

Diabetes & Cardiovascular Disease Review



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

Issue 1:
Redefining Diabetes Control

D *Diabetes & Cardiovascular Disease Review* is a bimonthly newsletter for healthcare providers brought to you by the American Diabetes Association and the American College of Cardiology. It is a central component of our new *Make the Link! Initiative*, aimed at reducing the morbidity and mortality associated with diabetes and cardiovascular disease (CVD).

- Our focus: the constellation of problems associated with diabetes – obesity, hypertension, hyperglycemia, and dyslipidemia.
- Our goal: to help your patients **make the link** between diabetes and CVD and reduce CVD complications.

The theme for this premier issue of *Diabetes and Cardiovascular Disease Review* is Redefining Diabetes Control. Future issues will explore topics related to diabetic CVD, such as hypertension in diabetes and the management of diabetic dyslipidemia. For more information, contact: MakeTheLink@diabetes.org.



What's Inside

- ▶ Reviews of key articles related to diabetes and CVD.
- ▶ An overview of recommended goals for control of glycemia, blood pressure, and lipids and key tests/exams.
- ▶ Information on the *ABCs of Diabetes* to copy and distribute to your patients with diabetes.

Redefining Diabetes Control

Cardiovascular disease (CVD) is a major complication and the leading cause of premature death among people with diabetes. Adults with diabetes are two to four times more likely to have heart disease or suffer a stroke than people without diabetes. Yet, according to a recent American Diabetes Association survey conducted by RoperASW, more than 65% of diabetic patients do not consider CVD to be a serious complication of diabetes, and only 18% of people with diabetes believe that they are at increased risk for CVD.

While there is much to learn about the relationship between diabetes and CVD, research has led to a greater understanding of the increased risks in patients with diabetes and the benefits of treatment.

Excess CVD Risk in Diabetes

Studies documenting the risk continue to accumulate:

- Based on 20 years of surveillance, the **Framingham Study** found a two- to threefold increased risk of clinical atherosclerotic disease in those with diabetes compared with nondiabetic patients – including intermittent claudication, congestive heart failure, and coronary heart disease. CVD mortality was about equal in men and women with diabetes.¹

- The **Multiple Risk Factor Intervention Trial (MRFIT)** demonstrated that the absolute risk of CVD death was three times higher for men with diabetes than for men without diabetes.² The increased risk of CVD death was present even after controlling for age, race, income, systolic blood pressure, cholesterol level, and smoking status. The risk associated with an increase in blood pressure, an increase

in blood cholesterol, or from the presence of multiple risk factors was much greater in men with diabetes than those without diabetes. The absolute excess CVD risk for men with diabetes was progressively greater than that in nondiabetic men with higher risk factor levels. Conclusions emphasized the importance of rigorous, sustained intervention in people with diabetes to control blood pressure, lower serum cholesterol, and abolish cigarette smoking.

- The **East/West Study** asked whether patients who have not had a myocardial infarction (MI) should be treated as aggressively for CVD risk factors as patients with a prior MI.³ In a seven-year review of more than 3,000 patients, investigators found that diabetic patients without a previous MI had as high a risk of MI as nondiabetic patients with a previous MI. They recommended treating CVD risk factors in diabetic patients as aggressively as in nondiabetic patients with a prior MI.

Diabetic patients without a previous MI had as high a risk of MI as nondiabetic patients with a previous MI.

- Using data from the **National Health and Nutrition Examination Study (NHANES)**, researchers examined whether people with diabetes had benefited from the decline in coronary heart disease mortality seen in the U.S. over the past 30 years.⁴ They compared findings from the early 1970s to the early 1980s and found that nondiabetic men experienced a 36.4% decline in age-adjusted heart disease mortality compared with only a 13.1% decline in those with diabetes. Age-adjusted heart disease

mortality declined 27% in non-diabetic women but increased 23% in diabetic women. The researchers concluded that the reduction in CVD risk factors and improved heart disease treatment, which theoretically reduced U.S. heart disease mortality, may have been less effective in people with diabetes, especially women.

