In the past two decades, nephropathy in type 2 diabetes has emerged as a major public health issue. The purpose of this presentation is to review the epidemiology of diabetic nephropathy, the controversy surrounding HbA1c and blood pressure as targets for treatment, the efficacy of blocking the renin-angiotensin system (RAS) pathway, and finally the available add-on therapies in patients with "escape."

**EPIDEMIOLOGY**—Diabetic nephropathy in type 1 and type 2 diabetes emerged as a major issue in the 1970s, but knowledge of albuminuria in patients without primary kidney disease goes back to the work of Senator (1), who found albumin excretion in the urine of roughly 10% of the general population, including individuals with diabetes. In 1891, Schmitz (2) found albuminuria in 10–26% of diabetic patients and discussed its etiology and prognostic implications.

Renal failure in patients with diabetes became a major issue when continuously increasing numbers of diabetic patients were admitted for renal replacement therapy—a veritable "medical catastrophe of worldwide dimension" (3). According to the U.S. Renal Data System report, diabetes accounted for 54% of new patients in 2007. The incidence of end-stage renal disease (ESRD) in diabetic patients is currently 155 patients per million per year; it decreased by 3.3% between 2006 and 2007. In recent years, the prevalence was ~600 patients per million per year, illustrating the dimension of the problem.

In our own local experience in Heidelberg (4), 49%, or 98 patients per million per year, admitted for renal replacement therapy had diabetes; of these patients, 6% had type 1 diabetes, and 94% had type 2 diabetes.

Recently, however, the rate of admission of type 2 diabetic patients for renal replacement therapy reached its plateau (5) in Denmark and in Europe in general. Observations in the Pima Indian population show that there is a significant decrease in the incidence of end-stage disease in type 2 diabetes that cannot be explained by higher mortality before end-stage renal failure has been reached (6). This observation suggests at least some efficacy of current treatment strategies.

**EPIDEMIOLOGY OF DIABETIC NEPHROPATHY**—Not all patients with diabetes who develop terminal renal failure suffer from classic Kimmelstiel-Wilson syndrome. In our experience (4), classic Kimmelstiel-Wilson syndrome with enlarged kidneys and heavy proteinuria was seen in 70% of patients. Terminal renal failure without major proteinuria and with small kidneys (presumably ischemic nephropathy) was seen in 11% of the patients, and diabetes in the presence of known primary kidney disease was seen in 19% of the patients.

A new development is the frequent occurrence of irreversible acute kidney injury, mostly acute-on-chronic kidney disease (7). Even when (partial) restoration of kidney function occurs, subsequent progression to terminal renal failure is more frequent and faster in diabetic compared with nondiabetic individuals (8).

In our Heidelberg series (9), the diagnosis of diabetes was not known to the referring physician in 11% of patients. It is remarkable that several registries noted that in ~15% of patients admitted for renal replacement therapy, apparent "de novo" diabetes appeared 1–2 years after the start of dialysis. This presumably reflects the fact that because of anorexia and weight loss in the preterminal stage, hyperglycemia had disappeared so that, on admission, the diagnosis of diabetes was missed.

Another important finding is the observation that a considerable proportion of patients with type 2 diabetes develop impaired renal function without having significant albuminuria (10,11). In a 15-year follow-up of 5,032 patients with initially normal serum creatinine, 28% developed creatinine clearance <60 mL/min, and 51% of these patients did not develop albuminuria (11). Similar results were observed in the National Health and Nutrition Examination Survey (12). Reduction of renal function in the absence of albuminuria is presumably the result of a disease of small arteries, as also suggested by the recent Japanese observation (13) that cerebral micro infarcts detected by magnetic resonance imaging predicted the doubling of serum creatinine in nonalbuminuric type 2 diabetic patients.

The natural history of diabetic nephropathy is not clear. It is known that albuminuria may precede the onset of overt diabetes. Albuminuria may even be a predictor of subsequent diabetes, as found in individuals with microalbuminuria (14). This result raises the possibility that even in the prediabetic stage, minor functional and morphological (15) renal abnormalities may exist.

