CHAPTER 58

Clinical Aspects of Diabetic Nephropathy

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The term "diabetic nephropathy" (DN) refers to the classic pathologic structural and functional changes seen in the kidneys of subjects with diabetes mellitus (DM) (either type 1 or type 2). Some differences exist in DN in patients with type 1 or 2 diabetes and may be clinically relevant, particularly with respect to their onset, natural history, and treatment.

In this chapter, we review the natural history and stages of DN, discuss the treatment of DN as it pertains to slowing its progression, and consider the future of the treatment of DN.

DEFINITIONS AND MEASUREMENT OF URINARY ALBUMIN EXCRETION

In order to consider the stages of DN, we must first define what is meant by the commonly encountered terms normoalbuminuria, microalbuminuria, and overt proteinuria (also known as macroalbuminuria). In the absence of kidney disease, the average amount of albumin excreted in the urine is 8 to 10 mg per day. Normoalbuminuria is arbitrarily defined as <30 mg per day. Microalbuminuria (MA) is defined as 30 to 299 mg per day, an amount sufficiently low enough often not to be detected by standard colorimetric test-strip (dipstick) methodologies. In order to measure MA, specialized immunoassays are required, including turbidimetric, nephelometric, and two-site immunometric tests.[1] Typically, these assays have a lower limit of detection of 2 to 10 mg per L.[2] A variety of clinical situations can increase urinary albumin excretion (UAE), including physical exercise, hyperglycemia, water loading, fever, seizure, and heart failure. Because the absolute magnitude of these increases in UAE are small, this can lead to temporary increases in UAE sufficient enough to misclassify a patient as having MA or not, but represent trivial changes in a patient with overt proteinuria. MA is considered persistent and clinically significant if it is present on two of three assays performed over a specified time period (usually 2 weeks), which helps to avoid the misclassification of a patient on the basis of the inherent variability in daily UAE. Overt proteinuria is so-named because the proteinuria is sufficient enough to activate the standard urinalysis dipstick, and corresponds to an albumin excretion of >300 mg per day. Once a patient has this level of proteinuria, there is little reason to measure the more expensive tests specifically for UAE. Albumin in general represents anywhere from 20% to 60% of total urinary protein excretion. The standard urinary dipstick actually measures all negatively charged proteins, rather than only albumin concentration. Because albumin is the most abundantly negatively charged protein found in urine, it is the principal urinary protein that is measured. In the presence of other conditions in which positively charged proteins are the principal proteins excreted in the urine (e.g., positively charged immunoglobulins), the standard dipstick may not be activated. Additionally, the dipstick is sensitive to the concentration of, but not the absolute amount of, albumin in a random or spot specimen.[3] A patient may have normal albumin excretion over the course of the day, but the concentration of charge in that spot specimen may be great enough to activate the dipstick.

To circumvent these issues with dipstick measurements of albuminuria, various other laboratory measures to specifically measure albumin or total protein excretion have been developed. Twenty-four-hour urinary collection, an overnight collection, or a random or first-morning void can be assayed. Total albumin concentration, total protein concentration, an albumin-to-creatinine ratio (ACR), or a protein-to-creatinine ratio (PCR) can be measured in any of these collections. The 24-hour collection is difficult and cumbersome for the patient to do, and is prone to both over- and under-collections. Collection errors can be partially corrected for by measuring an ACR or PCR in a 24-hour urine collection, and this may best reflect the patient's albuminuria or proteinuria. ACR or PCR in a random spot or first-morning urine is less cumbersome to the patient

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than a 24-hour collection, but are subject to error and variation, because albumin excretion increases in the upright versus prone position, or with exercise. An ACR or PCR in a first-morning urine will be more reproducible than a random spot urine, but will represent about 30% to 50% lower albumin excretion than an upright daytime urine. Due to its consistency, the first-morning void ACR may be the best method among these to predict renal events in type 2 diabetes and DN.[4]

NATURAL HISTORY OF DIABETIC NEPHROPATHY

The natural history of DN in type 1 diabetes was characterized by Kussman et al. in 1976.[5] They examined the death records of patients with juvenile-onset diabetes who were classified as having died from renal failure between 1962 and 1972, and characterized the time of onset of type 1 diabetes, onset of dipstick-positive proteinuria, onset of "early" and "late" renal failure (here defined as serum creatinine [SCr] >2.0 mg per dL and >5.0 mg per dL, respectively) in the 40% of subjects destined to develop DN, and death. Following the onset of type 1 diabetes, the onset of proteinuria occurred at 17.3 ± 6.0 years (mean ± standard deviation), early renal failure at 19.4 ± 5.4 years, late renal failure at 21.6 ± 6.3 years, and death at 22.1 ± 6.4 years. It should be emphasized that this was prior to the advent of the therapies discussed later to delay the progression of DN, and thus represents the true, untreated natural history of DN due to type 1 diabetes. With the development of assays capable of detecting lower amounts of UAE, MA was demonstrated to precede proteinuria in most patients 5 to 10 years after the onset of type 1 diabetes.[6] Figure 58.1 summarizes the natural history of DN due to type 1 diabetes, including the functional and structural changes which are described later (see Risk section, later).

The natural history of DN due to type 2 diabetes is nearly the same, but because the onset of type 2 diabetes cannot be pinpointed, patients may present for medical care at any stage of DN. Perhaps the most important difference in DN between types 1 and 2 diabetes stems from the fact that the onset of type 2 diabetes confers cardiovascular (CV) risk upon a patient that is equivalent to that risk conferred by having had a prior myocardial infarction (MI).[7] In other words, type 2 diabetes is an "MI equivalent." Thus, there is a risk of CV death at any stage along the natural history of DN due to type 2 diabetes[8,9] (Fig. 58.1), and death censors many patients with DN from progression to end-stage renal disease (ESRD). However, in patients with type 1 diabetes, the excess CV risk is not apparent until they have advanced renal disease, so most patients with type 1 diabetes and DN will reach ESRD.

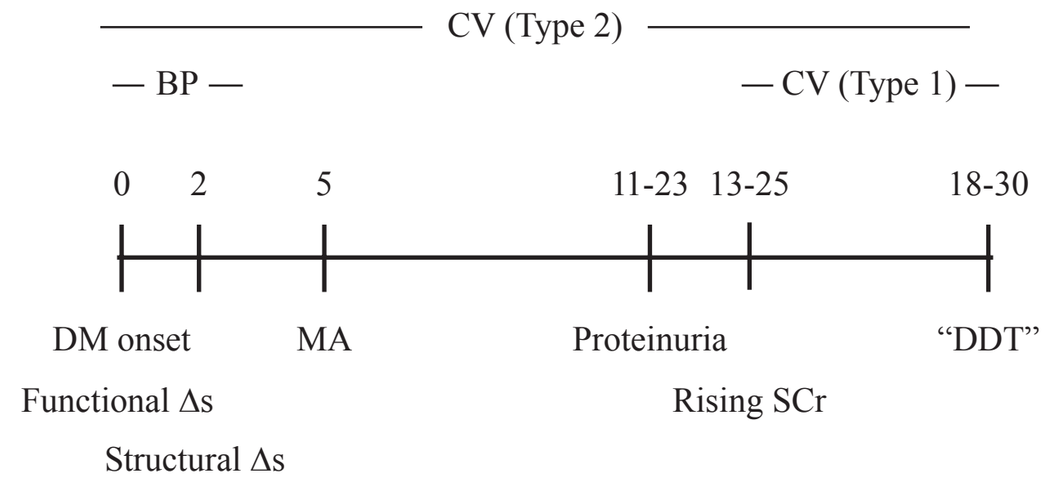


FIGURE 58.1 The natural history of untreated diabetic nephropathy due to type 1 diabetes. In the case of type 2 diabetes, the onset of diabetes is often unknown, and cardiovascular death may occur at any time point, censoring the patient's progression to end-stage renal disease. *BP*, deranged systemic blood pressure; *MA*, microalbuminuria; *DM*, diabetes mellitus; *DDT*, death, dialysis, or transplantation.