Pathogenesis of Diabetic CVD

While the pathogenesis of diabetic CVD is not yet fully understood, it is likely that it is directly influenced by the diabetic state because atherosclerotic lesions occur at an earlier age and with greater severity in people with diabetes.

Hyperglycemia can contribute to the endothelial cell dysfunction (which may play a central role in development of atherosclerosis) seen in diabetes. This dysfunction inhibits vasodilation and increases vascular smooth-muscle proliferation, thrombogenesis, and proatherogenic cellular processes. In the microcirculation, it may contribute to ischemia.

Hyperglycemia also may contribute to atherosclerosis by causing glycosylation of proteins. This leads to cross-linking of collagen and other extracellular matrix proteins in the arterial wall, producing arterial wall changes that increase susceptibility to atherosclerosis.

Hypertension and hyperlipidemia also cause dysfunction of endothelial cells that contributes to the atherosclerotic process. Glycosylation of lipoproteins occurs, changing their behavior. Glycosylated LDL is more atherogenic because it is more likely to be oxidized and taken up by macrophages to form foam cells.

Lipid Abnormalities⁵

Type 2 diabetes patients usually do not have concentrations of LDL cholesterol significantly different from those seen in nondiabetic patients. However, they typically have smaller, denser, oxidized LDL particles, which may increase atherogenicity even with normal LDL levels. Additionally, type 2 diabetic patients usually have elevated triglycerides (particularly increased VLDL) and decreased HDL, both risk factors for CVD. This triad of abnormalities, called atherogenic dyslipidemia, usually is seen in those with premature coronary artery disease. In those with diabetes, it confers a CVD risk

equal to or exceeding that of a high-risk LDL cholesterol level of 150-220 mg/dl.

Concomitant Risk Factors

Type 2 diabetes is associated with a clustering of risk factors often called the metabolic syndrome or the insulin resistance syndrome. These risk factors include insulin resistance, hypertension, elevated triglycerides, low HDL cholesterol, obesity, a prothrombotic state, and endothelial dysfunction. Insulin resistance, defined as the body's impaired ability to use insulin effectively, is directly involved in the pathogenesis of type 2 diabetes and may be linked to the development of atherosclerosis.

The metabolic syndrome clearly affects the development of both CVD and diabetes. The National Cholesterol Education Program (NCEP) has identified the metabolic syndrome as a secondary target of therapy in addition to LDL lowering.⁶ The NCEP recommends that the diagnosis of the metabolic syndrome be made when three or more of the associated risk factors are present (see Table 1).

Reducing Cardiovascular Events in Patients with Diabetes

Accumulating evidence shows that CVD can be reduced in patients with diabetes. Interventions that have been shown to decrease CVD events in persons with diabetes include the treatment of hypertension and hyperlipidemia, aspirin therapy, use of ACE inhibitors, and smoking cessation. The United Kingdom Prospective Diabetes Study demonstrated that lowering blood pressure significantly reduces strokes, diabetes-related deaths, heart failure, and microvascular complications in patients with type 2 diabetes.⁷ Lipid management aimed at lowering LDL cholesterol, raising HDL cholesterol, and reducing triglycerides has been shown to decrease macrovascular disease and mortality in patients with type 2 diabetes, particularly those who have had prior cardiovascular events.⁸ The benefits of cholesterol lowering with statin medication in reducing CVD events also has been demonstrated in diabetic patients with average cholesterol levels and in individuals with impaired fasting glucose.^{9,10} ACE inhibitors have been shown to decrease cardiovascular events in type 2 diabetes

Table 1.
Clinical Identification of the
Metabolic Syndrome⁶

Risk Factor	Defining Level
Abdominal obesity (waist circumference)	
Men	>102 cm (>40 inches)
Women	>88 cm (>35 inches)
Triglycerides	≥150 mg/dl
HDL cholesterol	
Men	<40 mg/dl
Women	<50 mg/dl
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dl

NCEP recommends that the metabolic syndrome be diagnosed when three or more of the above risk factors are present.

patients with or without hypertension.¹¹ Studies have documented the benefits of aspirin therapy¹² and smoking cessation¹³ in reducing CVD.

