Blood pressure control

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21.10.1 Diabetes mellitus and the kidney 4981 of moderately increased albuminuria or progression of retinop- athy. However, the study was closed early because of excess car- diac deaths and it was not powered for microvascular endpoints. Nonetheless, there is now debate as to the role of intensive glucose control in people with type 2 diabetes, and a recognition that tar- gets will need to be adjusted for the individual taking into account comorbidities and age. There is continuing controversy as to whether intensive glycaemic control alone can prevent the progression of moderately increased albuminuria to severely increased albuminuria. Careful analysis of the DCCT cohort failed to show an impact, but a post hoc ana- lysis of the Joslin Clinic nephropathy cohort demonstrated a slower progression in terms of rate of loss of GFR in those with better gly- caemic control. It is likely that other factors such as blood pres- sure control are of more importance for progression once UAER exceeds 30 to 40 mg/day. Results from the DCCT/EDIC cohort have shown a reduction in the number of patients in the intensively treated versus conventional arm who went on to develop an esti- mated glomerular filtration rate (eGFR) of less than 60 ml/min per 1.73 m2 (incident rates of 1.6 vs 3.0/1000 person years; P = 0.006), but no effect on rates of endstage renal disease, partly because of the remarkably few individuals who reached this endpoint (8 vs 16 respectively; P = 0.10). The UKPDS showed a positive benefit of intensive therapy on the rate of doubling of serum creatinine at 12 years (0.91% vs 3.52%; P <0.003) in patients with type 2 dia- betes, but the numbers were also very small. A meta-analysis has shown no effect of intensive glycaemic control on hard nephrop- athy endpoints in type 2 diabetes. Pancreas transplantation in type 1 patients has demonstrated that long-term (10 years) complete gly- caemic normalization can reverse established pathological changes in native (nontransplanted) glomeruli. Thus glomerulopathy may take as long to reverse as it does to develop, and many studies of intensive control to date may have been of too short a duration, and glycaemic correction inadequate. Blood pressure control There have been many studies of antihypertensive therapy in diabetic nephropathy. For clarity, these will be dealt with under three head- ings: primary prevention (of moderately increased albuminuria), secondary prevention (of severely increased albuminuria), and ter- tiary prevention (of endstage renal disease and death). Primary prevention The EURODIAB Controlled Trial of Lisinopril in Insulin- dependent Diabetes (EUCLID) studied normotensive type 1 diabetic patients with a UAER between 5 and 20 µg/min and dem- onstrated a significant reduction in albuminuria after 2 years, but no impact on the numbers developing moderately increased albu- minuria. This finding has been confirmed recently by the Diabetic Retinopathy Candesartan Trials (DIRECT) and RASS (Renin– Angiotensin System Study) studies. The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) studied 1204 hyper- tensive type 2 patients with normoalbuminuria and demonstrated a significant reduction in the numbers developing moderately increased

albuminuria after 3 years on trandolapril (6%), com- pared to verapamil (11.9%), or placebo (10%). The HOPE and ADVANCE studies also showed a significant benefit in patients at high cardiovascular risk. However, these findings were not con- firmed in normotensive or well-controlled hypertensive patients in DIRECT. In the UKPDS, the number of hypertensive patients developing a urinary albumin concentration of more than 50 mg/ litre at 6 years was 2.3% in the tight (blood pressure 144/82 mmHg) and 12.5% in the less tight (blood pressure 154/87 mmHg) groups (P <0.009). Secondary prevention Most studies have shown a short- to medium-term benefit of antihypertensive therapy on UAER in the moderately increased albuminuric range, with drugs blocking the renin–angiotensin system seeming to be more effective. In mainly European patients with type 1 diabetes, a meta-analysis has shown an adjusted risk reduction of more than 60% for the de- velopment of severely increased albuminuria comparing ACE in- hibitors with placebo. The angiotensin II receptor blocker irbesartan has demonstrated a similar magnitude of effect in moderately in- creased albuminuric type 2 diabetic patients. Thus, blockade of the renin–angiotensin system by any means appears to confer benefit in terms of a reduction in the numbers of patients developing severely Table 21.10.1.3 Comparison of intensive versus conventional therapy in the prevention of moderately increased albuminuria in type 1 (DCCT + EDIC) and newly diagnosed type 2 (UKPDS) patients Study Number Ethnicity Duration of study (years) Achieved HbA1c Moderately severe albuminuria Intensive (%) Conventional (%) Intensive (%) Conventional (%) RRR (%) DCCT European (96%) 9 7.2 (normal <6.05) 9.1 (UAER

> 40 mg/day) No retinopathy 726 15 27 44 Retinopathy 715 27 42 35 EDIC 1112 8 8.0 8.2 6.8 15.8 57 UKPDS 3867 European 81% Indian Asian 10% Afro- Caribbean 8% 9 7.0 (normal 6.2) 7.9 19.2 (UAC 50 mg/litre) 25.4 24 DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications Study; RRR, relative risk reduction; UAC, urinary albumin concentration, annual; UAER, urinary albumin excretion rate, annual 4-h collections (biannual for EDIC); UKPDS, United Kingdom Prospective Diabetes Study.

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