STAGES OF DIABETIC NEPHROPATHY

DN has been characterized according to its traditional stages—glomerular hyperfiltration, MA, overt proteinuria, abnormal renal clearance, and renal failure—which have been derived from the natural history of DN described previously. These stages can really be considered a continuum of injury to the kidney (Fig. 58.2). There is evidence that there are markers for the risk of developing nephropathy which occur prior to the onset of MA. This alternative scheme for classifying DN allows us to consider the risk of developing nephropathy, clinicopathologic injury, and renal failure. These terms and a similar classification construct are in use for acute kidney injury (AKI).[10]

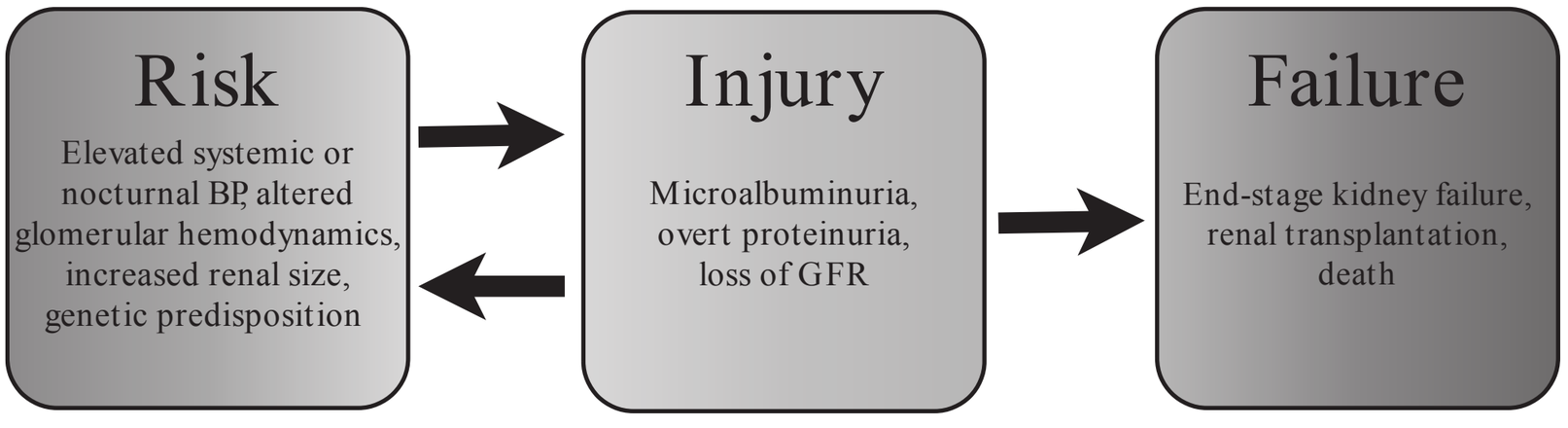


FIGURE 58.2 Classification scheme for diabetic nephropathy.

Risk

Approximately 40% of patients with diabetes develop clinically significant DN.[8,11–26] A variety of clinical, epidemiologic, familial, and genetic factors predict the risk of the development of DN (Table 58.1). Longer prepubertal duration of type 1 diabetes and prepubertal hyperglycemia increase the risk of postpubertal MA.[24] Older age at the time of diagnosis of type 1 and type 2 diabetes appears to increase the risk of DN,[19,27,28] but specifically in Pima Indians, it seems that the onset of type 2 diabetes prior to the age of 20 years confers a fivefold risk for ESRD in middle age as compared to onset after age 20.[22] A longer duration of diabetes is associated with an increased risk of DN,[29] but a majority of patients with diabetes (60%) do not ever develop clinically significant DN. Even slight elevations in body mass index (BMI) are associated with a higher risk of DN in patients with type 2 diabetes.[30] Very mild elevations of UAE (even within the normoalbuminuric range) predict a greater risk of development of DN.[30–34] In a 10-year prospective observational cohort, baseline UAE was 9 mg per 24 hours in those subjects who remained normoalbuminuric, but was 13 mg per 24 hours in those who ultimately developed MA or overt proteinuria.[31]

In the earliest stages of the changes to the kidney in diabetes there are both elevations in systemic blood pressure (BP) and glomerular hyperfiltration, which portend more serious injury. The earliest detectable marker of deranged BP regulation in type 1 diabetes is elevated nocturnal systolic BP. An early study demonstrated this correlation with systolic and diastolic BP obtained via 24-hour ambulatory BP monitoring (ABPM).[35] Elevation of nocturnal systolic BP was demonstrated in a prospective longitudinal cohort analysis of 75 adolescents and young adults with type 1 diabetes and normal urinary albumin excretion,[36] in which nocturnal systolic BP elevation by ABPM preceded and predicted the onset of MA. The risk of development of MA was 70% lower in those subjects with a normal nocturnal dipping status, even in those subjects with poor metabolic control (a known predictor of MA, see later text).

Elevated systemic BP at the time of diagnosis of diabetes is associated with the later development of DN, in both types 1 and 2 diabetes. In a cohort of patients with type 1 diabetes followed for 20 years after the onset of diabetes, those patients who were ultimately destined to develop DN (20 years later) had statistically significantly higher systolic and diastolic BP at the time of diagnosis of diabetes compared to those who never developed DN (mean BP 122/76 mm Hg in those subjects who did not develop MA, as compared to 128/80 mm Hg in those who did).[6] Further supporting the role of elevated systemic BP as a risk factor for the development of DN, Parving et al.[12] characterized the prevalence of hypertension (HTN) (defined, at the time, as >160/95 mm Hg or on antihypertensive medications) in 982 subjects with type 1 diabetes attending a diabetes clinic, stratified according to albumin excretion. The presence of HTN strongly correlated with DN, such that HTN was present in 19%, 30%, and 65% of subjects with normo-, micro-, and overt proteinuria. Due to this high prevalence of hypertension at the time of diagnosis of type 2 diabetes, the presence of HTN is less predictive of the risk of developing DN in the future in type 2 rather than type 1 diabetes.[37–39]

Glomerular filtration rate (GFR) is higher at the onset of diabetes as compared to weight- and age-matched controls, both in types 1[40–42] and 2 diabetes.[43] In their study of 13 males with type 1 diabetes of short duration (mean duration 2.4 years), Christiansen et al.[42] demonstrated that iothalamate-GFR was increased in diabetes (144 vs. 113 mL per min), as were renal plasma flow and kidney volume (assessed by hippuran and ultrasound, respectively). Glomerular function was investigated in type 2 diabetic Pima Indians,[43] which demonstrated that iothalamate-GFR was 140 versus 122 mL per min in diabetic subjects as compared to nondiabetic controls, and was higher in subjects with impaired versus normal glucose tolerance (before the

58.1 Risk Factors for the Development of Diabetic Nephropathy

- Older age of diabetes onset[19,25,27] (type 1); younger age of onset in Pima Indians[22] (type 2)
- Elevated systemic BP[6,25,30,32] (type 1 and type 2)
- Nocturnal systolic BP elevation[36] (type 1)
- Elevated 24-hour ambulatory systolic and diastolic BP[35] (type 1)
- Increased body mass index[26] (type 1 and type 2)
- Increased waist-to-hip ratio[26] (type 1 and type 2)
- Longer diabetes duration[25,29] (type 1 and type 2)
- Increased baseline albumin excretion rate[30–34] (type 1 and type 2)
- Poor glycemic control[6,25,26,30,31] (type 1 and type 2)
- High level of low-density lipoprotein[25,26] (type 1 and type 2)
- Male sex[6] (type 1)
- African Americans, Polynesian, Maori, and Hispanic American race[13,54,61] (type 1 and type 2)
- Retinopathy, any diabetic, presence of[31] (type 1, less so type 2)
- Smoking[31] (type 2)
- High triglycerides, fasting[25,26] (type 1 and type 2)
- Genetic factors[70–72] (type 1 and type 2)
- Family history of diabetic nephropathy[63–68] (type 1 and type 2)

onset of diabetes).[44] Although glomerular hyperfiltration is common at the time of diagnosis of diabetes, those patients destined to develop DN have, on average, higher GFR than those patients with diabetes who never develop DN.[45,46] Despite the correlation between higher GFR at the onset of DM and the risk of developing DN, there is no absolute cut-off level of GFR above which DN develops with certainty in the future. Various mediators of hyperfiltration[47–49] have been postulated, including alterations in eicosanoids, nitric oxide, atrial natriuretic peptide, and transforming growth factor-beta. Treatment with continuously infused insulin for 2 years (via insulin pump) moderates the hyperfiltration in type 1 diabetes.[50]

Renal size is also increased in early diabetes.[51] Christiansen et al.[42] demonstrated that males with type 1 diabetes had mean renal volume of 278 mL per 1.73 m^2 versus 224 mL per 1.73 m^2 for nondiabetic control males, a significant increase of 24%. Treatment with insulin for 3 months was shown to reduce kidney size in newly diagnosed men with type 1 diabetes.[52] Interestingly, kidney size remains larger at ESRD in those patients with ESRD due to diabetes than from other causes.[53] In one study, renal length was estimated using ultrasonography, and mean right renal length was 9.9 versus 8.8 cm (DN vs. no DN); mean left renal length was 10.0 versus 9.1 cm.