Impact on Clinical Care

While controlling hyperglycemia remains a cornerstone in diabetes care, the identification and treatment of other CVD risk factors are also vital. The American Diabetes Association recommends a comprehensive approach to diabetes care that focuses on the management of blood glucose and CVD risk factors, particularly hypertension and dyslipidemia. Included in this issue is a summary of key goals and treatment recommendations.

Future issues of *Diabetes and Cardiovascular Disease Review* will explore topics related to diabetic CVD. Each issue will feature a reproducible education tool that you can use with your patients to help them make the link between diabetes and CVD. ■

References:

1. Kannel WB, McGee DL: Diabetes and cardiovascular disease. The Framingham study. *JAMA* 241:2035-8, 1979
2. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 3:650-54, 1980
3. Haffner SM, Lehto S, Ronemaa T, Pyorala K, Laasko 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

4. Gu K, Cowie CC, Harris MI: Diabetes and decline in heart disease mortality in US adults. *JAMA* 281:1291-97, 1999
5. Henry RR: Preventing cardiovascular complications of type 2 diabetes: focus on lipid management. *Clinical Diabetes* 19:113-120, 2001
6. 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* 285:2486-97, 2001
7. UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 317:703-713, 1998
8. Haffner SM: Management of dyslipidemia in adults with diabetes (Technical Review). *Diabetes Care* 21:160-178, 1998
9. Goldberg RB, Mellies MJ, Sacks FM, Moya LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E: Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. *Circulation* 98:2513-9, 1998
10. Haffner SM, Alexander CM for the Scandinavian Simvastatin Survival Study Group. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels. *Arch Intern Med* 159:2661-67, 1999
11. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 355:253-59, 2000
12. Colwell JA: Aspirin therapy in diabetes (Technical Review). *Diabetes Care* 20:1767-1771, 1997
13. Haire-Joshu D, Glasgow RE, Tibbs TL: Smoking and diabetes (Technical Review). *Diabetes Care* 22:1887-1898, 1999

Help Your Patients Make the Link Between Diabetes and Cardiovascular Disease

Enclosed is a patient education tool titled *Be Smart About Your Heart: Control the ABCs of Diabetes* that you may reproduce and use in your practice. Produced by the National Diabetes Education Program and the American Diabetes Association, this tool provides essential information on diabetic cardiovascular disease and includes a wallet

card to help people with diabetes track their ABC numbers (A1C, Blood Pressure, and Cholesterol).

This tool also is available in a two-color brochure format. Health professionals can order 25 **free** copies by calling the National Diabetes Information Clearinghouse at 1-800-438-5383. ■

CAN TYPE 2 BE PREVENTED?

Yes, according to the Diabetes Prevention Program, a major NIH clinical study recently concluded. Participants were overweight and had impaired glucose tolerance (IGT), defined as a 2-hour OGTT result between 140 and 199 mg/dl or fasting blood glucose levels between 95 and 126 mg/dl. They were randomized to receive: placebo; metformin; or intensive lifestyle intervention (training in low fat and low calorie diet, 150 minutes weekly of moderate exercise, such as walking, and behavior modification). About 10% of those in the placebo group developed diabetes per year. **The development of diabetes was decreased by 58% with lifestyle interventions and by 31% with metformin.** Lifestyle modification worked in all groups, particularly in those aged 60 and older.

