CME CREDIT

CHRISTIAN E. NASR, MD
Department of Endocrinology and Metabolism, Cleveland Clinic

BYRON J. HOOGWERF, MD
Department of Endocrinology and Metabolism, Cleveland Clinic

CHARLES FAIMAN, MD
Chairman, Department of Endocrinology and Metabolism, Cleveland Clinic

S. SETHU K. REDDY, MD
Department of Endocrinology and Metabolism, Cleveland Clinic

UNITED KINGDOM PROSPECTIVE DIABETES STUDY (UKPDS)

Effects of glucose and blood pressure control on complications of type 2 diabetes mellitus

ABSTRACT

The United Kingdom Prospective Diabetes Study (UKPDS) showed that intensive treatment (ie, glucose-lowering drugs, with a goal fasting blood glucose level of 108 mg/dL) decreases the microvascular complications of type 2 diabetes mellitus. We summarize the key study results and their implications for clinical management of type 2 diabetes mellitus.

PATIENTS WITH TYPE 2 DIABETES mellitus experience fewer microvascular complications such as retinopathy and nephropathy if they undergo intensive treatment to achieve normal blood glucose levels. However, the effect of intensive treatment on macrovascular complications (ie, myocardial infarction, stroke) and on mortality is not yet established.

These were the principal findings of the 20-year United Kingdom Prospective Diabetes Study (UKPDS), which was recently reported.[1–4] The study also addressed whether sulfonylureas increase the risk of cardiovascular complications, whether insulin causes atherosclerotic complications, whether metformin in intensive treatment affects complication rates in overweight patients, and whether tight blood pressure control affects risk.

Although the UKPDS did not answer all the questions it posed, it provided valuable insight into key issues in diabetes care. This article summarizes the key findings and their implications for management of type 2 diabetes mellitus.

DOES TREATMENT REDUCE COMPLICATIONS OF TYPE 2 DIABETES?

Type 2 diabetes mellitus is associated with increased morbidity and mortality from macrovascular and microvascular complications. Yet, until recently, we had little data to show that controlling the blood glucose level would prevent these complications.

The concept that glucose is the "culprit" in the complications of diabetes mellitus is based on the observation that microvascular complications such as retinopathy and nephropathy occur in all types of diabetes mellitus, irrespective of genetic predisposition. Moreover, observational studies[5,6] suggested a relationship between the degree of hyperglycemia and the prevalence and severity of diabetic complications.

However, the much-debated University Group Diabetes Program (UGDP) study,[7] published in 1970, showed no benefit from treating type 2 diabetes with insulin or sulfonylureas. In fact, the results suggested that tolbutamide (a first-generation sulfonylurea) and phenformin (a biguanide oral hypoglycemic agent withdrawn from the market in the United States) might even be associated with *increased* cardiovascular events and mortality.

Subsequently, the Diabetes Control and Complications Trial (DCCT)[8] showed that tight control of blood glucose levels decreases the incidence of microvascular complications in type 1 diabetes, and the Kumamoto University (Japan) study[9] found similar results

A complex, 20-year study finds intensive treatment beneficial in type 2 diabetes

in patients with type 2 diabetes. However, these studies were not designed to assess effects on macrovascular complications, the primary cause of morbidity in patients with type 2 diabetes.[10]

STUDY DESIGN

The UKPDS study started in 1977 and closed on September 30, 1997.

Inclusion and exclusion criteria

Between 1977 and 1991, general practitioners in the United Kingdom referred all patients ages 25 to 65 with newly diagnosed type 2 diabetes mellitus to the 23 participating UKPDS hospitals (FIGURE 1).[1] Patients were eligible if they had a fasting plasma glucose concentration greater than 108 mg/dL on two mornings 1 to 3 weeks apart. This glucose level was selected because it was just above the normal limit for the reference range.

Among the exclusion criteria were ketonuria, a serum creatinine concentration greater than 2.0 mg/dL, evidence of coronary or vascular events, laser phototherapy for retinopathy, malignant hypertension, or severe concurrent illness.

Early studies showed conflicting results from treating type 2 diabetes

Diet run-in

The 5,102 patients who entered the study all followed a "prudent diet" for the first 3 to 4 months. During this period, 149 patients were excluded because their fasting plasma glucose levels decreased to 108 mg/dL or less, and 744 were excluded because their fasting plasma glucose levels increased to more than 270 mg/dL.