African Americans, Asians, Polynesians, Maori, Native Americans, and Hispanic Americans with diabetes all have an increased risk of developing DN as compared to Caucasians with diabetes.[13,54–61] The overall incidence of diabetes-related ESRD in Jefferson County, Alabama, was 3.4 times higher in African Americans than in Caucasians[56]; similarly, the incidence was 4.4 times higher among African Americans with ESRD reported to the Michigan Kidney Registry from 1974 to 1983.[13] In Mexican Americans studied in the Texas Kidney Health Program over the period 1978 to 1984, the incidence of diabetes-related ESRD was six times higher than in non-Hispanic whites.[59] The prevalence of DN (as estimated by a single dipstick assessment of MA) in a global cohort of type 2 diabetes was nearly 40% higher in Asians, and 30% higher in Hispanics, than in Caucasians.[54] In addition to certain groups having an increased risk of developing DN, it appears that some have an accelerated rate of decline of renal function once DN is established.[62]

In those families in which multiple members have diabetes, the presence of DN in one member predicts an increased risk of DN in other family members.[63–68] An early report demonstrated that there was evidence of DN in 83% of the siblings of probands who had undergone renal transplantation for DN.[63] In this study, the presence of nephropathy in the proband was the only significant predictor of the presence of it in the sibling. These clinical observations have led to studies[69] to identify genetic markers that predict the development of DN. Candidate genes span many gene classes, and were recently summarized,[70] but include glucose transporter 2, kininogen, adiponectin, transforming growth factor-beta II and III, catalase, endothelial nitric oxide synthase, apolipoprotein E, tissue inhibitor of metalloproteinase 3,[71] and angiotensin-I converting enzyme.[72] Identification of genes involved in the pathogenesis of DN will likely help direct the development of novel agents to treat it.

Injury

Albuminuria (from MA to overt proteinuria) and loss of GFR represent a spectrum of pathologic diabetic injury to the kidneys. We review these forms of diabetic kidney injury in turn.

MA has traditionally been considered the hallmark of DN, and the earliest clinical feature of it. MA occurs in patients with either type 1 or type 2 diabetes. Approximately 10% to 20% of patients with type 1 diabetes develop MA after 5 to 15 years of diabetes.[11] It is important to note, however, that not all patients with type 1 diabetes develop DN. The cumulative incidence of MA was approximately 30% to 40% at 20 years in a cohort of subjects characterized from the onset of type 1 diabetes,[6] but there appears to be an upper limit of nearly 55%, after 40 years of type 1 diabetes.[29]

The prevalence of MA in type 2 diabetes ranges in large trials and a global cohort from 25% to 45% after approximately 10 years of diabetes, but may be present at the time of diagnosis of diabetes.[8,37,54,73] The presence of MA, or even overt proteinuria, at the time of diagnosis of diabetes in patients with type 2 DM may reflect the delay in diagnosis of DM, in type 2 as compared to type 1 diabetes. The prevalence of MA varies by age, with older adults more likely to have MA at the time of diagnosis of diabetes,[74] and race; it is highest in Asians and Hispanics and lowest in Caucasians.[54,75] It was estimated that 2.0% of patients will transition to persistent MA from normoalbuminuria per year (based on data from the United Kingdom Prospective Diabetes Study [UKPDS]).[8] MA is associated with increased CV mortality compared to patients with type 2 diabetes and no MA,[8] with a relative risk for all-cause mortality (which is driven predominantly by CV mortality) of 1.9.[76]

The majority of patients with MA who survive progress to overt proteinuria, and the presence of MA is the single most important risk factor for progression to overt proteinuria.[6,11,29,31,77–80] In type 1 diabetes, risk factors for progression to overt proteinuria include higher baseline urinary albumin excretion rate, poor glycemic control, the presence of diabetic retinopathy, smoking,[31] higher systemic blood pressure, and dyslipidemia.[6]

In type 2 diabetes, the transition rate from MA to overt proteinuria in newly diagnosed patients with diabetes was 2.8% per year in the UKPDS. The observed prevalence of overt proteinuria was 5.3% at 10 years, and 7.1% at 15 years.[8] The rates of conversion are likely higher in certain ethnicities, and have been well characterized in Pima Indians, in whom they are highest.[44]

However, not every patient with MA will progress to overt proteinuria, and some patients may spontaneously regress from MA to normoalbuminuria,[6,76] or they may do so after effective treatment (see later text, Therapy of Diabetic Nephropathy). In an individual patient, this regression from MA to normoalbuminuria may be a reflection of misclassification of the patient as having MA in the first place, because the method

used to measure MA has an inherent insensitivity, and there is variability in albumin excretion during the course of the day or with intercurrent illness or exercise (see previous section, Definitions and Measurement of Urinary Albumin Excretion). Regression in a cohort more likely reflects a true clinical phenomenon in a subgroup of diabetic patients. This regression from persistent MA to normoalbuminuria was characterized in type 1 diabetes in a study of 386 subjects in a single center in which the cumulative incidence of regression was 58% over 6 years.[81] Factors associated with regression included younger absolute age, MA of shorter duration, better lipid status, better glycemic control, and lower systolic BP. Intervention in the care of these patients likely contributed to the regression. Regression of MA is associated with a reduced risk of subsequent CV events,[82] and may therefore be a treatment goal in and of itself.

Once proteinuria is established, renal function inevitably declines (see section later, Failure), with faster rates of decline in renal function seen with higher amounts of proteinuria.[83,84] It is important to note that in the classic study by Kussman et al. (see previous), overt proteinuria begins before GFR has begun to decline. In general, MA and overt proteinuria precede the decrease in GFR in type 1 diabetes; indeed, albuminuria is practically a prerequisite for loss of GFR. In a study of nearly 600 subjects with type 1 diabetes and normoalbuminuria or MA,[85] the risk of loss of GFR over 8 to 12 years was 9% with normal albumin excretion, 16% with MA regression (MA at least halved), 32% with stable MA, and 68% with progressive MA (MA at least doubled). The single most important predictor of the loss of renal function in patients with diabetes is the degree of proteinuria. However, small studies and a global cross-sectional cohort of patients with type 2 diabetes[54,86–92] have reported small subpopulations of patients with normoalbuminuria or MA and reduced GFR, such that 17% of subjects with normoalbuminuria and 27% of subjects with MA had significant kidney dysfunction.[86] The design of the global cohort study[54] precludes exact clarification of the causes for this decreased GFR. Many possibilities exist to explain these subpopulations of patients—including misclassification, treatments that decreased albuminuria and slowed, but did not halt, the loss of renal function, and renal injury not related to DN, such as unresolved AKI. In patients with type 1 diabetes, the presence of decreased GFR in the absence of MA has been associated with worse glomerular histology than in those patients with MA.[93] Alternately, other biopsy studies in patients with type 2 diabetes have demonstrated higher amounts of proteinuria associated with worse glomerular lesions.[94] Overall, in both patients with type 1 and type 2 diabetes, the worse the proteinuria, the faster the rate of decline of renal function, leading many to argue that decreasing proteinuria should be a goal or clinical endpoint of therapy.

Failure

Once loss of GFR has begun, the patient with DN begins a near inexorable decline toward dialysis, renal transplant, or death. Untreated, the rate of loss of GFR in type 1 diabetes may be as high as 7 to 12 mL/min/1.73 m^2 per year.[95,96] In type 2 diabetes in Pima Indians, the average decline was 11 mL/min/1.73 m^2 per year.[44] This rate of decline in GFR can also be quantified as transition rates along the spectrum of diabetic injury, which were estimated in the UKPDS. The annual rate of transition from overt proteinuria to renal failure was 2.3%, from overt proteinuria to death 4.6%, and from renal failure to death was 19.2%.[8] Additionally, the UKPDS, not designed as a renal study, and with infrequent (yearly) measurement of renal function, suggested that there was a greater incidence of CV death than progression of DN, at every stage of DN under consideration in the study.[8] However, analysis of a large cohort of well-characterized patients with DN, proteinuria, and low GFR, obtained from two large multinational renal clinical trials with frequent (quarterly) measurement of renal function (see later), showed that the risk of ESRD was significantly more common than CV death in the whole cohort, with an incidence rate ratio (IRR) of 4.92, and more common than all-cause mortality (IRR 2.61).[9] Finally, the renal prognosis of type 1 diabetes has improved, as estimated by the decreasing incidence of ESRD over time, characterized in a very large prospective cohort of patients with type 1 diabetes.[19] These data highlight the variability of the competing risks of progression, failure, and death.

DIAGNOSIS AND CLINICAL MANAGEMENT OF DIABETIC NEPHROPATHY

We discussed the factors that predict the development of the various stages of DN, and presented a framework to consider the likelihood of progression from one stage of DN to another. However, the clinician, faced with a patient with diabetes and markers of chronic kidney disease (e.g., proteinuria, hematuria, or decreased GFR), must assign some likelihood that the disease under consideration is actually DN. In type 1 diabetes, the epidemiology of DN and the presence of proliferative diabetic retinopathy help determine the likelihood that DN is present. For example, if massive proteinuria is present within 5 years of the diagnosis of type 1 diabetes, it is unlikely to be due to DN; conversely, the onset of proteinuria more than 25 years after the diagnosis of type 1 diabetes makes DN less likely (Fig. 58.1). Additionally, because 95% of patients with type 1 diabetes and DN also have diabetic retinopathy,[15] the absence of retinopathy may imply some kidney lesion other than DN.

