Treatment of Hypertensive Diabetic Patients

Michael Tuck, MD

This article briefly reviews the literature on the incidence of hypertension in the diabetic population, the risks associated with this combination of conditions, and the nonpharmacologic and other therapies available to lower blood pressure in these patients. Although several studies of nonpharmacologic therapies and diuretics are considered, the emphasis is on the reported advantages and disadvantages of β-blockers, centrally acting agents, α-adrenergic–blocking agents, calcium-channel blockers, and angiotensin-converting enzyme inhibitors. *Diabetes Care* 11:828–32, 1988

Although the incidence of high blood pressure in the diabetic population is not precisely known, it appears to be considerably higher than that in the nondiabetic population (1–4). When adjustments are made for the effect of age, the prevalence of hypertension is relatively higher in those with type I (insulin-dependent) than in those with type II (non-insulin-dependent) diabetes (5). Coexisting hypertension and diabetes act as additive risk factors to accelerate vascular complications. The Framingham study found that the risk of cardiovascular disease is higher in diabetic patients, especially diabetic women; the impact was greatest for intermittent claudication and congestive heart failure and less noticeable in coronary artery disease. The Whitehall study, however, demonstrated that the risk for coronary artery disease is higher in hypertensive than in normotensive diabetic patients (6).

From the Department of Medicine, UCLA Medical School, Los Angeles; and the Endocrinology Section, Veterans Administration Medical Center, Sepulveda, California.

Address correspondence and reprint requests to Michael Tuck, MD, Endocrinology Section, Department of Medicine, Veterans Administration Medical Center, 16111 Plummer Street, Sepulveda, CA 91343.

According to DuPree and Meyer (7), the mortality rate of diabetic patients with systolic pressure >160 mmHg is four times that of other diabetic patients. The incidence of cerebral vascular disease is twice as high in hypertensive as in normotensive diabetic patients (8). High blood pressure also accelerates the decline in renal function in patients with diabetic nephropathy (9,10). Epidemiologic studies have also found an association between blood pressure levels and diabetic retinopathy (11,12).

The most predictable form of hypertension in diabetic patients is that developing with the onset of diabetic nephropathy and renal insufficiency. This form is noted frequently in patients with type I diabetes. In patients with type II diabetes, the onset of hypertension is associated with obesity, advancing age, and the coexistence of essential hypertension. Isolated systolic hypertension is common in older diabetic patients. Although renal failure, obesity, age, and essential hypertension account for much of the hypertension in diabetes, other factors related to primary metabolic alterations and secondary complications may contribute to abnormal blood pressure regulation. Changes in the cardiovascular control systems, such as the renin-angiotensin-aldosterone system (13–27), the sympathetic nervous system (28–31), vascular reactivity (30,32–35), and sodium and volume homeostasis (36–42), that have been reported in diabetes mellitus may contribute to abnormal blood pressure regulation.

SELECTION OF THERAPY

Because the risks associated with hypertension and diabetes are additive with respect to cardiovascular disease, and because blood pressure reduction slows the

progression of diabetic nephropathy, early intervention is warranted in diabetic hypertension. Antihypertensive agents can introduce new risks in diabetic patients, which necessitate a systematic comparison of the various classes of antihypertensive agents in diabetic patients.

Nonpharmacologic therapy. Nonpharmacologic therapy of hypertension, such as sodium restriction and weight reduction, would seem to be the logical first step to treatment of the diabetic hypertensive patient. Although obese patients can experience considerable reductions in blood pressure during weight reduction (43), long-term maintenance of normal weight and blood pressure has not been documented for this group.

Moderate sodium restriction, to ~2 g of sodium daily, can reduce elevated blood pressure. It seems reasonable to stress sodium restriction as part of the overall dietary program in diabetic patients, who usually have ongoing interactions with physicians and dietitians. The advantages of sodium restriction over diuretic therapy in blood pressure control include maintenance of normal body potassium stores and avoidance of the metabolic complications associated with administration of diuretics.

Diuretic agents. Diuretic therapy is a logical choice in hypertensive diabetic patients, because volume dependence is a component of hypertension in many of these patients. Thiazide diuretics are recommended when renal function is normal; when the serum creatinine level is >176.8 μM (conversion factor 88.4), loop diuretics should be used.