Stratification by weight

The 4,209 remaining patients were divided into two groups according to weight. Those weighing more than 120% of their ideal body weight (n = 1,704) were deemed obese; the other 2,505 were deemed non-obese.

Randomization in non-obese patients

Non-obese patients were randomly assigned to two main treatment groups: conventional treatment and intensive treatment.

Conventional treatment. Patients in the conventional treatment group had a goal fasting plasma glucose level of 270 mg/dL or less. To achieve this, they attended the clinics every 3 months and received dietary advice. If they developed marked hyperglycemia (fasting plasma glucose > 270 mg/dL) or symptoms of hyperglycemia (thirst, polyuria), they were randomized again to receive either insulin or a sulfonylurea, with the aim of keeping the fasting plasma glucose below 270 mg/dL without symptoms.

Intensive treatment. Patients in the intensive treatment group had a goal fasting plasma glucose level of 108 mg/dL or less. To achieve this, they were assigned to receive one of two types of drugs: a sulfonylurea (either the first-generation sulfonylurea chlorpropamide or one of the second-generation sulfonylureas glibenclamide [the British equivalent of glyburide] or glipizide) or insulin.

Randomization in obese patients

Obese patients were randomly assigned to *three* main treatment groups: conventional treatment, intensive treatment, or metformin treatment.

Conventional treatment, as described above. (If their fasting plasma glucose levels increased above 270 mg/dL, obese patients in this group were randomized again to receive either insulin, a sulfonylurea, or metformin.)

Intensive treatment, as described above.

Metformin treatment, with a goal fasting plasma glucose level of 108 mg/dL.

Add-on therapy

In 1990, the investigators noted that in the intensive treatment group fasting blood glucose and hemoglobin A_{1c} (HbA_{1c}) levels were continuing to increase in spite of maximum sulfonylurea therapy. Therefore, an amendment to the protocol assigned both obese and non-obese patients either to continue treatment with a sulfonylurea alone or to have metformin added.

Clinical endpoints

The study protocol defined three types of endpoints[1]:

Individual clinical endpoints, which included fatal myocardial infarction, nonfatal myocardial infarction, sudden death, heart