These epidemiologic findings are not as useful in type 2 diabetes, however. The concordance rate of DN and diabetic retinopathy is only about 60% to 65% in type 2 diabetes,[94,97–101] thus the absence of retinopathy is not as strong a predictor of other nondiabetic renal diseases. Additionally, because the onset of diabetes is less reliably known in type 2 than in type 1, one cannot readily rely on the natural history to exclude DN. Thus, a systematic evaluation for other causes of kidney disease (a thorough history and physical examination, and selected laboratory and imaging tests) must be utilized to distinguish which patients may benefit from a renal biopsy.

It is incumbent on the practicing nephrologist to assess whether something other than diabetes is the cause of kidney disease. Such an approach was undertaken in a prospective biopsy study,[94] in which patients were carefully screened for history, physical, or serologic evidence of a disease other than DN. Diabetic glomerulosclerosis was responsible for the renal clinical findings in 94% of patients with type 2 diabetes. Two distinct glomerular lesions were found, classical Kimmelstiel-Wilson (KW) nodules and mesangial sclerosis; proliferative retinopathy was associated with KW glomerulopathy, and patients with mesangial sclerosis more frequently had no evidence of retinopathy, or retinal microaneurysms only. Importantly, there was no cut-off level for proteinuria above which DN was not found to be the cause for the underlying glomerular lesion, since the range of proteinuria reported in this study was 700 mg per day to 18 g per day.

The presence of hematuria is also not sufficient to suggest the presence of a renal lesion other than DN. In a study of 68 subjects with the clinical diagnosis of DN, 62% of them had hematuria, as assessed on a single urine examination.[102] Dysmorphic red blood cells (acanthocytes), indicative of glomerular hematuria, however, were only present in 4% of subjects with clinical DN, but were present in 40% of subjects with known glomerular lesions.

Hence, if a patient with diabetes has diabetic retinopathy (type 1 diabetes), the onset of proteinuria in the expected time frame (type 1), and no history, physical, or serologic evidence to support another disease (type 1 and 2) such as systemic lupus erythematosus, a renal biopsy is rarely indicated because an alternate diagnosis that would be treated differently is rarely found.

Once the diagnosis of DN is established, there are some unique features to the clinical management of the patient with renal insufficiency and diabetes. Thirty to 45% of insulin is metabolized by the kidney. As GFR decreases, any available insulin lasts longer, and patients are thus at greater risk for hypoglycemic episodes if doses of hypoglycemic medications are not reduced. Furthermore, most oral hypoglycemic agents are metabolized by the kidney, and if hypoglycemia does develop, it is prolonged far longer than it would be in a patient with diabetes and normal renal function, necessitating hospitalization for observation in many cases. Metformin is contraindicated in patients with SCr $\geq$1.5 mg per dL due to its association with severe metabolic acidosis (lactic acidosis) in these patients.

The most common cause of type IV renal tubular acidosis (RTA) or hyperkalemic hyperchloremic metabolic acidosis is diabetes. Thus, at any level of kidney function, these patients are at risk for hyperkalemia and metabolic acidosis. Treating this specific tubular transport defect with a low potassium diet, diuretics (often requiring high-dose loop or very potent thiazide agents), and base supplementation can be critical and allow these patients to receive continuous, uninterrupted therapy with renin angiotensin system (RAS) inhibitors (see later text) which would otherwise be limited by hyperkalemia.

The presence of diabetes is a risk factor for developing acute kidney injury (AKI) due to intravenous iodinated contrast, volume depletion, and nonsteroidal anti-inflammatory agent use. Because unresolved AKI can hasten a patient's course to ESRD, all patients with diabetes and their physicians should be educated to avoid these potential nephrotoxic exposures. Lastly, due to advanced vascular disease often present in patients with diabetes, early access planning for dialysis is prudent.

TREATMENT OF DIABETIC NEPHROPATHY

Few therapies exist to treat DN, and treatment focuses on slowing the progression of DN from each stage to the next. Here we summarize the major clinical findings that direct DN treatment and outline the progress of ongoing trials, the results of which will likely direct future care.

Glycemic Control

The role of poor glycemic control in the progression of DN was first demonstrated in epidemiologic studies. The effect of improved glycemic control on the progression of DN has been tested in large clinical trials in both type 1 and type 2 diabetes. The definitive evidence in type 1 diabetes that intensive therapy with insulin delays the onset and slows the progression of diabetic nephropathy comes from the Diabetes Control and Complications Trial (DCCT).[103] Conducted from 1983 to 1993 in the United States and Canada, the DCCT randomized 1441 subjects aged 13 to 39 with type 1 diabetes to conventional versus intensive insulin control (goal hemoglobin A1c in the intensive arm $<$6.05%) and followed them for a mean of 6.5 years. The median A1c was 9.1% versus 7.3% for conventional versus intensive control. Intensive control demonstrated a relative risk reduction (RRR) of 39% for the development of MA, and a RRR of 56% for the development of overt proteinuria. Intensive blood sugar control was also associated with a reduction in the development of retinopathy and neuropathy. The tradeoff for improved renal outcomes was an increased incidence of severe hypoglycemic events (62 vs. 19 events/100 patient-years in the intensive vs. conventional control). Despite these successes, there was no reduction in CV events in DCCT (probably as a result of the very few events due to the relative youth of the cohort).

After the trial was ended, 1,375 subjects volunteered to participate in the Epidemiology of Diabetes Interventions and Complications (EDIC) study.[104] Note that all subjects had been advised to either remain at or convert to intensive control at the closeout period of DCCT. Not unsurprisingly, glucose control "converged" in each former treatment arm, and remained in alignment with one another (overall mean A1c 7.8% vs. 7.9% for former conventional vs. former intensive control, at EDIC year 11[105]). Despite the convergence of glycemic control, the development of MA and overt proteinuria were reduced (53% and 86%, respectively) by intensive control, in those subjects who did not experience a renal outcome in DCCT, after 4 (additional) years of follow-up in

EDIC. After 8 years of follow-up, the prevalence of HTN was greater in the conventional versus intensive arm (40.3% vs. 29.9%, P < 0.001).[106] There were no statistically significant differences in subjects requiring dialysis or transplantation, but there were more episodes of SCr >2 mg per dL in the conventional arm through year 8 of EDIC. Interestingly, there was a 42% reduction in the cumulative incidence of a first CV event after 10 years of EDIC follow-up. This CV benefit (of 6.5 years of intensive glucose control) was not apparent at 10 years (the end of DCCT), but by 20 years (corresponding to 10 years' follow-up in EDIC) it was, despite the fact that glycemic control was no longer different between the two groups.

In type 2 diabetes, the UKPDS tested the same hypothesis.[107] A total of 3,867 patients with newly diagnosed type 2 diabetes were randomized to intensive glucose control with oral agents or insulin, or to conventional therapy (dietary therapy). The mean achieved A1c was 7.0% in the intensive control arm as compared to 7.9% for the conventional arm. Subjects randomized to intensive control had a reduction in any diabetes-related endpoint, but no reduction in the renal outcomes of interest (development of MA, overt proteinuria, or a doubling of serum creatinine). Since UKPDS, three large trials (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE], Action to Control Cardiovascular Risk in Diabetes [ACCORD], and the VA Diabetes Trial [VADT])[73,108,109] have collectively studied nearly 25,000 subjects to try to elucidate any benefit of intensive glucose control in type 2 diabetes. Table 58.2 summarizes the findings of these three trials. The CV effects ranged from no benefit to increased CV risk associated with intensive glycemic control, and there was either no renal benefit or, in one study, a reduction in albuminuria. There was a significant increase in hypoglycemia in all the intensive groups. Thus, it seems that intensive control is of demonstrated benefit in type 1 diabetes, but is of unproven benefit in type 2 diabetes. Currently, the American Diabetes Association recommends an A1c goal for nonpregnant adults of <7% for microvascular risk reduction.[110]

Blood Pressure Control

Numerous large well-designed clinical trials across many populations of patients have demonstrated that systolic BP on average below 140 mm Hg reduces the incidence of CV events compared to systolic BP ≥140 mm Hg.[111–114] Unfortunately, most of these trials excluded patients with chronic kidney disease. However, observational studies have linked the presence of HTN to the development of MA or overt proteinuria in patients with diabetes.[54,115–117] Finally, there is a strong and continuous correlation between higher achieved blood pressures and worse renal outcomes in numerous epidemiologic and longitudinal cohort studies in patients with diabetes.