For additional information, refer to the following sources:

Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393-403, 2002

<http://www.niddk.nih.gov/patient/patient.htm> ■

The American Diabetes Association Bookstore

has all the essential resources that you and your patients need for complete diabetes care. From clinical education to teaching curricula, PowerPoint presentations to patient self-care, ADA is the authoritative source:

- Therapy for Diabetes Mellitus and Related Disorders
- Medications for the Treatment of Diabetes
- Intensive Diabetes Management

Many,
many more titles
available

Visit us online at
store.diabetes.org

Or call 1-800-232-6733
today for your free catalog!

Heart-Healthy Exercise = Diabetes Prevention

Get the Only Comprehensive Reference on Exercise and Diabetes

Covers all aspects of exercise in diabetes. The latest information on exercise and diabetes prevention, benefits and precautions for patients, exercise physiology, and the practical aspects of designing an effective diabetes exercise treatment plan. 718 pages, \$69.95 Order from the American Diabetes Association: call **1-800-232-6733**; online store.diabetes.org



Criteria for the Diagnosis of Diabetes

1. Symptoms of diabetes and a casual plasma glucose ≥ 200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
OR
2. FPG ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.
OR
3. 2-h PG ≥ 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. The OGTT is not recommended for routine clinical use. Different criteria are used to diagnosis gestational diabetes in pregnant women.

Recommendations for Glycemic Control

	Normal	Goal	Additional Action Suggested*
Plasma glucose values [†]			
Average preprandial (mg/dl)	<110	90-130	<90 or >150
Average bedtime (mg/dl)	<120	110-150	<110 or >180
Whole blood glucose values [‡]			
Average preprandial (mg/dl)	<100	80-120	<80 or >140
Average bedtime (mg/dl)	<110	100-140	<100 or >160
A1C (%)	<6	<7	>8

These values are for nonpregnant adults. Patients with comorbid diseases, the very young and older adults, and others with unusual conditions or circumstances may warrant different treatment goals. *Values above/below these levels are not “goals” nor are they “acceptable” in most patients. They are an indication for a significant change in the treatment plan. “Additional action suggested” depends on individual patient circumstances. Such actions may include enhanced diabetes self-management education, comanagement with a diabetes team, referral to an endocrinologist, change in pharmacological therapy, initiation of or increase in SMBG, or more frequent contact with the patient. A1C is referenced to a nondiabetic range of 4.0-6.0% (mean 5.0%, SD 0.5%). †Values calibrated to plasma glucose. ‡Measurement of capillary blood glucose.

Blood Pressure and Lipid Goals (for nonpregnant adults)

Blood Pressure (mmHg)		Lipids (mg/dl)	
Systolic	<130	Total Cholesterol	<200
Diastolic	<80	LDL-C	<100
		HDL-C	>45 (men) and >55 (women)
		Triglycerides	<150

For patients with an isolated systolic hypertension of ≥ 180 mmHg, the goal is a blood pressure <160 mmHg. For those with systolic blood pressure of 160-179, the goal is a reduction of 20 mmHg. If these goals are achieved and well tolerated, further lowering to 140 mmHg may be appropriate.

These guidelines have been condensed from the American Diabetes Association’s Standards of Medical Care for People with Diabetes. They do not reflect all the actions that should be provided by health professionals in the management of diabetes. Full text of the Association’s Clinical Practice Recommendations, including the Standards of Medical Care, is available at www.diabetes.org.

Recommendations for Patients with Diabetes

Key Tests/Exams

Test/Exam	Frequency
Weight	Each regular diabetes visit
Blood pressure	Each regular diabetes visit
A1C	<ul style="list-style-type: none"> ▶ Quarterly if treatment changes or not meeting goals ▶ At least 2 times/year if stable
Lipid profile	Yearly (less frequently if normal)
Microalbumin measurement	Yearly (if indicated)
Dilated eye exam	Yearly
Comprehensive foot exam	At least yearly (more often in patients with high-risk foot conditions)

Special Situations

Smoking cessation	Emphasize and assist as much as possible
Aspirin therapy	Enteric-coated aspirin (81-325 mg/day) as secondary prevention for CVD. Consider for primary prevention in high-risk patients (e.g., family history of CVD, smoking, hyperlipidemia, hypertension, albuminuria, over age 30 years).
Patients ≥55 years and at least one CVD risk factor other than diabetes	Consider ACE inhibitors (if not contraindicated) for patients with diabetes ≥ age 55 years with hypertension or at least one other CVD risk factor to reduce the risk of cardiovascular events.