Unfortunately, diuretic therapy is associated with a range of metabolic abnormalities that may have an adverse impact in diabetic patients. In patients with type II diabetes, diuretic-induced hypokalemia that is dose related can impair insulin release and worsen glucose tolerance (44). In addition, hypokalemia could be an independent risk for ventricular ectopia in diabetic patients who have coronary artery disease and cardiomyopathy. A potassium-sparing diuretic should be used to prevent diuretic-induced hypokalemia in diabetic patients with normal renal function but not in patients with renal failure, who may have hypoaldosteronism and a tendency for potassium retention.

Diuretic agents produce elevations in low-density lipoproteins and very-low-density lipoproteins. These diuretic-induced lipoprotein abnormalities with modest elevations in cholesterol levels may be transient, and their long-term significance has not yet been established (45). However, in the diabetic patient with hypertension and accelerated atherosclerotic disease, even small diuretic-induced lipid alterations could be significant.

In the elderly diabetic patient receiving diuretic therapy, the risk of hyperosmolar coma is increased, requiring close monitoring of glucose and electrolytes.

β-Blockers. Because cardiac output and the activity of the renin-angiotensin system are reduced in diabetic hypertensive patients, β-blockers, which lower blood pressure by decreasing cardiac output and acting on the renin-angiotensin system, may be less effective antihypertensive agents in this population. Several studies, however, have indicated that these agents do lower blood pressure in diabetic patients (46). β-Blocker therapy may be useful in younger diabetic patients with hypertension who have high pulse rates and in diabetic patients with coronary artery disease and tachyarrhythmias. In patients with coronary artery disease or cardiomyopathy, however, β-blockade, which leads to decreased myocardial contractility, can produce congestive heart failure (47).

Because β-blockade inhibits β-adrenergic–mediated insulin secretion, these agents can impair insulin release and worsen glucose tolerance in type II diabetic patients, although actual glycemic excursions are usually moderate (48). The opposite can occur in patients with type I diabetes, in whom β-blockers accentuate insulin-induced hypoglycemia. These agents also mask some (e.g., anxiety, tachycardia, tremor) but not all (e.g., sweating) of the symptoms of hypoglycemia. Use of cardioselective β-blockers may obviate this effect on insulin-induced hypoglycemia in type I diabetic patients (49, 50).

A less appreciated complication of β-blocker therapies is their elevation of total peripheral resistance, causing vasoconstriction and reduced regional blood flow to most peripheral vascular beds. Because there is an increased incidence of peripheral vascular disease in the diabetic population, the vasoconstrictive effect of β-blockade could severely impair exercise tolerance and intensify intermittent claudication. Another concern with vascular disease in diabetic patients is that both cardioselective and nonselective β-blocking agents elevate very-low-density lipoprotein triglyceride levels and reduce high-density lipoprotein levels. These agents should be used with caution in diabetic patients with hyperlipidemia.

Centrally acting agents. The centrally acting agents methyldopa, clonidine, and guanabenz are effective in lowering blood pressure in diabetic patients with hypertension but have the predictable side effects of sedation and dry mouth. The new transdermal delivery system for clonidine may offer increased compliance and reduced side effects in this population (51).

Because these agents are α-agonists, and because α_2-stimulation can inhibit insulin secretion, centrally acting agents can decrease insulin release and worsen glucose tolerance. Both clonidine and guanabenz cause mild impairment of glucose-stimulated insulin release, but this has little effect on long-term glycemic control in diabetic patients (52,53). Methyldopa does not alter glucose control, but it should be used cautiously in diabetic patients because its use, as with other α-agonists, can be associated with orthostatic hypotension, sexual dysfunction, dry mouth, and lethargy.

α-Adrenergic–blocking agents. Prazosin, the peripheral α_1-receptor antagonist, effectively reduces blood pressure in diabetic hypertensive patients without altering metabolic control or sexual function (54). However, the side effect of first-dose orthostatic hypertension may be a problem in diabetic patients with clinical or sub-

clinical autonomic neuropathy. Reactive sodium and volume retention may render these agents less effective with long-term administration.

Calcium-channel–blocking agents. The efficacy and safety of several calcium-channel–blocking agents have been tested in clinical trials in hypertensive diabetic patients. These agents have several potential advantages as first-line therapy in this population. They do not impair central or peripheral nervous system activity, cause sodium retention, or aggravate vascular disease and may have minimal effects on sexual function.