In newly diagnosed patients with diabetes, the UKPDS compared the impact of randomization to one of two levels of blood pressure control on the development of micro- and

58.2 There is No Compelling Benefit of Intensive Glucose Control in Type 2 Diabetes

	ACCORD	ADVANCE	VADT
Population	n = 10,251 with CV event or risk	n = 11,140 with CV event or risk factor	n = 1,791 with poor BP control
Age (years, mean)	62	66	60
Duration of diabetes (years)	10	8	11.5
On insulin at baseline (%)	39/8.1%	1.5/7.2%	54/9.4%
Hemoglobin A1c, baseline	8.1%	7.2%	9.4%
A1c target (%)	<6.0% vs. 7–7.9	<6.5% vs. routine care (achieved 6.3% vs. 7.0%)	6.9% vs. 8.4% (1.5% difference)
Primary outcome	Increased total and CV mortality in intensive group	No benefit on CV outcomes, reduction in microvascular events	No benefit
Renal outcome	No benefit	Albuminuria reduced 21%	No benefit
Hypoglycemia (%)	16.2	2.7	21.2

ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; ACCORD, Action to Control Cardiovascular Risk in Diabetes; VADT, VA Diabetes Trial; CV, cardiovascular; BP, blood pressure.

macrovascular complications.[118] Over a mean of 8.4 years of follow-up, with achieved BP control of 144/82 versus 154/87 in the two arms, the risk of any complication of diabetes or death from diabetes, adverse CV events, and the composite of microvascular complications were dramatically decreased in the lower BP arm.[119] The study did not demonstrate any benefit of lower BP on the renal endpoints, namely proteinuria or doubling of SCr, but it was not designed as a renal study, and renal outcomes were tested only yearly.

Additionally, early studies on small numbers of diabetic subjects suggested that BP control could reduce the rate of loss of GFR in patients with established DN.[120,121] However, the intensive systolic BPs achieved were far higher than 140 mm Hg. The benefits of systolic BP goals below 140 mm Hg in patients with diabetes with or without kidney disease have been more difficult to demonstrate. The Appropriate Blood Pressure in Diabetes (ABCD) trial[122] randomized 480 normotensive subjects with type 2 diabetes to intensive (mean achieved BP approximately 128/75) versus moderate BP control (mean achieved BP approximately 137/81). After 5 years of follow-up, the development of MA or overt proteinuria was measured. There was a reduction in the development of MA and overt proteinuria in the group randomized to the intensive BP control, but there was no difference in the primary outcome of the study (creatinine clearance).

Similarly, a small study in type 1 diabetes[123] and advanced DN randomized subjects to a mean arterial pressure (MAP) of 92 mm Hg versus 100 to 107 mm Hg (treated with ramipril) and followed them for 2 years. In this case, proteinuria again improved in the lower BP arm, but increased in the higher.

The landmark study which addressed the issue of intensive BP control in type 2 diabetes is the ACCORD trial.[108] All subjects in ACCORD were randomized to intensive or standard glycemic control, and 4,733 of the participants were also randomized to intensive (systolic <120 mm Hg) or standard (systolic <140 mm Hg) BP control.[124] At 1 year, mean systolic BP was 119.3 mm Hg versus 133.5 mm Hg in the two groups, respectively. There was no reduction in the rate of the primary composite outcome of fatal and nonfatal major CV events (Fig. 58.3). Intensive BP control was associated with

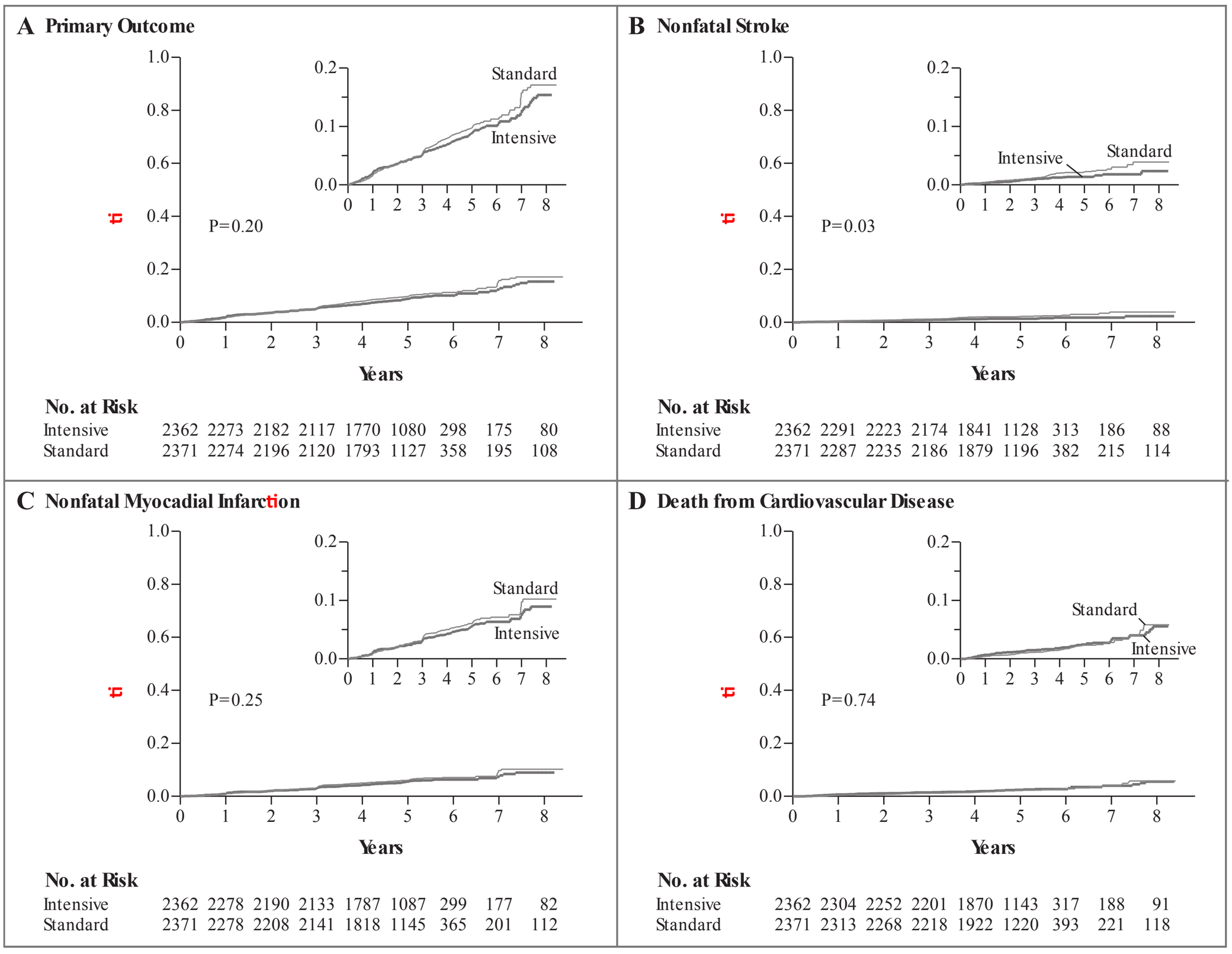


FIGURE 58.3 Targeting a systolic blood pressure of 120 mm Hg does not reduce the rate of cardiovascular events in type 2 diabetes, as compared to 140 mm Hg. (Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575–1585.)

a reduction in albuminuria, but no difference in ESRD, and an increased risk of AKI requiring dialysis. There were nearly three times more adverse events attributed to antihypertensive therapies in the intensive control arm, including more episodes of hypotension, bradycardia, hyper-, and hypokalemia. Not unsurprisingly, lower systolic BP reduced the risk of stroke, but this study was not powered to detect a cerebrovascular outcome. It took nearly 3.5 versus 2.3 BP medications to control BP in the intensive versus standard arms, respectively.

The Irbesartan Diabetic Nephropathy Trial (IDNT) and Reduction in End-Points in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial convincingly demonstrated that the use of the angiotensin receptor blockers (ARBs) reduce the rate of loss of renal function in type 2 diabetes and DN (see later text, Inhibition of the Renin-Angiotensin System).[125,126] Although the patients were not randomized to different levels of BP control, it was clear that patients who entered with more poorly controlled BP were more likely to develop renal failure. However, in both the RENAAL and IDNT studies, achieved BP had a more profound effect on the primary outcome than did the baseline BP.[127–129] In other words, achieving BP control is important, even in the face of prior uncontrolled BP. Those patients who had a reduction in their systolic BP at month 6 or 12 (from baseline) had reduced risk of ESRD as compared to those who did not.[129] It took an average of three other antihypertensive agents to achieve BP control, however. When the effect of BP control was analyzed in IDNT, it appeared that there was a J-curve to the CV risk, as the risk of renal outcomes plateaued at systolic BP <130 mm Hg, but more importantly, all-cause mortality increased at systolic BP <120 mm Hg.[128]

Thus, it is clear that across the continuum of blood pressure in patients with diabetes, risks for CV events and progression of renal disease are high at the high end of the continuum, and are reduced progressively by lowering BP, but there may be a point beyond which further reductions in BP may be harmful. Below this point, although there may be less proteinuria, there is no difference in CV risk (save for stroke), or the risk of renal failure, and there are increased renal adverse events. Current guidelines recommend <130/80 for most patients with type 2 diabetes and DN, but with individualization.