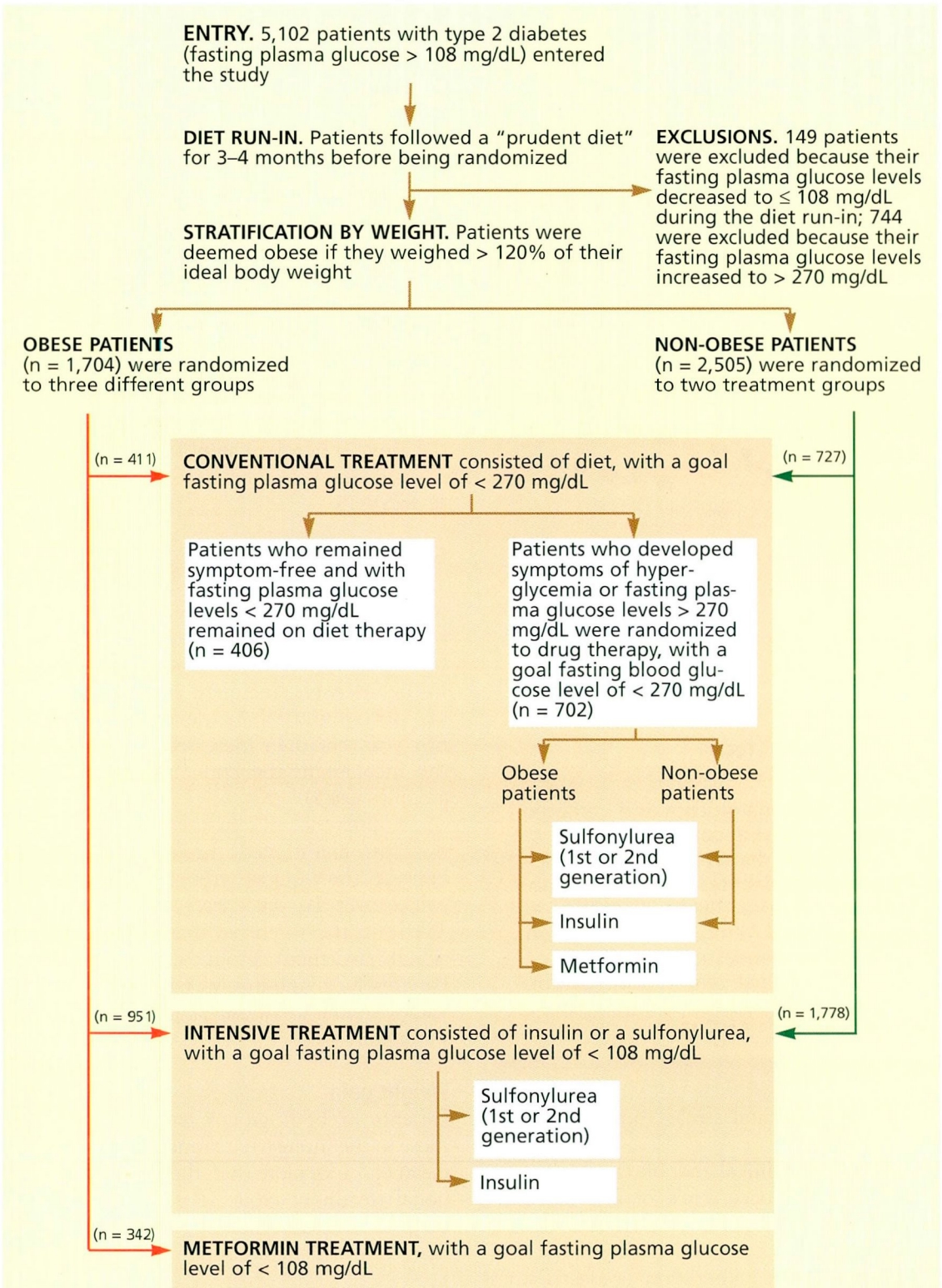

FIGURE 1. Patient selection and randomization criteria for the UKPDS. Baseline characteristics included mean age 53 years; mean body mass index 28 kg/m^2; mean fasting plasma glucose 144 mg/dL; mean hemoglobin A_{1c} 7.1%; hypertension was present in 38%.

Inclusion, exclusion, and treatment groups in the UKPDS trial

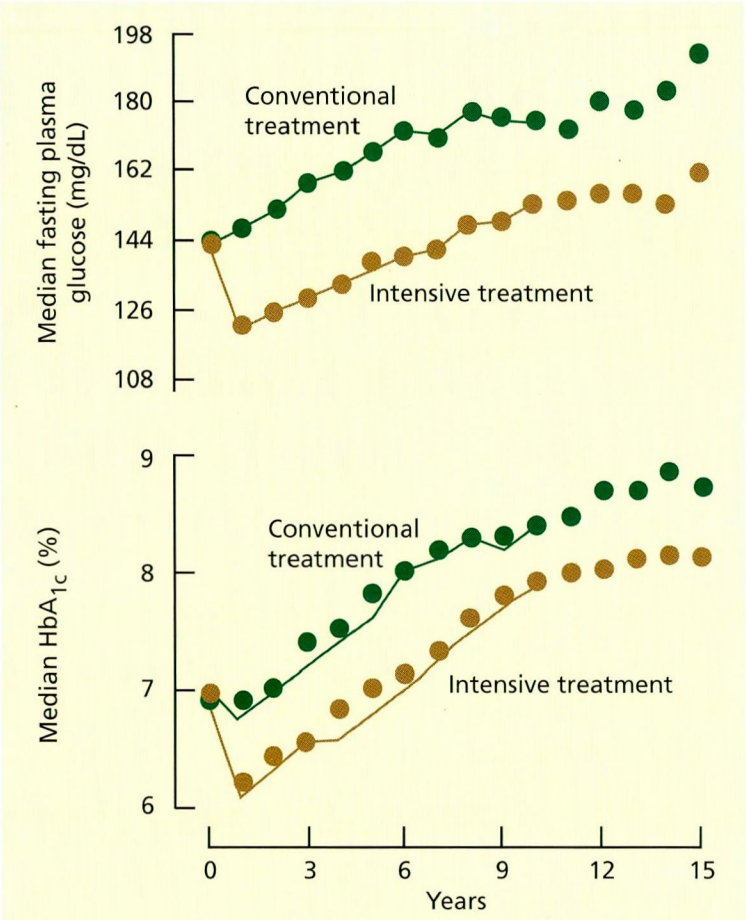

FIGURE 2. Median fasting plasma glucose and hemoglobin A_{1c} values in patients receiving conventional or intensive treatment for type 2 diabetes mellitus in the United Kingdom Prospective Diabetes Study. Although the goal fasting glucose level was 108 mg/dL in the intensive treatment group (vs 270 mg/dL in the conventional treatment group), these measures of glycemic control rose steadily after the first year in both groups.