Studies in animals show that these agents reduce insulin secretion (55,56); however, the vast majority of studies in humans have shown that therapeutic doses of verapamil, diltiazem, and nifedepine do not affect fasting or postprandial glucose levels in diabetic and nondiabetic patients (57–59). It remains to be established whether calcium antagonists have the beneficial effects on renal hemodynamics and protein excretion in diabetic patients as reported with angiotensin-converting enzyme (ACE) inhibitors.

ACE inhibitors. The ACE inhibitors have several potential benefits in the treatment of diabetic hypertension, especially in the presence of renal disease. Several studies have demonstrated the efficacy and safety of captopril in the treatment of diabetic hypertension (60–63). Captopril also has favorable effects on carbohydrate homeostasis. As glucose-clamp experiments show, captopril increases insulin sensitivity for skeletal muscle glucose uptake, which could improve glycemic control (64). Captopril inhibition of kinin degradation may mediate this effect.

In diabetes mellitus, the kidney undergoes several early adaptive hemodynamic changes, including hyperfiltration and increased intraglomerular pressure (65). Evidence from animal models indicates that glomerular capillary hyperperfusion and hypertension can initiate glomerular structural injury (66). In addition, a family history of hypertension and an elevated lithium-sodium countertransport in erythrocytes may be markers for diabetic patients with a susceptibility to develop renal disease (67). Reduction in systemic arterial pressure retards the development of renal failure and reduces proteinuria (9,10). However, all antihypertensive agents may not be equally effective in retarding renal damage in diabetes, because the reduction in systemic blood pressure may not alter intraglomerular pressure. In diabetic rats, triple-drug antihypertensive therapy did not reduce intraglomerular pressure and proteinuria, whereas the ACE inhibitor captopril lowered these parameters (68).

ACE inhibitors have been shown to improve the glomerular filtration rate and decrease albuminuria in diabetic patients with renal disease (69–71). ACE inhibition may have a role in treating diabetic nephropathy by reducing intraglomerular arterial pressure. ACE inhibitors may improve renal function even in normotensive diabetic patients with nephropathy. In a 6-mo study of normotensive diabetic patients with mild nephropathy and persistent microalbuminuria, it was found that enalapril decreased the albumin excretion rate without major changes in systemic blood pressure (72). In a long-term study in diabetic hypertensive patients, captopril administration over a 2-yr period decreased the rate of renal deterioration, as indicated by the glomerular filtration rate (71). These findings underscore the importance of arterial pressure in the progression of diabetic nephropathy. ACE inhibitors may be considered as first-line antihypertensive agents in diabetic patients with hypertension.

CONCLUSIONS

Although dietary and other nonpharmacologic approaches are promising, they need to be studied more thoroughly in the long-term control of blood pressure in the diabetic hypertensive population. In monotherapy, the Working Group on Hypertension in Diabetes recommends that the first choice of antihypertensive agents be either a diurectic β-blocker, calcium antagonist, or ACE inhibitor (47). If a diuretic alone is inadequate, an ACE inhibitor or the other agents might be used in conjunction with diuretic therapy.

REFERENCES

1. Sowers JR, Tuck ML: Hypertension associated with diabetes mellitus, hypocalcemic disorders, acromegaly and thyroid disease. *Clin Endocrinol Metab* 10:631–50, 1981
2. Fuller JH: Epidemiology of hypertension associated with diabetes mellitus. *Hypertension* 7 (Suppl. 2):113–17, 1985
3. Rubler S: Cardiac manifestations of diabetes mellitus. *Cardiovasc Med* 2:823–35, 1977
4. National Diabetes Data Group: *Diabetes in America*. Washington, DC, U.S. Govt. Printing Office, 1985 (DHEW publ. no. 85–1468)
5. Kannell WB, McGee DL: Diabetes and cardiovascular risk factor: the Framingham study. *Circulation* 59:8–13, 1979
6. Reid DD, Brett GZ, Hamilton PJS, Jarrett RJ, Keen H, Rose G: Cardiorespiratory disease and diabetes among middle-aged male civil servants: a study of screening and intervention. *Lancet* 1:469–73, 1974
7. DuPree EA, Meyer MB: Role of risk factors in complications of diabetes mellitus. *Am J Epidemiol* 112:100–12, 1980
8. Kuller LH, Dorman JS, Wolf PA: Cerebrovascular disease and diabetes. In *Diabetes in America*. National Diabetes Data Group, Ed. Washington, DC, U.S. Govt. Printing Office, 1985 (DHEW publ. no. 85–1468)
9. Mogensen CE: Long-term antihypertensive treatment inhibiting progression of diabetic nephropathy. *Br Med J* 285:685–88, 1982
10. Parving H-H, Anderson AR, Hommel E, Smidt U: Effects of long-term antihypertensive treatment on kidney function in diabetic nephropathy. *Hypertension* 7 (Suppl. 2):114–17, 1985
11. Knowler WC, Bennett PH, Ballintine EJ: Increased inci-

