with diabetes, it was estimated that the number needed to treat to prevent one event in only 3 years was 14. The authors encouraged providers to treat patients with statins based on their risk for CVD events and not on the LDL value alone. In the diabetes setting, this regimen suggests erring on the side of treatment to lower LDL levels, even if the level is ~100 mg/dl. This regimen also suggests giving greater consideration to initiating treatment for lipid disorders with statins and using lifestyle management as adjunctive therapy, opposed to the current approach of using lifestyle management as the primary therapy and only using pharmacological agents when lifestyle management does not result in the patient reaching treatment goals.

Recommendations at a Glance for Patients With Diabetes

General recommendations
- Lowering LDL cholesterol to <100 mg/dl is the primary therapy goal for adults.
- Lower triglycerides to <150 mg/dl.
- Raise HDL cholesterol to >45 mg/dl in men and >55 mg/dl in women.

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, repeat lipid assessments every 2 years.
- In children >2 years of age, perform a lipid profile after diagnosis of diabetes and when glucose control has been

established. If values are considered low risk and there is no family history, assessments should be repeated every 5 years.

Treatment

- MNT focusing on the reduction of saturated fat and cholesterol intake, weight loss, and increased physical activity has been shown to improve the lipid profile in patients with diabetes.
- Patients who do not achieve lipid goals with lifestyle modifications require pharmacological therapy.
- Statins should be used as first-line pharmacological therapy for LDL lowering.
- Therapy with fibrates in patients with low HDL has been shown to reduce CVD rates and progression of carotid intimal medial progression.
- When prescribing fibrates or niacin in combination therapy with a statin, care is needed to minimize the risk of adverse effects. ■

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Make the Link!
Patient Page

Cholesterol, Triglycerides, and Diabetes

What is cholesterol?

Cholesterol is a type of fat in your blood. There are different types:

► LDL cholesterol:
LDL cholesterol is sometimes called "bad" cholesterol. It can narrow or block your blood vessels. Narrowed vessels can raise your risk of a heart attack or stroke. Keeping your LDL cholesterol low protects your heart.

► HDL cholesterol:
HDL cholesterol is sometimes called "good" cholesterol. It helps remove deposits from the inside of your blood vessels and stops the blood vessels from getting blocked. Keeping your HDL cholesterol high protects your heart.

What are triglycerides?

Triglycerides are another type of fat in your blood. High triglycerides raise your risk of a heart attack or stroke. Keeping your triglycerides low protects your heart.

Why should people with diabetes be concerned about cholesterol?

Diabetes raises your risk of heart attack and stroke. Cholesterol problems are common in people with diabetes and raise your risk for heart attack and stroke even more.

What are cholesterol and triglyceride targets for people with diabetes?

For most people with diabetes, target levels are:
- LDL cholesterol: <100 mg/dl
- HDL cholesterol: >45 mg/dl for men and >55 mg/dl for women
- Triglycerides: <150 mg/dl

If my cholesterol and triglyceride levels are off-target, what can I do?

If your numbers are not on target, you can take these steps:
- Work with a dietitian to develop your own meal plan.
- Use less oil, butter, margarine, and other fats when cooking.
- Choose low-fat dairy products.
- Eat small servings of meat, fish, and poultry.
- Eat more fruits and vegetables.
- Choose whole-grain bread and cereal.
- Try to exercise for 30 minutes most days.
- Follow your health care provider's instructions for taking medicine.
- If you smoke, get help to quit.

Several medicines can help you reach your target cholesterol goals. Talk with your health care provider about the best medicine for you. You may need more than one medicine to reach your target numbers.

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Make the Link!
Patient Page

Cholesterol At-a-Glance

- Cholesterol problems are common in people with diabetes.
- High LDL (bad) cholesterol, high triglycerides, and low HDL (good) cholesterol levels can raise your risk for heart attack and stroke.
- If your cholesterol numbers are off target, talk with your health care provider about what you can do. Meal planning, exercise, and medicines can help you reach your target goals.