Inhibition of the Renin-Angiotensin System

Drugs which block the RAS (i.e., angiotensin converting enzyme [ACE] inhibitors, ARBs, direct renin inhibitors, and mineralocorticoid antagonists) have demonstrated benefits to block the deleterious effects of angiotensin II on the kidney in animal models of DN, across the full spectrum of diabetic injury. These agents have been studied at each stage of DN, starting with the prevention of the development of MA.

Drugs which block the RAS have been studied in type 1 and type 2 diabetes in patients with normoalbuminuria to delay or prevent the development of MA. In type 1 diabetes, the Renin-Angiotensin System Study (RASS) evaluated losartan versus enalapril versus placebo for 5 years in subjects with normal BP and normoalbuminuria.[130] The 5-year cumulative incidence of MA was 17 versus 4.0 versus 6.0 (losartan vs. enalapril vs. placebo), thus, neither losartan nor enalapril prevented the development of MA in type 1 diabetes. The ARB candesartan was tested in the Diabetic Retinopathy Candesartan Trials (DIRECT) Program,[131] of which the DIRECT-Prevent 1 and the DIRECT-Protect 1 trials randomized patients with type 1 diabetes and normoalbuminuria to candesartan versus placebo and followed them for 5 years. The 5-year cumulative incidence of MA was 2.56% versus 2.32% (candesartan vs. placebo) in DIRECT-Prevent 1, and 7.36% versus 7.26% in DIRECT-Protect 1. Taken together, RASS and the DIRECT program suggest that the use of RAS inhibition is ineffective in the prevention of microalbuminuria in patients with type 1 diabetes.

In type 2 diabetes, the use of ramipril[132] in the Heart Outcomes Prevention Evaluation (HOPE) trial did not statistically significantly prevent the development of MA in type 2 diabetes. A trial in the DIRECT Program (see previous text), the DIRECT-Protect 2, studied candesartan in subjects with type 2 diabetes, normoalbuminuria, and either normal BP or controlled HTN. In the 725 normotensive subjects, MA developed in 13.9% versus 16.7% of subjects (candesartan vs. placebo), but in the 1,180 subjects with HTN, there was no difference in the development of MA over 5 years (15.34% vs. 15.30% of subjects, candesartan vs. placebo). The DIRECT Program was not powered for this renal endpoint, but the primary analysis suggested that candesartan did not prevent MA in type 2 diabetes. The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT)[133] randomized 1,204 subjects to one of four arms (placebo, trandolapril, verapamil, or trandolapril plus verapamil) for at least 3 years, with a goal BP of 120/80 mm Hg. The use of trandolapril and trandolapril plus verapamil reduced the development of MA, but verapamil alone was similar to placebo. A post-hoc analysis suggested that trandolapril and BP reduction both independently reduce the risk of development of MA.[134] The Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial studied the ARB olmesartan, following 4,449 subjects for a median of 3.2 years. There was a statistically significant baseline and follow-up BP difference between the olmesartan and placebo arms, but in the primary analysis, olmesartan prevented or delayed the onset of MA, with MA developing in 8.2% versus 9.8% of subjects (olmesartan vs. placebo) (Fig. 58.4). The trial was not designed to assess for CV outcomes, but there were more fatal CV events in the olmesartan group.[135] Thus it appears that use of RAS inhibition may prevent the development of MA in type 2 diabetes, but this intermediate outcome may be of uncertain value for the prevention of hard renal endpoints, and the value to the health care system has not been proven for these interventions as they have been for other stages of DN (see later text).

Many small clinical studies demonstrated that inhibition of the renin-angiotensin system reduced the number of patients with type 1 diabetes and MA who progressed to overt proteinuria,[136–142] in both hypertensive and normotensive subjects.

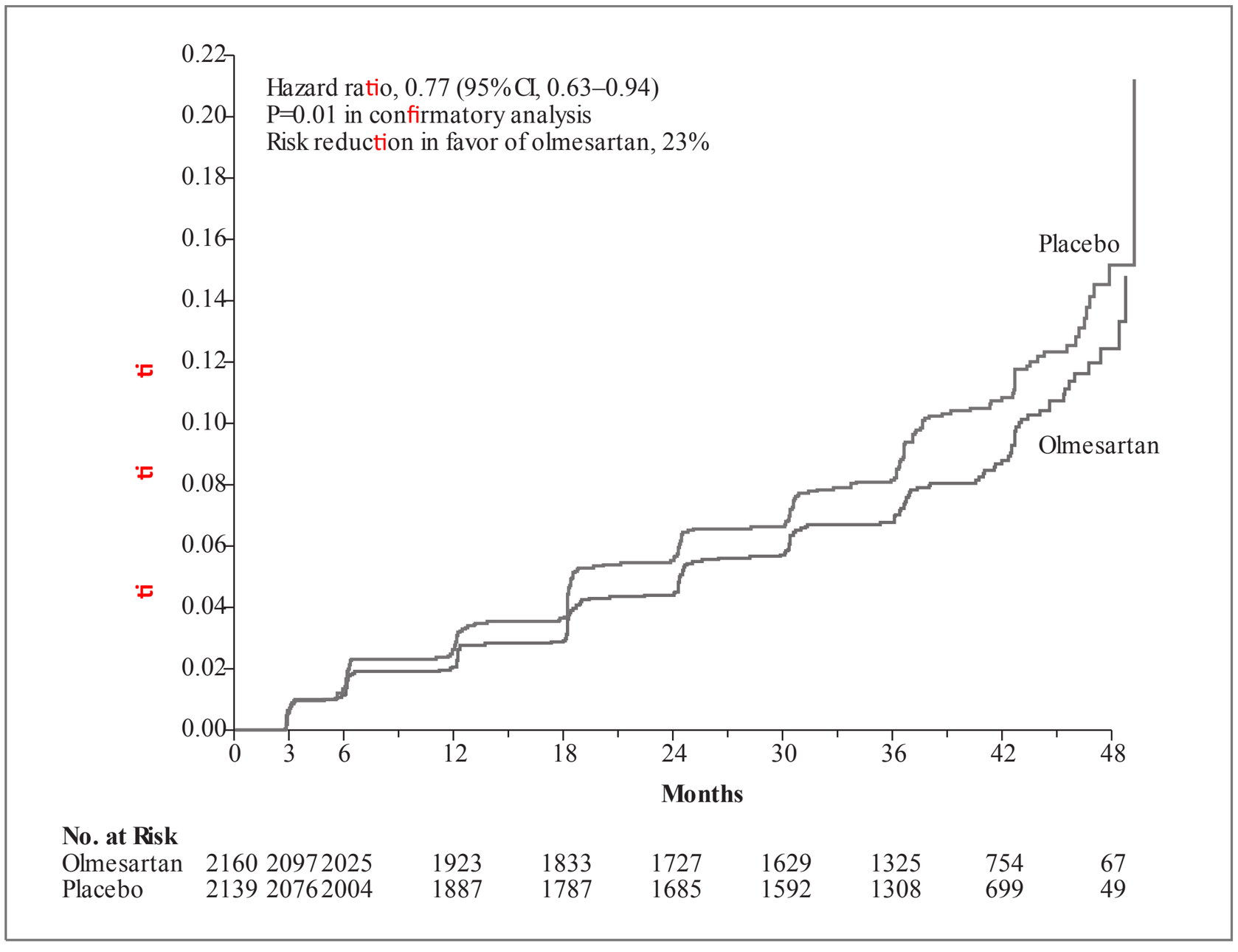


FIGURE 58.4 Olmesartan delays or prevents the development of microalbuminuria in type 2 diabetes, in the ROADMAP trial. (Haller H, Ito S, Izzo JL, et al. Olmesartan for the delay or prevention of microalbuminuria in Type 2 diabetes. *N Engl J Med*. 2011;364:907–917.)

In type 2 diabetes, therapy with the ARB irbesartan was studied to assess its impact on the development of overt proteinuria in subjects with established MA. The Effect of Irbesartan in the Development of Diabetic Nephropathy in Patients with Type 2 Diabetes (IRMA-2) trial[143] randomized 590 subjects with type 2 diabetes and MA to placebo, irbesartan 150 mg daily, or irbesartan 300 mg daily, for 2 years. Irbesartan reduced the risk of the development of overt proteinuria (defined here as >200 mg per day) as compared to placebo, with the 300 mg daily dose further reducing the number of patients who progressed from MA to overt proteinuria (Fig. 58.5). This trial demonstrates the importance of dose on efficacy.