Determining Body Mass Index (BMI) From Height and Weight

Height (in.)	Body Mass Index (kg/m ²)					Overweight					Obese			
	19	20	21	22	23	24	25	26	27	28	29	30	35	40
58	91	96	100	105	110	115	119	124	129	134	138	143	167	191
59	94	99	104	109	114	119	124	128	133	138	143	148	173	198
60	97	102	107	112	118	123	128	133	138	143	148	153	179	204
61	100	106	111	116	122	127	132	137	143	148	153	158	185	211
62	104	109	115	120	126	131	136	142	147	153	158	164	191	218
63	107	113	118	124	130	135	141	146	152	158	163	169	197	225
64	110	116	122	128	134	140	145	151	157	163	169	174	204	232
65	114	120	126	132	138	144	150	156	162	168	171	180	210	240
66	118	124	130	136	142	148	155	161	167	173	179	186	215	247
67	121	127	134	140	146	153	159	166	172	178	185	191	223	255
68	125	131	138	144	151	158	164	171	177	184	190	197	230	262
69	128	135	142	149	155	162	169	176	182	189	196	203	236	270
70	132	139	146	153	160	167	174	181	188	195	202	207	243	278
71	136	143	150	157	165	172	179	186	193	200	208	215	250	286
72	140	147	154	162	169	177	184	191	199	206	213	221	258	294
73	144	151	159	166	174	182	189	197	204	212	219	227	265	302
74	148	155	163	171	179	186	194	202	210	218	225	233	272	311
75	152	160	168	176	184	192	200	208	216	224	232	240	279	319
76	156	164	172	180	189	197	205	213	221	230	238	246	287	328

Body mass index, or BMI, is the measurement of choice to determine obesity. BMI is a formula that takes into account both a person's height and weight. BMI is a person's weight in kilograms divided by height in meters squared ($BMI = kg/m^2$). To determine BMI, find the appropriate height in the left-hand column. Move across the row to the given weight. The number at the top of the column is the BMI for that height and weight.

BMI classification: overweight 25-29.9, obese ≥30. Obesity is an indication for further clinical evaluation.

The BMI measurement poses some of the same problems as weight-for-height tables. BMI does not provide information on a person's percentage of body fat or take into consideration the person's body fat distribution.

Even LDL <130 mg/dl Predicts CVD Risk in People with Diabetes

ABSTRACT

Howard BV, Robbins DC, Sievers ML, Lee ET, Rhoades D, Devereux RB, Cowan LD, Gray RS, Welty TK, Go OT, Howard WJ: LDL Cholesterol as a Strong Predictor of Coronary Heart Disease in Diabetic Individuals With Insulin Resistance and Low LDL: The Strong Heart Study. *Arterioscler Thromb Vasc Biol.* 20:830-835, 2000

QUESTION

LDL cholesterol often is not elevated in individuals with diabetes. Rather, dyslipidemia characterized by elevated triglycerides, decreased HDL cholesterol and small dense LDL particles frequently accompanies diabetes. What is the relative importance of diabetic dyslipidemia and LDL cholesterol in determining CVD risk in people with diabetes?

DESIGN

Observational study of the Strong Heart Study population evaluated first between 1989 and 1992 and then at follow-up, averaging 4.8 years later.

SETTING

Indian Health Service hospitals and clinics in Arizona, Oklahoma, and North and South Dakota.