SOURCE: FROM THE UK PROSPECTIVE DIABETES STUDY GROUP, REFERENCE 1.

failure, angina, fatal stroke, nonfatal stroke, and 14 others.

Aggregate clinical endpoints, which comprised the first occurrence of any diabetes-related endpoint, diabetes-related death, death from any cause, any myocardial infarction, any stroke, amputation or death from peripheral vascular disease, and any microvascular endpoint.

Surrogate endpoints, which included progression of retinopathy, neuropathy, microalbuminuria, proteinuria, and a twofold increase in plasma creatinine.

Hypertension substudy

The Hypertension in Diabetes Study, a trial embedded within the UKPDS, attempted to determine whether treatment aiming for a near-normal blood pressure reduces morbidity and mortality. Hypertensive patients were assigned to undergo either:

Tight blood pressure control (a goal of 150/85 mm Hg or less, with either the beta-blocker atenolol or the angiotensin-converting enzyme inhibitor captopril); or

Less-tight blood pressure control (a goal of 180/105 mm Hg or less, with antihypertensive drugs other than atenolol and captopril.)[1]

RESULTS

Glycemic control

The median follow-up for endpoint analysis was 10.0 years. In the conventional treatment group, fasting plasma glucose levels and HbA_{1c} values increased steadily over 10 years. In the intensive treatment group, fasting plasma glucose and HbA_{1c} decreased during the first year, but then increased in parallel with the increase in the conventional treatment group (FIGURE 2).[1]

A difference in measures of glycemic control was maintained throughout the study between the assigned groups. Median HbA_{1c} values over 10 years were 11% lower ($P < .0001$) in the intensive than in the conventional treatment group (7.0% vs 7.9%). Patients receiving insulin had median HbA_{1c} values similar to those of patients receiving sulfonylureas.

Weight gain

Patients in both groups gained weight, but those in the intensive treatment group gained a mean of 3.1 kg more than those in the conventional treatment group ($P < .0001$). Patients assigned to insulin therapy gained more weight than those assigned to sulfonylurea therapy.

Hypoglycemia

One of the disadvantages of intensive therapy was an increased risk of hypoglycemia.[1] Most of the hypoglycemic episodes were

TABLE 1

Effect of intensive vs conventional treatment for type 2 diabetes in the UKPDS

SELECTED CLINICAL ENDPOINTS, 10-YEAR DATA	EVENTS/1,000 PATIENT-YEARS (%)		RISK REDUCTION (%)	*P* VALUE
	INTENSIVE TREATMENT*	CONVENTIONAL TREATMENT†		
Any diabetes-related endpoint	40.9	46.0	12	.029
Diabetes-related deaths	10.4	11.5	10	.34
All-cause mortality	17.9	18.9	6	.44
Myocardial infarction	14.7	17.4	16	.052
Stroke	5.6	5.0	—	.52
SELECTED SURROGATE ENDPOINTS, 12-YEAR DATA	%	%		
Neuropathy	30.2	32.8	8	.42
Microalbuminuria	23.0	34.2	33	.000054

*Sulfonylurea or insulin treatment, with a goal fasting blood glucose level < 108 mg/dL
†Diet therapy, with a goal fasting blood glucose level < 270 mg/dL

SOURCE: ADAPTED FROM THE UK PROSPECTIVE DIABETES STUDY (UKPDS) GROUP, REFERENCE 1

mild. During the first 10 years of the study, rates for any hypoglycemic episode were highest for insulin, followed by glibenclamide, chlorpropamide, metformin, and conventional treatment in decreasing order of frequency.