In type 1 diabetes as well as in the presence of normoalbuminuria, the width of the basal membrane was found to be increased, even when the measured
recently confirmed that this is also true with respect to renal end points: a relatively short period of intensified treatment reduced the long-term hazard ratio of microvascular disease (including renal end points) by ∼20%. In the recent Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study comprising 11,140 type 2 diabetic patients, 5,571 subjects were given intensified treatment with glinide in addition to the routine antidepressant medication that was administered to the control group. The achieved HbA1C in the intensified treatment group was 6.5 vs. 7.3% in the control group: intensified treatment reduced renal end points by 21%, e.g., prevention of one renal event per 20 patients after 5 years of treatment (25). It is of note that the response of microvascular events to intensified blood glucose control was seen earlier than the response of macrovascular events (26).

There has recently been some controversy about the importance of lowering Hba1c with respect to renal end points. The Veterans Affairs Diabetes Trial (VADT) (27) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) studies failed to document a significant reduction of renal events by intensified glycemic control in type 2 diabetic patients, but a valid argument has been raised that these were patients with longstanding type 2 diabetes and considerable preexisting end-organ damage.

With respect to glycemic intervention, it is also of note that recent studies show that glitazones affect renal disease by not only lowering Hba1c, but they also have direct effects on renal injury, independent of glycemia, e.g., attenuation of podocyte injury in nondiabetic proteinuric models of renal disease (28). Renal benefit is not only seen in experimental nondiabetic kidney disease, and the same may also be true in nondiabetic proteinuric human kidney disease (29,30).

Renal reabsorption of filtered glucose will become an important target for treatment of diabetes in the future. The sodium glucose type transporter 2 (SGLT2) in the S1 segment of the proximal tubule can be blocked by selective inhibitors (31) derived from phlorizin. These inhibitors induce natriuresis and, as a result of sodium loss, cause a moderate decrease in blood pressure with an upregulation of RAS (presumably increasing the effectiveness of RAS blockade). An added benefit of glucosuria is weight loss.

Target Blood Pressure—In the Kaiser Permanente cohort, blood pressure predicted subsequent uremia in individuals without renal disease at baseline. This was also found for blood pressure
values between 120 and 140 mmHg both in nondiabetic and even more so in diabetic individuals (40). In diabetic patients, it is of note that, conversely, hyperglycemia is also a risk factor for onset of hypertension as shown in type 1 diabetes in the DCCT–Epidemiology of Diabetes Interventions and Complications (EDIC) study (41), presumably by triggering renal mechanisms.

The use of office blood pressure measurements as an indicator of renal damage is problematic. Both in nondiabetic and diabetic patients, office blood pressure measurements were the least predictive indicator of nephropathy, retinopathy, coronary heart disease, etc. (42). Self-measured morning blood pressure (and even better, 24-h ambulatory blood pressure) was much more predictive.

A recent meta-analysis (43) concluded that, in type 2 diabetic patients, treatment of hypertension to the target of 135/80 mmHg caused definite improvement with less evolution of diabetic sequelae, including renal sequelae. The authors concluded that lowering blood pressure aggressively is presumably the most important factor in the prevention of pathological events in type 2 diabetic patients.

In principle, this conclusion is supported by the analysis of Mancia et al. (44) in controlled trials, in which patients (including diabetic patients) were randomized to more aggressive or less aggressive blood pressure-lowering interventions; benefits from lower blood pressure were seen in all but one (underpowered) trial. The analysis of de Galan et al. (45) showed that reduction of blood pressure reduced renal events in type 2 diabetic patients even when the blood pressure at baseline was in the normotensive range, but this apparently applies only to patients in early stages without major target organ damage.

In the IDNT trial, however, Berl et al. (46) found that higher pulse pressure increased all-cause mortality, and lower diastolic pressure was specifically associated with a higher risk of myocardial infarction. This finding is in line with the observation that pulse pressure and by implication, low diastolic pressure (below 70 mmHg), may reduce coronary perfusion in patients with preexisting cardiovascular disease and thus increase the risk of myocardial infarction (but not the risk of stroke) (47).

It has recently become increasingly clear that a single target blood pressure is not appropriate for all diabetic patients and that lowering blood pressure should be less aggressively pursued in patients with preexisting cardiovascular problems. Obviously, a single target blood pressure does not fit all diabetic patients.