PATIENTS

4,549 American Indians (2,034 with diabetes) age 45 to 74 years at baseline, from multiple tribes. This cohort is known to have a high prevalence of type 2 diabetes, insulin resistance, and the characteristic dyslipidemia of elevated triglycerides, low HDL, and small dense LDL.

INTERVENTION

Baseline and follow-up exams included a personal interview and a physical exam.

Fasting blood samples were obtained for evaluation of lipids and lipoproteins (total cholesterol and triglycerides; VLDL, LDL and HDL cholesterol; and VLDL triglycerides), insulin, creatinine, fibrinogen, and HbA_{1c}. A 75 gm OGTT and a 12-lead ECG were performed. Percentage of Indian heritage was computed to the nearest quarter.

MAIN OUTCOME MEASURES

The incidence of fatal and nonfatal CVD events in those with and without diabetes were evaluated in relation to CVD risk factors.

MAIN RESULTS

Those with diabetes, compared with those with normal glucose tolerance, had lower LDL cholesterol and significantly elevated triglycerides, lower HDL, and smaller LDL particle size. Significant independent predictors of CVD in those with diabetes included higher LDL cholesterol levels, older age, macroalbuminuria, lower HDL cholesterol levels, fibrinogen, and lower percent body fat. While the causes of the inverse relationship between obesity and CVD were unclear, the authors noted several possibilities. For example, the study did not completely account for weight loss occurring in individuals with long duration of diabetes, especially those with kidney

disease who are at high risk for CVD. Hypertension was not found to be a significant independent predictor of CVD in diabetes unless albuminuria was removed from the model.

A 10 mg/dl increase in LDL was associated with a 12% increase in CVD risk. CVD incidence was higher in those with LDL levels >100 mg/dl than in those with levels <100 mg/dl.

A 10 mg/dl decrease in HDL was associated with a 22% increase in CVD risk.

CONCLUSION

LDL cholesterol is a strong independent predictor of CVD in people with diabetes, even at levels below 130 mg/dl and when components of diabetic dyslipidemia are considered.

COMMENT

The study provides strong support for the American Diabetes Association's recommendations to aggressively control CVD risk factors in diabetes including the lowering of LDL to <100 mg/dl and prevention of proteinuria. ■

Funding Source: National Heart, Lung, and Blood Institute.

For Correspondence: Barbara V. Howard, PhD at bvh1@mhg.edu

Any Albuminuria is a Risk Factor for Cardiovascular Events – With or Without Diabetes

ABSTRACT

Heart Outcomes Prevention Evaluation (HOPE) Study Investigators: Albuminuria and Risk of Cardiovascular Events, Death, and Heart Failure in Diabetic and Nondiabetic Individuals. *JAMA* 286:421-426, 2001

QUESTION

What is the relationship between the degree of albuminuria and CVD risk?

DESIGN

Sub analysis of the Heart Outcomes Prevention Evaluation study population, a cohort study with a median follow-up of 4.5 years.

SETTING

Centers in 19 countries in Europe and South and North America.

PATIENTS

Patients ≥55 years of age with a history of either CVD (5,545) or diabetes and at least one CVD risk factor (3,498) and a baseline urine albumin/creatinine ratio (ACR) measurement.

INTERVENTION

Observational study restricted to the 97% of HOPE participants, randomized to 10 mg ramipril or placebo q.d. for whom baseline urine albumin measurements were available.

MAIN OUTCOME MEASURES

Cardiovascular events (MI, stroke or CVD death), all-cause death, and hospitalization for congestive heart failure.

MAIN RESULTS

At baseline, microalbuminuria (MA) defined as ACR ≥ 2 mg/mmol was detected in 32.6% of those with diabetes and 14.8% of those without diabetes. MA increased the adjusted relative risk (RR) of major cardiovascular events by 1.83, all-cause deaths by 2.09, and hospitalization

Continued on page 7

Ramipril Yields CVD and Renal Benefits in Type 2 Adults (HOPE & MICRO-HOPE)

ABSTRACT

Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of Ramipril on Cardiovascular and Microvascular Outcomes in People with Diabetes Mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 335:253-9, 2000

QUESTION

Diabetes is a strong risk factor for CVD and renal disease. Will the ACE inhibitor ramipril lower these risks in people with diabetes?