dence of retinopathy in diabetics with elevated blood pressure. *N Engl J Med* 302:645–50, 1980
12. Chahal P, Inglesby D, Sleightholm M, Kohner EM: Blood pressure and the progression of mild background diabetic retinopathy. *Hypertension* 7 (Suppl. 2):79–83, 1985
13. Christlieb AR, Munichoodappa C, Braaten JT: Decreased responses of plasma renin activity to orthostasis in diabetic patients with orthostatic hypotension. *Diabetes* 23:835–40, 1974
14. Campbell IW, Ewing DJ, Anderton JL, Thompson JF, Horn DB, Clarke BF: Plasma renin activity in diabetic autonomic neuropathy. *Eur J Clin Invest* 6:381–85, 1976
15. Fernandez-Cruz A Jr, Noth RH, Lassman MN, Hollis JB, Mulrow PJ: Low plasma renin activity in normotensive patients with diabetes mellitus: relationship to neuropathy. *Hypertension* 3:87–92, 1981
16. Tuck ML, Sambhi MP, Levin L: Hyporeninemic hypoaldosteronism in diabetes mellitus: studies of the autonomic nervous system control of renin release. *Diabetes* 28:237–46, 1979
17. Perez GO, Lespier L, Jacobi J: Hyporeninemia and hypoaldosteronism in diabetes mellitus. *Arch Intern Med* 137:852–55, 1977
18. Christlieb AR: Nephropathy, the renin system and hypertensive vascular disease in diabetes mellitus. *Cardiovasc Med* 2:417–31, 1978
19. Drury PL, Bodansky HJ: The relationship of the renin-angiotensin system in type I diabetes to microvascular disease. *Hypertension* 7 (Suppl. 2):84–89, 1985
20. Burden AC, Thurston H: Plasma renin activity in diabetes mellitus. *Clin Sci* 56:255–59, 1979
21. Day R, Leutscher J, Gonzales C: Occurrence of big renin in human plasma, amniotic fluid and kidney extracts. *J Clin Endocrinol Metab* 40:1078–84, 1975
22. DeLeiva A, Christlieb AR, Melby JC, Grahan CA, Day RR, Leutscher JA, Zager PG: Big renin and biosynthetic defect of aldosterone in diabetes mellitus. *N Engl J Med* 295:639–43, 1976
23. Hsueh WA, Carlson EJ, Leutscher JA, Grislis G: Activation and characterization of inactive big renin in plasma of patients with diabetic nephropathy and unusual active renin. *J Clin Endocrinol Metab* 51:535–43, 1980
24. Fujii S, Shimojo N, Wada M, Funae Y: Plasma active and inactive renin in patients with diabetes mellitus. *Endocrinol Jpn* 27:65–72, 1980
25. Bryer-Ash M, Ammon RA, Leutscher JA: Increased inactive renin in diabetes mellitus without evidence of nephropathy. *J Clin Endocrinol Metab* 56:557–61, 1983
26. Leutscher JA, Kraemer FB, Wilson DM, Schwartz HC, Bryer-Ash M: Increased plasma inactive renin in diabetes mellitus: a marker for microvasculature complications. *N Engl J Med* 312:1412–17, 1985
27. Misbin RI, Grant MB, Pecker MS, Atlas SA: Elevated levels of plasma prorenin (inactive renin) in diabetic and nondiabetic patients with autonomic dysfunction. *J Clin Endocrinol Metab* 64:964–68, 1987
28. Christensen NJ: Catecholamines and diabetes mellitus. *Diabetologia* 16:211–24, 1979
29. Beretta-Piccoli C, Weidmann P, Ziegler W, Gluck Z, Keusch G: Plasma catecholamines and renin in diabetes mellitus. *Klin Wochenschr* 57:681–91, 1979
30. Beretta-Piccoli C, Weidmann P: Exaggerated pressor responsiveness to norepinephrine in non-azotemic diabetes mellitus. *Am J Med* 71:829–35, 1981