**Blocking the RAS Pathway**—In the past, there was much discussion about the specific renal benefit provided by ACE inhibition. The meta-analysis of Jafar et al. (48) showed clearly that ACE inhibitors are only superior to alternative antihypertensive treatments in patients that have proteinuria >1 g/day. In nonproteinuric patients, a specific benefit from blocking the RAS pathway is not well documented. Furthermore, the analysis of Pohl et al. (49) in the IDNT study showed that lowering blood pressure has a much greater impact on renal end points than the blocking of RAS with irbesartan.

A major problem with blocking the RAS pathway is the phenomenon of escape, i.e., the return of protein excretion to baseline values after months or years. This phenomenon is well known in nondiabetic kidney disease (Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients [ESCAPE] study [50]) and is also common in proteinuric diabetic kidney disease (51).

**ADD-ON THERAPY**—In the treatment of patients with escape, reduction in salt intake, increased diuretic treatment, and an increased dose of ACE inhibitors or angiotensin receptor blockers (ARBs) above the recommended doses for antihypertensive treatment is a logical first step. The study of Mehdi et al. (52) showed that in proteinuric patients who were treated with 80 mg/day lisonopril and in whom escape had occurred, the addition of 25 mg/day spironolactone was more effective than 100 mg/day losartan. The results of the ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study indicate that the combination of ACE inhibitors and ARBs does not provide additional benefit. In diabetic patients with escape, spironolactone or eplerenone has been shown to cause secondary reduction of proteinuria (53,54).

An additional intervention is the renin blocker aliskiren, which when given in addition to ARBs caused in the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study significant further reduction of albuminuria in type 2 diabetic patients (55). Studies on hard renal end points are forthcoming.

Wenzel et al. (56) reported that in early stages of type 2 diabetes with nephropathy, the endothelin (ET₃) receptor blocker avosentan reduced albuminuria, but in more advanced kidney disease, avosentan caused an unacceptable rate of heart failure and pulmonary edema (57). Therefore, avosentan is clearly contraindicated in advanced diabetic nephropathy (58).

Preliminary data show that the vitamin D receptor activator paricalcitol at a dose of 1 µg and 2 µg/day reduces albuminuria further by ~20% in type 2 diabetic patients with CKD (59).

**New Targets of Intervention**—The established interventions target primarily the glomerulus, i.e., proteinuria and glomerulosclerosis. It has become increasingly clear that in advanced stages, tubulointerstitial fibrosis is an important treatment target. Fibrosis is driven via transforming growth factor β, chemokine receptors, receptor for advanced glycation end products, and nuclear factor-κB, i.e., by inflammation as well as by hypoxia and many other processes. These pathologies have become the target of experimental and preliminary clinical studies.

**Acknowledgments**—No potential conflicts of interest relevant to this article were reported.

**References**

1. Gansevoort RT, Ritz E. Hermann Senator and albuminuria: forgotten pioneering work in the 19th century. Nephrol Dial Transplant 2009;24:1057–1062

2. Schmitz R. Ueber die prognostische Bedeutung und die Aetiologie der Albuminurie bei Diabetikern. Berliner Klinische Wochenschrift 1891;28:373–377

3. Ritz E, Rychlik I, Locatelli F, Halimi S. End-stage renal failure in type 2 diabetes: a medical catastrophe of worldwide dimensions. Am J Kidney Dis 1999;34:795–808

4. Schwenger V, Müssig C, Hergesell O, Zeier M, Ritz E. Incidence and clinical characteristics of renal insufficiency in diabetic patients. Dtsch Med Wochenschr 2001;126:1322–1326

5. Sørensen VR, Hansen PM, Heaf J, Feldt-Rasmussen B. Stabilized incidence of albuminuria: forgotten pioneering studies of interest relevant to this article were reported.