Reduction in microvascular endpoints

Patients assigned intensive treatment had a 25% risk reduction in microvascular endpoints compared with conventional treatment ($P = .0099$). Most of this difference was due to a 28% reduction in cases of retinopathy requiring photocoagulation in the intensive treatment group. At 12 years, there was a 33% risk reduction for microalbuminuria. The risk reduction was similar in the three intensive treatment groups. No difference was noted between conventional and intensive treatments in deterioration in visual acuity, measures of autonomic neuropathy, reported impotence, evidence of silent myocardial infarction, or peripheral vascular disease (TABLE 1).[1]

Mortality

Diabetes-related mortality did not differ between the intensive and conventional groups. There were no differences in the rates of myocardial infarction or diabetes-related death between participants assigned to sulfonylurea or insulin therapies.

Cardiovascular effects

Patients in the intensive treatment group had a 16% lower incidence of myocardial infarction, but the trend did not achieve statistical significance ($P = .052$). The UKPDS data did not indicate any adverse cardiovascular effects from sulfonylureas or insulin or metformin alone.

Effects of metformin use

Patients assigned to intensive blood glucose control with metformin had a 32% lower risk ($P = .0023$) of developing any diabetes-related endpoint than those randomized to conventional control. Those assigned to metformin also had a greater risk reduction than those assigned sulfonylurea or insulin ($P = .0034$). These endpoints included macrovascular and microvascular complications.[2]

On the other hand, the addition of metformin to a sulfonylurea was associated with an increased risk of cardiovascular events and death from all causes,[2] and when compared to

Aggressive glucose lowering reduced the incidence of microvascular disease

TABLE 2

Effect of tight vs less-tight blood pressure control in patients with type 2 diabetes in the UKPDS

SELECTED CLINICAL ENDPOINTS, 10-YEAR DATA	EVENTS PER 1,000 PATIENT-YEARS		RISK REDUCTION (%)	*P* VALUE
	TIGHT CONTROL*	LESS-TIGHT CONTROL†		
Any diabetes-related endpoint	50.9	67.4	24	.0046
Diabetes-related deaths	13.7	20.3	32	.019
All-cause mortality	22.4	27.2	18	.17
Myocardial infarction	18.6	23.5	21	.13
Stroke	6.5	11.6	44	.013
Microvascular disease	12.0	19.2	38	.0092
Heart failure	3.6	8.1	56	.0043
SELECTED SURROGATE ENDPOINTS, 7.5-YEAR DATA	%	%		
Progression of retinopathy	34.0	51.3	34	.0038
Deterioration in vision	10.2	19.4	47	.003

*Goal blood pressure ≤ 150/85 mm Hg, achieved with captopril or atenolol
†Goal blood pressure ≤ 180/105 mm Hg, achieved with antihypertensive drugs other than captopril or atenolol

SOURCE: ADAPTED FROM UK PROSPECTIVE DIABETES STUDY GROUP, REFERENCE 3

single-agent therapy, the overall risk was still higher than that of conventional therapy.

Tight management of hypertension reduced both micro- and macrovascular complications and mortality

Blood pressure control

The mean blood pressure during follow-up was 144/82 mm Hg in the group assigned to tight blood pressure control and 154/87 in the group assigned to less-tight control. Patients in the tight-control group had significantly lower rates of diabetes-related endpoints, diabetes-related deaths, strokes, and microvascular endpoints and a trend toward a reduction in all-cause mortality (TABLE 2). Up to 30% of patients in the tight-control group required three or more medications to achieve target blood pressure.[3,4]

Captopril and atenolol were equally effective in reducing blood pressure and the risk of macrovascular endpoints.[4] This observation suggests that blood pressure reduction of itself may be more important than the type of antihypertensive drug used.

Compliance with medication was higher in the captopril group than in the atenolol group (78% vs 65%, $P < .0001$).

Similar proportions of patients developed clinical-grade proteinuria (≥ 300 mg/L).[4]

CONCLUSIONS

Conclusive findings

The UKPDS showed that intensive therapy decreased the incidence of diabetic complications, thus confirming the reduction in microvascular complications of diabetes mellitus as reported in the DCCT[8] and the Kumamoto study.[9] The relative reduction in risk for microvascular complications was comparable to that seen in the DCCT and to that predicted by previous studies.[5]

Inconclusive findings

Effect on cardiovascular disease. The UKPDS did not prove whether intensive glycemic control influences cardiovascular disease. Although the rate of myocardial infarction was 16% lower in the intensive treatment group than in the conventional treatment group, the trend did not meet study criteria for statistical significance ($P = .052$). On the average, for each increase of 1% in HgA_{1c}, the risk of developing coronary artery disease increased by 11%.[11] This increase is similar to the risk relationship predicted by observational cohort studies of glycemic con-

trol and reduction in risk for macrovascular disease.