31. Ferris JB, O'Hare JA, Kelleher CCM, Sullivan PA, Cole MM, Ross HF, O'Sullivan DJ: Diabetic control and the renin-angiotensin system, catecholamines and blood pressure. *Hypertension* 7 (Suppl. 2):58–63, 1985
32. Christlieb AR, Janka H-U, Kraus B, Gleason RE, Icasas-Cabral EA, Aiello L, Cabral B, Solano A: Vascular reactivity to angiotensin II and to norepinephrine in diabetic subjects. *Diabetes* 25:268–74, 1976
33. Drury PL, Smith GM, Ferris JB: Increased vasopressor responsiveness to angiotensin II in type I (insulin dependent) diabetic patients without complications. *Diabetologia* 27:174–79, 1984
34. Weidmann P, Beretta-Piccoli C, Trost BN: Pressor factors and responsiveness in hypertension accompanying diabetes mellitus. *Hypertension* 7 (Suppl. 2):33–42, 1985
35. Trujillo AL, Tuck ML: Salt sensitivity and vascular reactivity in the hypertension of diabetes mellitus. *Meet Am Soc Hypertension, New York, June 16, 1987.*
36. McQuarrie I, Thompson WH, Anderson JA: Effects of excessive sodium and potassium salts on carbohydrate metabolism and blood pressure in diabetic children. *J Nutr* 11:77–101, 1936
37. De Chatel R, Weidmann P, Flammer J, Ziegler WH, Beretta-Piccoli E, Veter W, Reubi FC: Sodium renin, aldosterone, catecholamines and blood pressure in diabetes mellitus. *Kidney Int* 12:412–21, 1977
38. Weidmann P, Beretta-Piccoli C, Keusch G, Gluck Z, Mujagic M, Grimm M, Meier A, Ziegler WH: Sodium volume factor, cardiovascular reactivity and hypotensive mechanism of diuretic therapy in mild hypertension associated with diabetes mellitus. *Am J Med* 67:779–84, 1979
39. O'Hare JP, Ferris JB, Brady D, Twomey B, O'Sullivan DJ: Exchangeable sodium and renin in hypertensive diabetic patients with and without nephropathy. *Hypertension* 7 (Suppl. 2):43–48, 1985
40. O'Hare JP, Roland JM, Walters G, Corrall RJM: Impaired sodium excretion in response to volume expansion induced by water immersion in insulin-dependent diabetes mellitus. *Clin Sci* 71:403–409, 1986
41. O'Hare JP, Anderson JV, Millar ND, Corrall RJM, Bloom SR: The relationship of the renin-angiotensin-aldosterone system to atrial nutriuretic peptide during volume expansion in diabetics with and without nephropathy. *Int Symp New Challenges in Diabetes, Copenhagen, November 9, 1987*
42. DeFronzo RA: The effect of insulin on renal sodium metabolism: a review with clinical implications. *Diabetologia* 21:165–71, 1981
43. Tuck ML, Sowers J, Dornfield L, Kjedzik G, Maxwell M: The effect of weight reduction on blood pressure, plasma renin activity and plasma aldosterone levels in obese patients. *N Engl J Med* 304:930–33, 1981
44. Conn JW: Hypertension, the potassium ion and impaired carbohydrate tolerance. *N Engl J Med* 21:1135–43, 1965
45. Burris JF, Freis ED: Thiazides do not cause long-term increases in serum lipid concentrations. *Arch Intern Med* 145:2264–65, 1985
46. Christlieb AR: Treating hypertension in the patient with diabetes mellitus. *Med Clin N Am* 66:1373–88, 1982
47. The Working Group on Hypertension in Diabetes: Statement on hypertension in diabetes mellitus. *Arch Intern Med* 147:830–42, 1987
48. Struthers AD, Murphy MB, Dollery CT: Glucose during antihypertensive therapy in patients with diabetes mellitus. *Hypertension* 7 (Suppl. 2):95–101, 1985
49. Lager I, Blohme G, Smith U: Effect of cardioselective and