6. Pavkov ME, Knowler WC, Bennett PH, Looker IC, Krakoff J, Nelson RG. Increasing incidence of proteinuria and declining
incidence of end-stage renal disease in diabetic Pima Indians. Kidney Int 2006;70:1840–1846
7. Chantriel F, Enache I, Bouiller M, et al. Abysmal prognosis of patients with type 2 diabetes entering dialysis. Nephrol Dial Transplant 1999;14:129–136
8. Venkatachalam MA, Griffin KA, Lan R, Geng H, Saikumar P, Bidani AK. Acute kidney injury: a springboard for progression in chronic kidney disease. Am J Physiol Renal Physiol. 3 March 2010 [Epub ahead of print]
9. Schwenger V, Mussg C, Hersgesell O, Zeier M, Ritz E. Incidence and clinical characteristics of renal insufficiency in diabetic patients. Dtsch Med Wochenschr 2001;126:1322–1326
10. MacIsaac RJ, Tsalamandris C, Panagiotopoulos S, Smith TJ, McNeil KJ, Jerums G. Nonalbuminuric renal insufficiency in type 2 diabetes. Diabetes Care 2004;27:195–200
11. Retnakaran R, Cull CA, Thorne KI, Adler SG. Nodular glomerulosclerosis in a patient with metabolic syndrome without diabetes. Nat Clin Pract Nephrol 2008;4:S333
12. Kramer HJ, Nguyen QD, Curhan G, Hsu CY. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA 2003;289:3273–3277
13. Uzo T, Kida Y, Shirahashi N, et al. Cerebral microvascular disease predicts renal failure in type 2 diabetes. J Am Soc Nephrol 2010;21:520–526
14. Halimi JM, Bonnet F, Lange C, Balkau B, Tichet J, Marre M, DESIR Study Group. Urinary albumin excretion is a risk factor for diabetes mellitus in men, independently of initial metabolic profile and development of insulin resistance. The DESIR Study. J Hypertens. 2008;26:2198–2206
15. Mac-Moune Lai F, Szeto CC, Choi PC, et al. Isolate diffuse thickening of glomerular capillary basement membrane: a renal lesion in prediabetes? Mod Pathol 2004;17:1506–1512
16. Caramori ML, Fioretto P, Maurer M. Low glomerular filtration rate in normoalbuminuric type 1 diabetic patients: an indicator of more advanced glomerular lesions. Diabetes 2003;52:1036–1040
17. Altiparmak MR, Pamuk ON, Pamuk GE, Apaydin S, Ozbay G. Diffuse diabetic glomerulosclerosis in a patient with impaired glucose tolerance: report on a patient who later develops diabetes mellitus. Neth J Med 2002;60:260–262
18. Souraty P, Nast CC, Mehrotra R, Barba L, Martina J, Adler SG. Nodular glomerulosclerosis in a patient with metabolic syndrome without diabetes. Nat Clin Pract Nephrol 2008;4:639–642
19. Ruggenenti P, Remuzzi G. Time to abandon microalbuminuria? Kidney Int 2006;70:1214–1222
20. Atkins RC, Briganti EM, Lewis JB, et al. Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. Am J Kidney Dis 2005;45:281–287
21. Kilpatrick ES, Rigby AS, Atkin SL. ALC variability and the risk of microvascular complications in type 1 diabetes: data from the Diabetes Control and Complications Trial. Diabetes Care 2008;31:2198–2202
22. Bilous R. Microvascular disease: what does the UKPDS tell us about diabetic nephropathy? Diabet Med 2008;25(Suppl. 2):25–29
23. Pirart J. Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973 (3rd and last part) (author's transl). Diabetes Metab 1977;3:245–256
24. Holman RR, Paul SK, Bethal MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
25. Pouiller NR. Blood pressure and glucose control in subjects with diabetes: new analyses from ADVANCE. J Hypertens Suppl 2009;27:53–58
26. Patel A, MacMahon S, Chalmers J, et al. Intensive insulin-glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
27. Duckworth W, Abraira C, Mortiz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
28. Kanjanabuch T, Ma LJ, Chen J, et al. PPAR-gamma agonist protects podocytes from injury. Kidney Int 2007;71:1232–1239
29. Joy MS, Gipson DS, Diike M, et al. Phase I trial of rosiglitazone in FSGS: III. Report of the Font study group. BMC Nephrol 2010;11:2
30. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care 2009;32:650–657
31. Schneider CA, Ferrannini E, Defronzo R, Scherhnaner G, Yates J, Erdman E. Effect of pioglitazone on cardiovascular outcome in diabetes and chronic kidney disease. J Am Soc Nephrol 2008;19:182–187