How will I know if my cholesterol levels are OK?

Have your health care provider check your cholesterol levels at least once a year.

I'm not sure I can handle all this…

It's hard enough to deal with diabetes every day. Worrying about cholesterol and triglycerides may make you feel overwhelmed. If this happens, talk to someone. You could call a friend or family member, or talk with someone on your health care team. Support groups can help, too. To find a support group in your area, or for more information about cholesterol and diabetes, call the American Diabetes Association at **1–800–342–2383**.

My Health Care Professional

My Cholesterol and Triglyceride Levels

Long-term goal for my LDL cholesterol: _____
Long-term goal for my HDL cholesterol: _____
Long-term goal for my triglycerides: _____

Date							
LDL cholesterol							
HDL cholesterol							
Triglycerides							

My Action Plan:

1. _____
2. _____
3. _____
4. _____
5. _____

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Key Global Literature

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Londahl M, Katzman P, Nilsson A, Ljungdahl L, Prutz, KG: Cardiovascular prevention before admission reduces mortality following acute myocardial infarction in patients with diabetes. ***J Intern Med*** **251:325–330, 2002**

FINDINGS

The objective of this study was to quantify the prevalence of use of pharmacological treatment for cardiovascular prevention in patients with and without diabetes at admission after acute myocardial infarction (AMI). The data on such treatment was then related to short- and long-term mortality. All patients discharged from the Department of Internal Medicine at Helsingborg Hospital in 1996 and 1997 with a principal diagnosis of AMI were included in the study. A total of 673 patients with AMI were registered, of which 117 (17.4%) had diabetes. No differences in 30 days (17.1 vs. 15.3%) or 1-year (24.8 vs. 27.4%) mortality were seen between the diabetic and control groups, whereas the 2-year mortality was significantly higher in the diabetic group (40.2 vs. 29.1%). Abnormal cardiovascular risk factors occurred more often in the diabetic group, and the use of aspirin, ACE inhibitors, statins, and diuretics was significantly more frequent. In patients treated with aspirin, the combination with either statin or ACE inhibitor, or both, no differences were seen in 30 days or 1- or 2-year mortality between the groups.

SIGNIFICANCE

It is well recognized that patients with diabetes have an increased mortality after suffering from AMI, and patients with diabetes have several risk factors for cardiovascular disease. In contrast to earlier studies, this study did not find an increased 30-day and 1-year mortality in patients with diabetes suffering from AMI. This discrepancy was linked to a high frequency of pharmacological cardiovascular prevention. This finding supports the hypothesis that survival of a diabetic patient after AMI could be affected by factors operating before the infarction.

IMPACT

Once again, prevention is not only better than a cure, but it also may make a cure more efficient. This may be the first data signal (albeit in a small selected population) indicating that we may be turning the tide of cardiovascular risk for patients with diabetes. ■

Schrier RW, Estacio RO, Esler A, Mehler P: Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. ***Kidney Int*** **61:1086–1097, 2002**

FINDINGS

This study was a prospective, randomized, double-blind, placebo-controlled trial that evaluated the effect of intensive (10 mmHg below the baseline diastolic blood pressure [DBP]) versus moderate (80–89 mmHg) DBP control on diabetic vascular complications in 480 "normotensive" type 2 diabetic patients. Patients in the moderate therapy group were given placebo, while the patients randomized to intensive therapy received either nisoldipine or enalapril. The mean follow-up was 5.3 years. Mean blood pressure (BP) in the intensive group was 128 ± 0.8/75 ± 0.3 mmHg versus 137 ± 0.7/81 ± 0.3 mmHg in the moderate group ($P < 0.0001$). Although no difference was demonstrated in creatinine clearance (a primary end point), a lower percentage of patients in the intensive group progressed from normoalbuminuria to microalbuminuria ($P = 0.012$) and microalbuminuria to overt albuminuria ($P = 0.028$). The intensive BP control group also demonstrated less progression of diabetic retinopathy ($P = 0.019$) and a lower incidence of stroke ($P = 0.03$). The results were the same whether enalapril or nisoldipine was used as the initial antihypertensive agent.