nonselective beta-blockage on the hypoglycaemic response in insulin dependent diabetics. *Lancet* 1:458–62, 1979
50. Deacon SP, Karunanayake A, Barnett D: Acebutolol, atenolol and propanolol and metabolic responses to acute hypoglycaemia in diabetics. *Br Med J* 2:1255–59, 1977
51. Wallin JD, Krane NK, Bergman S, Morgan M: The use of transcutaneous clonidine hydrochloride in the patient with diabetes mellitus and mild hypertension. *J Clin Hypertens* 1:315–21, 1985
52. Guthrie GP, Miller RE, Kotchen TA, Koenig S: Clonidine in patients with diabetes and mild hypertension. *Clin Pharmacol Ther* 34:713–17, 1983
53. Gutin M, Tuck ML: Concomitant guanabenz and hydrochlorothiazide therapy in diabetic patients with hypertension. *Curr Ther Res* 43:775–85, 1988
54. Lipson LG: Special problems in treatment of hypertension in the patient with diabetes mellitus. *Arch Intern Med* 144:1829–31, 1984
55. Dominic JA, Miller RE, Anderson J, McAllister RC: Pharmacology of verapamil. II. Impairment of glucose tolerance by verapamil in the conscious dog. *Pharmacology* 20:196–202, 1980
56. De Martinis LD, Barbarino A: Calcium antagonists and hormone release. I. Effects of verapamil on insulin release in normal subjects and patients with islet cell tumor. *Metabolism* 29:599–604, 1980
57. Donnelly T, Harrower ADB: Effect of nifedipine on glucose tolerance and insulin secretion in diabetic and non-diabetic patients. *Curr Med Res Opin* 6:690–93, 1980
58. Trost N, Weidmann P, Beretta-Piccoli C: Antihypertensive therapy in diabetic patients. *Hypertension 7* (Suppl. 2):102–108, 1985
59. Trost BN, Weidmann P: Effects of calcium antagonists on glucose homeostasis and serum lipids in non-diabetic and diabetic subjects: a review. *J Hypertens* 5 (Suppl. 4):S81–104, 1987
60. Sullivan PA, Kelleher M, Twomey M, Dineen M: Effect of converting enzyme inhibition on blood pressure, plasma renin activity and plasma aldosterone in hypertensive diabetics compared to patients with essential hypertension. *J Hyptertens* 3:359–63, 1985
61. Passa P, LeBlanc H, Marre M: Effects of enalapril in insulin-dependent diabetic subjects with mild to moderate uncomplicated hypertension. *Diabetes Care* 10:200–204, 1987
62. Mathews DM, Wathen CG, Bell D, Collier A, Muir AL, Clarke BF: The effect of captopril on blood pressure and glucose tolerance in hypertensive non-insulin dependent diabetes. *Postgrad Med J* 62 (Suppl. 1):73–75, 1986
63. D'Angelo A, Sartari L, Gambaro G, Giannini S, Malvasi L, Benetollo T, Lauagnini T, Crepaldi G: Captopril in the treatment of hypertension in type I and type II diabetic patients. *Postgrad Med J* 62 (Suppl. 1):69–72, 1986
64. Rett K, Jauch KW, Wicklmayr M, Dietze G, Fink E, Mehnert H: Angiotensin converting enzyme inhibitors in diabetes: experimental and human experience. *Postgrad Med J* 62 (Suppl. 1):59–64, 1986
65. Hostetter TH, Rennke HG, Brenner BM: The case of intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. *Am J Med* 72:375–80, 1982
66. Brenner BM: Nephron adaptation to renal injury or ablation. *Am J Physiol* 249:F324–37, 1985
67. Krolewski AS, Canessa M, Warram JH, Laffel L, Christlieb AR, Knowler WC, Rand LI: Predisposition to hypertension and susceptibility to renal disease in insulin-dependent diabetes mellitus. *N Engl J Med* 318:140–45, 1988
68. Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM: Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest* 77:1925–30, 1986
69. Taguma Y, Kilamot Y, Futaki G, Ueda H, Monma H, Ishizaki M, Takahashi H, Sekino H, Sasaki Y: Effect of captopril on heavy proteinuria in azotemic diabetics. *N Engl J Med* 313:1617–20, 1985
70. Hommel E, Parving H-H, Methiesen E, Edsberg B, Damkjaier-Neilsen M, Giese J: Effect of captopril on kidney function in insulin dependent diabetic patients with nephropathy. *Br Med J* 293:467–70, 1986
71. Bjorck S, Nyberg G, Mulec H, Branerus G, Herlitz H, Aurell M: Beneficial effects of angiotensin converting enzyme inhibition on renal function in patients with diabetic nephropathy. *Br Med J* 293:471–74, 1986
72. Marre M, Leblanc H, Suarez L, Guyenne TT, Menard J, Passa P: Converting enzyme inhibition and kidney function in normotensive diabetic patients with persistent microalbuminuria. *Br Med J* 294:1448–52, 1987