32. Morath C, Zeier M, Dohler B, Schmidt J, Nawroth PP, Opelz G. Metabolic control improves long-term renal allograft and patient survival in type 1 diabetes. J Am Soc Nephrol 2008;19:1557–1563
33. Morikà T, Emoto M, Tabata T, et al. Glycemic control is a predictor of survival for diabetic patients on hemodialysis. Diabetes Care 2001;24:909–913
34. Hayashi K, Fukuhara S, Akiha T, et al. Diabetes, glycaemic control and mortality risk in patients on haemodialysis: the Japan Dialysis Outcomes and Practice Pattern Study. Diabetologia 2007;50:1170–1177
35. Oomichi T, Emoto M, Tabata T, et al. Impact of glycemic control on survival of diabetic patients on chronic hemodialysis: a 7-year observational study. Diabetes Care 2006;29:1496–1500
36. Williams ME, Lacson E Jr, Teng M, Olshun N, Lazarus JM. Hemodialyzed type I and type II diabetic patients in the US: characteristics, glycemic control, and survival. Kidney Int 2006;70:1503–1509
37. Drechsler C, Krane V, Ritz E, Marz W, Wanner C. Glycemic control and cardiovascular events in diabetic hemodialysis patients. Circulation 2009;120:2421–2428
38. Scherhnaner G, Ritz E, Scherhnaner GH. Strict glycemic control in diabetic patients with CKD or ESRD: beneficial or deadly? Nephrol Dial Transplant 2010;25:2044–2047
39. Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. Arch Intern Med 2005;165:923–928
40. de Boer IH, Kestenbaum B, Rue TC, et al. Insulin therapy, hyperglycemia, and hypertension in type 1 diabetes mellitus. Arch Intern Med 2008;168:1867–1873
41. Kamoi K, Miyakoshi M, Soda S, Kaneko S, Nakagawa O. Usefulness of home blood pressure measurement in the morning in type 2 diabetic patients. Diabetes Care 2002;25:2218–2223
42. Vijan S, Hayward RA. Treatment of hypertension in type 2 diabetes mellitus: blood pressure goals, choice of agents, and setting priorities in diabetes care. Ann Intern Med 2003;138:593–602
43. Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens 2009;27:2121–2158
44. de Galan BE, Perkovic V, Ninomiya T, et al. Lowering blood pressure reduces renal events in type 2 diabetes. J Am Soc Nephrol 2009;20:883–892
45. Berl T, Hunsicker LG, Lewis JB, et al. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropyathy Trial. J Am Soc Nephrol 2005;16:2170–2179
46. Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients...
with coronary artery disease be dangerous? Ann Intern Med 2006;144:884–893
48. Jafar TH, Schmid CH, Landa M, et al. Angiotensin-converting enzyme inhibitors and progression of non-diabetic renal disease: a meta-analysis of patient-level data. Ann Intern Med 2001;135:73–87
49. Pohl MA, Blumenthal S, Cordonnier DJ, et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. J Am Soc Nephrol 2005;16:3027–3037
50. Wühl E, Trivelli A, Picca S, et al. Strict blood-pressure control and progression of renal failure in children. N Engl J Med 2009;361:1639–1650
51. Schjoedt KJ, Andersen S, Rossing P, Tarnow L, Parving HH. Aldosterone escape during blockade of the renin-angiotensin-aldosterone system in diabetic nephropathy is associated with enhanced decline in glomerular filtration rate. Diabetologia 2004;47:1936–1939
52. Mehdi UF, Adams-Huet B, Raskin P, Vega GL, Toto RD. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. J Am Soc Nephrol 2009;20:2641–2650
53. Sato A, Hayashi K, Naruse M, Saruta T. Effectiveness of aldosterone blockade in patients with diabetic nephropathy. Hypertension 2003;41:64–68
54. Epstein M, Williams GH, Weinberger M, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. Clin J Am Soc Nephrol 2006;1:940–951
55. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK; AVOID Study Investigators. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med 2008;359:2433–2446
56. Wenzel RR, Littke T, Kuranoff S, et al. Avosentan reduces albumin excretion in diabetics with macroalbuminuria. J Am Soc Nephrol 2009;20:655–664
57. Mann JF, Green D, Jamerson K, et al. Avosentan for overt diabetic nephropathy. J Am Soc Nephrol 2010;21:527–535
58. Ritz E, Wenzel R. Endothelin receptor antagonists in proteinuric renal disease: every rose has its thorn. J Am Soc Nephrol 2010;21:392–394
59. de Zeeuw D, Agarwal R, Amdahl M, et al. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. Lancet 2010;376:1543–1551