SIGNIFICANCE

It is not known whether lowering BP in normotensive (by definition BP <140/90 mmHg) patients offers any beneficial results on vascular complications. Over a 5-year follow-up period, intensive (~128/75 mmHg) BP control in normotensive type 2 diabetic patients delayed the onset/progression of diabetic nephropathy and retinopathy and diminished the incidence of stroke. There does not appear to be any advantage in using ACE inhibitors at this early stage of the disease.

IMPACT

This study challenges the conventional definition of hypertension in diabetes and supports the American Diabetes Association blood pressure goal of <130/80 mmHg, irrespective of baseline BP. ■

New Patient Education Resource on Diabetic Cardiovascular Disease

The American Diabetes Association's premier patient education series, *The Diabetes Channel*, is debuting a new issue titled *Make the Link! Diabetes, Heart Disease, and Stroke*. This tool will provide tips on reducing a patient's risk for cardiovascular disease by managing the ABCs of diabetes (**A**1C, **B**lood pressure, and **C**holesterol). The issue has a patient-centered focus, features large print and full color, and is written at a fifth-grade reading level. The English version is now available, and a Spanish adaptation is underway.

One free review set of all 23 English Channel pieces and nine Spanish Channel pieces can be obtained by calling 1-800-DIABETES. Additional quantities can be purchased through 1-800-ADA-ORDER. ■

BARI 2D Offers New Opportunity for Patients With Type 2 Diabetes and Heart Disease

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study will investigate the best medical approaches for tackling heart disease in people with type 2 diabetes. BARI 2D is a randomized clinical trial that will study whether initial treatment with angioplasty, with or without stents, or bypass surgery is better than initial treatment with a medication-only program in patients with type 2 diabetes. The study also will compare two different medication approaches to controlling blood glucose.

Up to 2,800 patients will be enrolled in this study; all participants will have access to medications at no cost and will receive intensive diabetes self-management education. All patients in BARI 2D will be followed for a minimum of 5 years to assess mortality, heart attack, stroke, angina and other CVD events, quality of life, and cost of treatment. The University of Pittsburgh Graduate School of Public Health is leading 40 top medical centers across the United States and Canada in the study. BARI 2D is being funded by the National Heart, Lung and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, and select pharmaceutical companies.

BARI 2D is enrolling men and women with type 2 diabetes who have coronary heart disease, are otherwise in good health, and have a willingness to participate for at least 5 years and keep risk factors under good control. For additional information, visit www.bari2d.org. ■

Insulin Therapy in the 21st Century: A Program for the Primary Care Community

Join your colleagues for a half-day program focusing on the latest clinical information on insulin therapy. Leading experts in the field of diabetes will share their knowledge and treatment strategies for improving glycemic control in patients with type 1 and type 2 diabetes. Through lectures and case studies, this half-day education program will present the clinical information you need to work more effectively with your patients.

Program topics:

- Goals for insulin therapy
- Insulin options
- How to get patients started on insulin
- When to initiate treatment in type 2 diabetes
- How to individualize treatment and adjust regimens
- Strategies for improving compliance
- Complications associated with insulin use

Locations:

- Atlanta, GA
- Chicago, IL
- Miami, FL
- New York, NY
- Brooklyn, NY
- Boston, MA
- Dallas, TX
- Minneapolis, MN
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- San Francisco, CA
- Los Angeles, CA
- Nashville, TN
- Phoenix, AZ
- Washington, DC

Dates: January – July 2003

For the most up-to-date information, visit www.diabetes.org/meetings/insulin or contact fstigliano@diabetes.org. ■

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Diabetes & Cardiovascular Disease Review

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