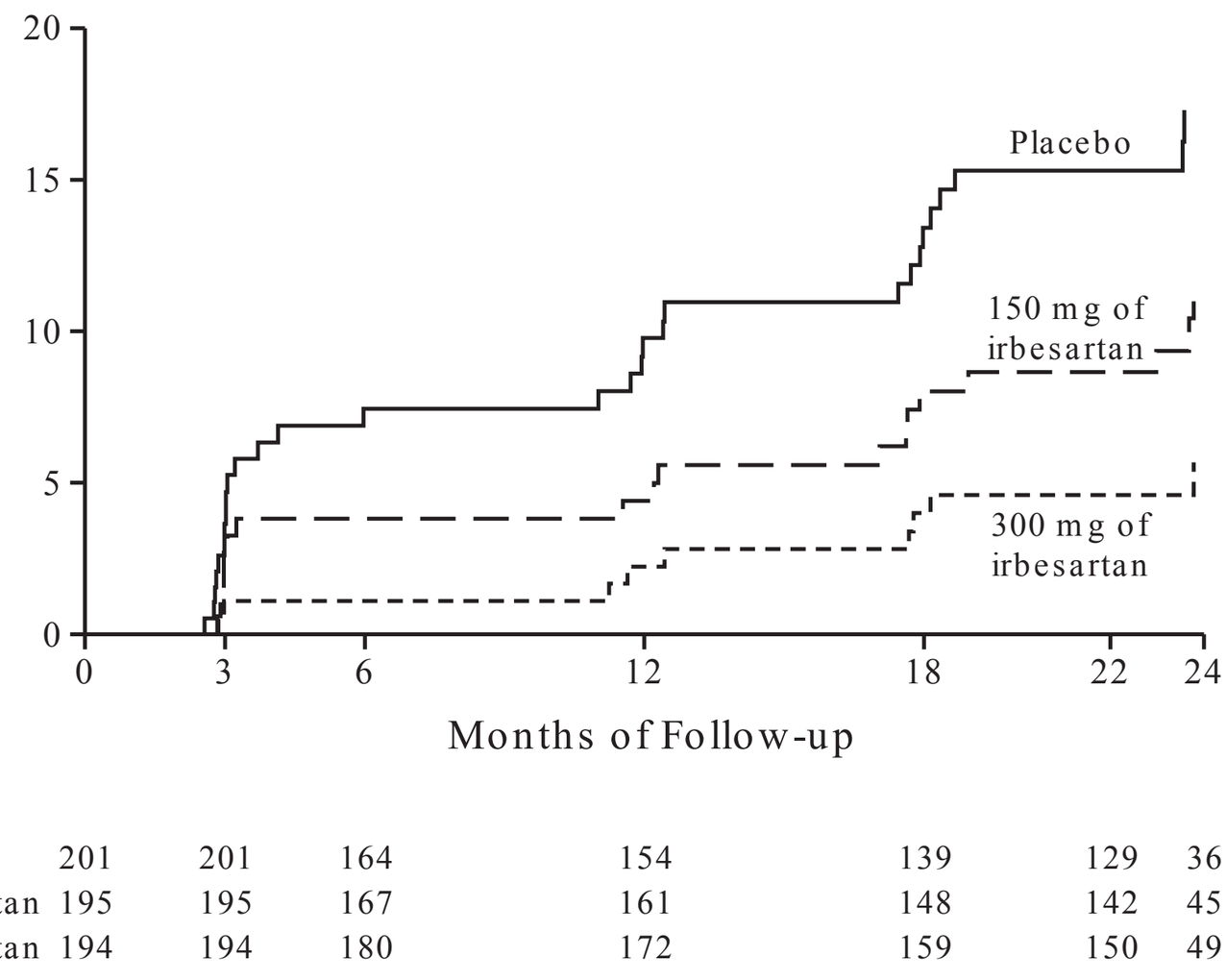


FIGURE 58.5 Irbesartan delays the progression from microalbuminuria to overt proteinuria in type 2 diabetes. Note there is a dose effect. (Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*. 2001;345:870–878.)

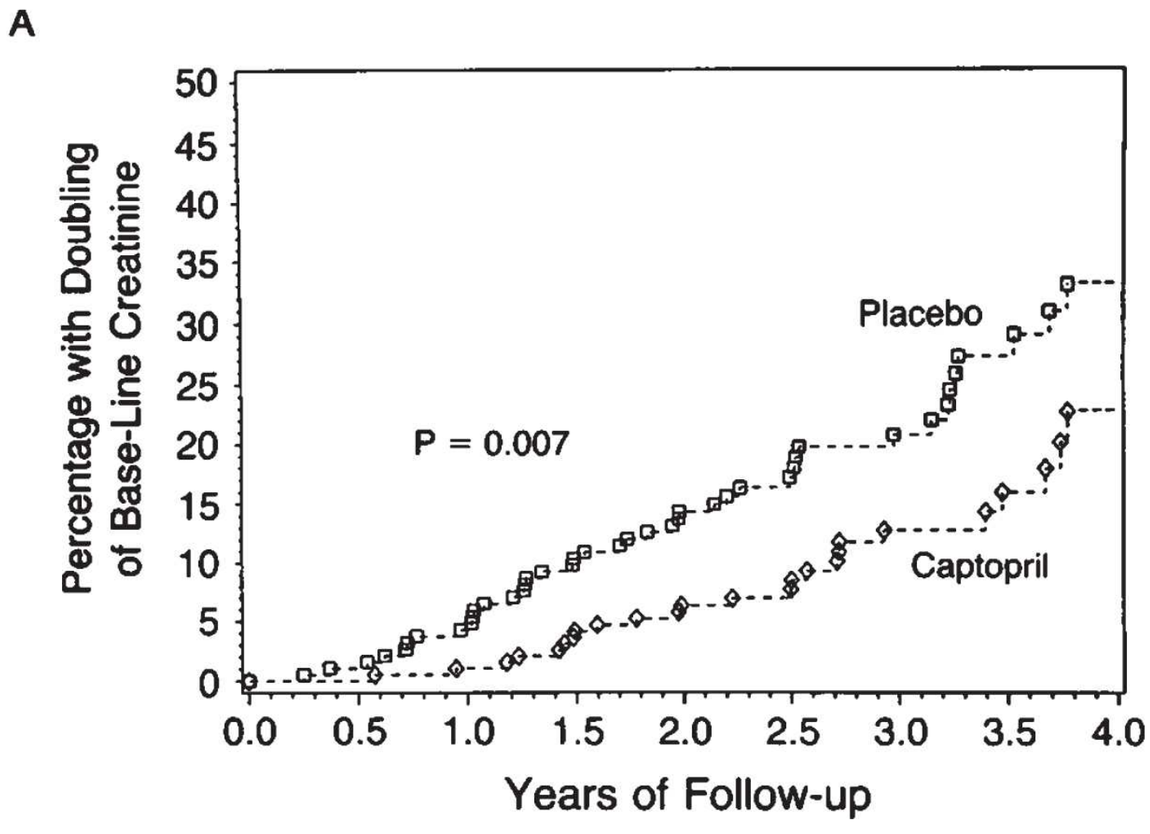
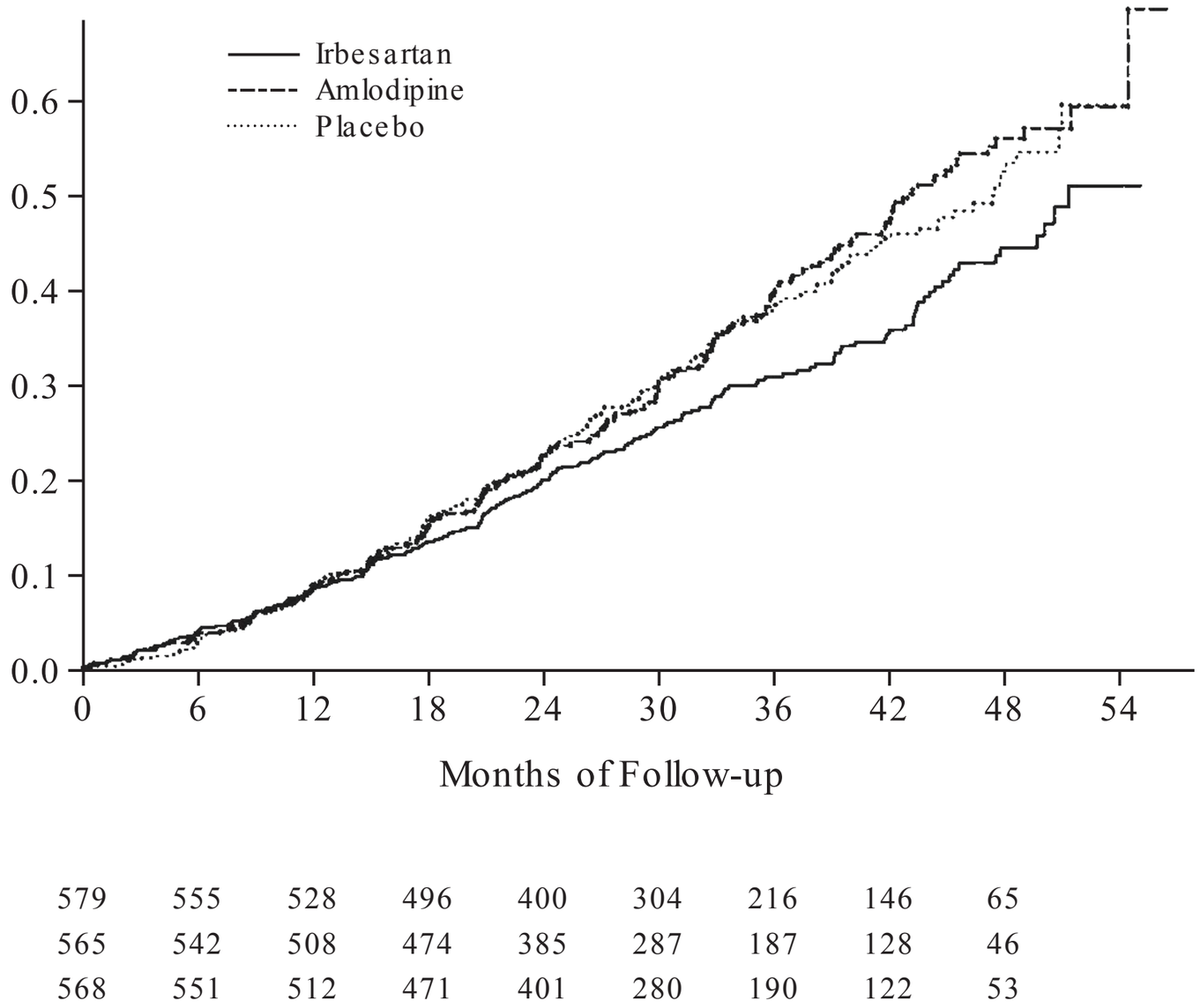