Differences among drugs. Each of the intensive therapies had comparable effects on the primary endpoints.[1] However, the complexity of the UKPDS design and redesign led to a tremendous overlap between the different treatment arms in terms of the treatments that patients actually received, making critical appraisal of the effects of the individual therapies on specific endpoints virtually impossible. Since the goal in the intensive therapy arm was to maintain established glucose targets, most patients needed the stepwise addition of glucose-lowering agents and eventually insulin. In the conventional therapy group, it was necessary to start glucose-lowering agents when symptoms occurred or when blood glucose increased to more than 270 mg/dL, so that in the end only a minority of patients remained on diet alone.

Adverse outcomes with metformin plus sulfonylureas. The UKPDS failed to resolve the issue of an apparent increase in adverse outcomes with sulfonylureas plus metformin. The interpretation of this substudy is fraught with difficulty due to possible selection bias and smaller numbers of subjects. However, these observations should not preclude the combined use of sulfonylureas and metformin as a sensible treatment combination.

SUMMARY OF CLINICAL IMPLICATIONS

- Glucose lowering is associated with a reduced risk for retinopathy and nephropathy.
- Glucose lowering *may* reduce the risk for coronary heart disease, although trends in the UKPDS did not achieve statistical significance.
- All the glucose-lowering drugs used in the UKPDS—sulfonylureas, insulin, and metformin—seemed to have a comparable effect on reducing the risk of diabetic complications.
- Used singly, insulin, sulfonylurea drugs, or metformin do not increase the risk for coronary heart disease in patients without preexisting coronary artery disease.
- In obese patients, metformin use may have greater benefit in reducing diabetes complications than other strategies.
- Because blood glucose levels increased steadily over time in the UKPDS, diet and medication regimens must be regularly reviewed and adjusted.
- Targeting HbA_{1c} values to 7.0% or less is appropriate in type 2 diabetes mellitus.
- The suggestion of possible adverse effects of the combination of metformin and a sulfonylurea must be further studied and, in our opinion, does not preclude their combined use in type 2 diabetes mellitus.
- Reducing blood pressure with either beta-blockers or angiotensin-converting enzyme inhibitors reduces the risk of macrovascular and microvascular diseases and diabetes-related deaths.

REFERENCES

1. **UK Prospective Diabetes Study Group.** Intensive blood-glucose control with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352:837–853.
2. **UK Prospective Diabetes Study Group.** Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes mellitus (UKPDS 34). Lancet 1998; 352:854–865.
3. **UK Prospective Diabetes Study Group.** Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). BMJ 1998; 317:703–713.
4. **UK Prospective Diabetes Study Group.** Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 39). BMJ 1998; 317:713–720.
5. **Klein R.** Hyperglycemia and microvascular and macrovascular disease in diabetes. Diabetes Care 1995; 18: 258–268
6. **Kuusisto J, Mykkanen L, Pyorala K, Laakso M.** NIDDM and its metabolic control predict coronary heart disease in elderly subjects. Diabetes 1994; 43:960–967.
7. **University Group Diabetes Program.** A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. Diabetes 1970; 19(Suppl 2):747–830.
8. **DCCT Research Group.** The effect of intensive diabetes treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus: The Diabetes Control and Complications Trial. N Engl J Med 1993; 329:978–986.
9. **Ohkubo Y, Kishikawa H, Araki E, et al.** Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non- insulin dependent diabetes mellitus: a randomized prospective 6-year study. Diabet Res Clin Pract 1995; 28:103–117.
10. **UK Prospective Diabetes Study Group.** A 9- year update of a randomized, controlled trial on the effect of improved metabolic control on complications in non-insulin- dependent diabetes mellitus (UKPDS 17). Ann Intern Med 1996; 124 (1 pt 2):136–145.
11. **Turner RC.** The UK prospective diabetes study: a review. Diabetes Care 1998; 21(Suppl 3):C35–C38.

ADDRESS: *S. Sethu K. Reddy, MD, Department of Endocrinology, A30, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.*