DESIGN

Randomized, double-blind, placebo-controlled trial with 2x2 factorial design and a median follow-up of 4.5 years.

SETTING

Community and academic practices in 19 countries in Europe and South and North America.

PATIENTS

3,577 patients ≥ 55 years of age with type 1 or type 2 diabetes included in the Heart Outcomes Prevention Evaluation (HOPE) study who had a previous cardiovascular event or at least one other CVD risk factor. Participants also had no clinical proteinuria, heart failure or low ejection fraction and were not taking ACE inhibitors.

INTERVENTION

Patients were randomized to 10 mg ramipril or placebo q.d. and 400 IU vitamin E or placebo daily. Follow-up

visits were at 1 month and then every 6 months.

MAIN OUTCOME MEASURES

In the MICRO-HOPE substudy, which included the 3,577 patients with diabetes in the HOPE study, the primary outcomes were MI, stroke, CVD death, and overt nephropathy.

MAIN RESULTS

The study was stopped 6 months early because of a consistent benefit of ramipril compared to placebo. Ramipril lowered the risk of the combined primary outcome (MI, stroke or CVD death) by 25%, MI by 22%, stroke by 33%, cardiovascular death by 37%, total mortality by 24%, revascularization by 17% and overt nephropathy by 24%. After adjustment for the changes in systolic and diastolic blood pressures, ramipril still lowered the risk of the combined primary outcome by 25%.

CONCLUSION

Ramipril was beneficial in reducing cardiovascular events and overt nephropathy in patients with diabetes. The cardiovascular benefits were greater than that attributable to the lowered blood pressure and were

seen irrespective of whether participants had prior cardiovascular events, hypertension, or microalbuminuria; were taking insulin or oral anti-hyperglycemic agents; or had type 1 or 2 diabetes. The benefit may be due to a protective effect of ACE inhibitors on endothelial cells or the arterial wall.

COMMENT

The results of this major study were long-awaited and should have a significant impact on clinical practice. Ramipril appears to be significantly protective for both the cardiovascular system and the kidney in middle-aged and elderly people with diabetes. It is unknown whether these beneficial effects are specific to ramipril or are a class effect.

Adherence to ramipril was 65% at the last visit. If adherence was higher, greater risk reductions may have been seen. ■

Funding Source: Medical Research Council of Canada, Hoechst-Marion Roussel; Astra Zeneca, King Pharmaceuticals, Natural Source Vitamin E Association, NEGMA, and the Heart and Stroke Foundation of Ontario.

For Correspondence: Dr. Hertz C. Goldstein at gerstein@mcmaster.ca

Albuminuria is a Risk Factor *Continued from page 6*

for congestive heart failure by 3.23, with similar RRs whether or not diabetes was present and after adjusting for other CVD risk factors.

Compared with the lowest quartile of ACR (<0.22 mg/mmol), RRs of the aggregate primary outcomes in the second quartile (ACR 0.22-0.57 mg/mmol) was 1.11, in the third quartile (ACR 0.58-1.62 mg/mmol), 1.38, and in the fourth quartile (ACR >1.62 mg/mmol), 1.97.

For every 0.4 mg/mmol increase in the ACR, the adjusted hazard of major cardiovascular events increased by 5.9%.

CONCLUSION

Any degree of albuminuria is a risk factor for cardiovascular events, whether or not diabetes is present. The risk increases with the ACR, starting well below the

traditional threshold for a diagnosis of MA, i.e., extending at least as low as 0.5 mg/mmol.

COMMENT

This study adds to the body of work indicating that MA reflects underlying vascular disease and is a strong independent risk factor for CVD. The American Diabetes Association recommends an annual test for the presence of microalbuminuria for patients with type 2 diabetes starting at diagnosis and in type 1 patients who have had diabetes >5 years. ■

Funding Source: Medical Research Council of Canada, Hoechst-Marion Roussel, Astra Zeneca, Natural Source Vitamin E Association, NEGMA, and King Pharmaceuticals.

For Correspondence: Dr. Hertz C. Goldstein at gerstein@mcmaster.ca

DO YOU RECOMMEND ASPIRIN?

The American Diabetes Association recommends that aspirin therapy be considered for adults with diabetes who have CVD or CVD risk factors. The CDC's Third National Health and Nutrition Examination Survey (1988-1994) found that **every adult in the U.S. with diabetes has at least one risk factor for CVD** and thus should be considered a potential candidate for aspirin therapy. Approximately 37% of those with CVD and 13% of those with risk factors had taken aspirin 15 or more times in the previous month. Conclusion: **major efforts are needed to increase aspirin use.** ■

News from the American Heart Association's Scientific Sessions 2001

Late-breaking findings from the largest randomized trial on cholesterol-lowering therapy were reported at the American Heart Association's recent Scientific Sessions. Conducted by the UK's Medical Research Council and British Heart Foundation, the Heart Protection Study (HPS) found that cholesterol-lowering therapy using statin drugs cuts the risk of heart attacks and strokes by about one-third in people who have diagnosed coronary disease and in those with diabetes, peripheral vascular disease, or a previous history of stroke.

HPS studied 20,000 volunteers aged 40-80 years, including about 6,000 people with diagnosed diabetes and 4,000 without a history of coronary heart disease (CHD). HPS specifically targeted groups of patients in which there was little direct evidence of benefit of cholesterol-lowering therapy – including

women; individuals over 70 years of age; people with diabetes and no prior CHD; those with non-coronary vascular disease; and people with average or below-average cholesterol levels. Volunteers were randomized to either simvastatin 40 mg daily or placebo. Treatment and follow-up continued for an average of five and one-half years.

Other Key Findings:

- HPS is the first study to confirm the benefit of cholesterol lowering in people with diabetes, regardless of history of CHD.
- Besides reducing heart attacks, cholesterol lowering with statins also lowers the risk for stroke and decreases coronary surgery, stroke, other vascular procedures, and hospitalizations for worsening angina.
- Major vascular events were reduced by about one-third in a variety of groups in which there previously was limited evidence, including women, individuals over 70 years of age, and patients with diabetes.
- In high-risk patients, including those with diabetes, cholesterol-lowering therapy produces substantial benefits even among those considered to have "below-average" cholesterol levels.
- About 5 years of statin therapy typically prevents heart attacks, strokes, or other vascular events in 100 of every 1,000 people with previous MI and 70 of every 1,000 people with diabetes.

Study results will be published shortly. For further information on HPS, refer to www.hpsinfo.org. ■

 **American Diabetes Association**
Cure • Care • Commitment™

Diabetes & Cardiovascular Disease Review

is published by the American Diabetes Association, 1701 North Beauregard Street, Alexandria, VA 22311.

Editors/Writers:

Samuel Abbate, MD, CDE
Phyllis Barrier, MS, RD, CDE
Diana Benzaia
Gwen Twillman

Design:

Minker Design

We are grateful to the following companies who have provided educational grants to support the American Diabetes Association/American College of Cardiology **Make the Link!**

Initiative: AstraZeneca LP; Bayer Corp.; Bristol-Myers Squibb Co.; Eli Lilly and Co.; GlaxoSmithKline; Merck & Co. Inc and Merck/Schering-Plough Pharmaceuticals; Monarch Pharmaceuticals and Wyeth-Ayerst Laboratories; Novartis Pharmaceuticals Corp.; and Pfizer Inc.