FIGURE 58.6 Captopril reduces the risk of the progression of diabetic nephropathy due to type 1 diabetes, as measured by doubling of serum creatinine **(A)** and by death or the need for dialysis or renal transplantation **(B)**. (Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med.* 1993;329:1456–1462.)

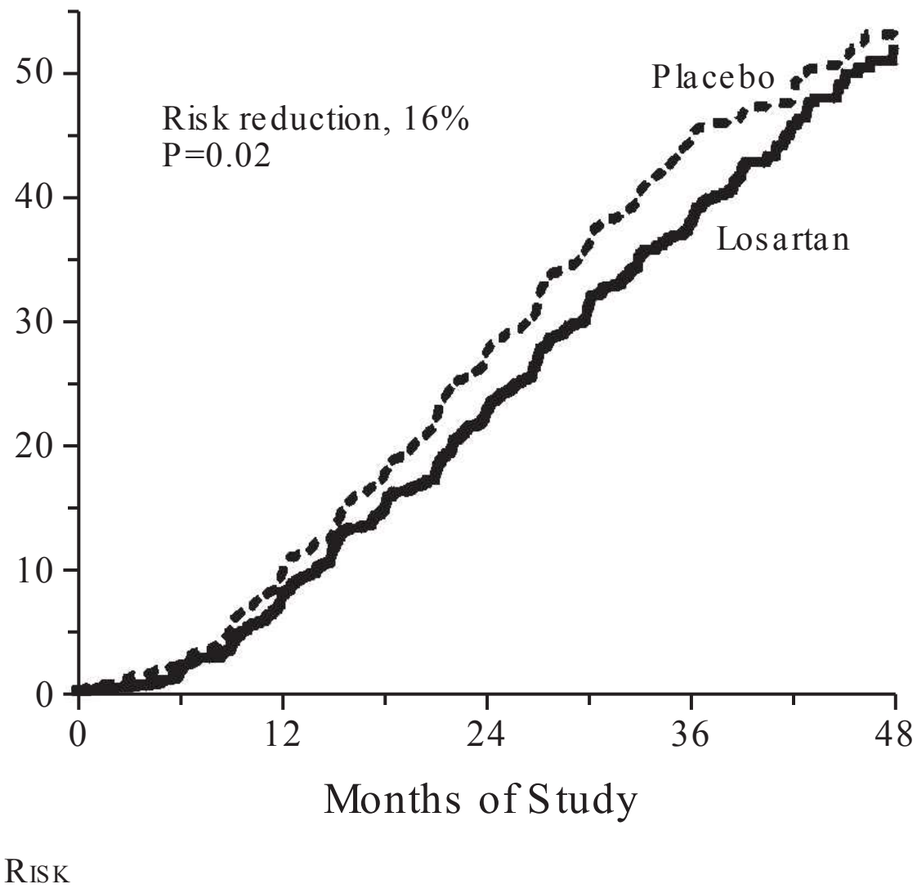
The first large trial to examine the role of ACE inhibitors in renoprotection in advanced DN[144] studied 409 subjects with type 1 diabetes, overt proteinuria (≥500 mg per day), and renal insufficiency (SCr ≤2.5 mg per dL). Subjects were randomized to captopril 25 mg three times daily or placebo, and could receive other antihypertensive agents to achieve BP control. There was a 48% reduction in the risk of doubling of SCr, as well as a similar reduction (50%) in the time to the composite endpoint of death, dialysis, or transplantation (Fig. 58.6). This trial confirmed the renoprotective effect of ACE inhibition in patients with type 1 diabetes and overt proteinuria, and was superior to BP control alone with other classes of antihypertensives.

In patients with type 2 diabetes and advanced nephropathy, the IDNT and RENAAL studies examined the effect of ARBs in type 2 diabetes, overt proteinuria, and renal failure. The IDNT randomized 1,715 subjects with HTN to irbesartan 300 mg daily, amlodipine 10 mg daily, or placebo, and followed them for 2.6 years. BP was targeted to <135/85 mm Hg and was obtained with agents other than calcium-channel blockers, ACE inhibitors, or ARBs. Irbesartan reduced the risk of the primary outcome of the composite of doubling of SCr, development of ESRD, or death, as compared to placebo or amlodipine (Fig. 58.7A). BP was similar in all three groups and not significantly different in the irbesartan and amlodipine groups.

Further supporting the efficacy of therapeutic intervention with an ARB, the RENAAL trial studied 1,513 subjects with type 2 diabetes and overt proteinuria for a mean of 3.4 years, and showed that treatment with losartan 100 mg daily was superior to placebo to reduce the risk of the composite endpoint doubling of SCr, ESRD, or death (Fig. 58.7B).



No. At Risk									
Irbesartan	579	555	528	496	400	304	216	146	65
Amlodipine	565	542	508	474	385	287	187	128	46
A Placebo	568	551	512	471	401	280	190	122	53



No. At Risk					
Placebo	762	689	554	295	36
B Losartan	751	692	583	329	52

FIGURE 58.7 Both irbesartan in IDNT **(A)** and losartan in RENAAL **(B)** have been shown to delay the progression of diabetic nephropathy in type 2 diabetes. (**A** from Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851–860. **B** from Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861–869.)

Taken together, IRMA2, IDNT, and RENAAL form a robust data set that convincingly show that ARBs reduce the progression of DN; the data from the IDNT and RENAAL were combined to form the Diabetes Mellitus Treatment for Renal Insufficiency Consortium (DIAMETRIC) database. Analysis of this dataset demonstrated robustly a strong beneficial effect of treatment with ARBs to delay or prevent doubling of SCr or ESRD (personal communication).[145]

The effect of an ARB on delaying the progression of DN from type 2 diabetes is independent yet additive to its effect on BP. This was demonstrated in post-hoc analyses of IDNT[128] and RENAAL[129] in which lower achieved systolic BP was associated with improved renal outcomes (Fig. 58.8).

In both the IDNT and RENAAL trials, baseline proteinuria was a predictor of the development of a renal endpoint.[84,125] More predictive, however, was what happened to the proteinuria at 6 to 12 months after randomization; a reduction in proteinuria during the course of these trials was associated with improved renal outcomes, particularly if it occurred early after randomization.[83,84] Arguably, medical therapy with RAS inhibition should be maximized to achieve the lowest amount of proteinuria possible.

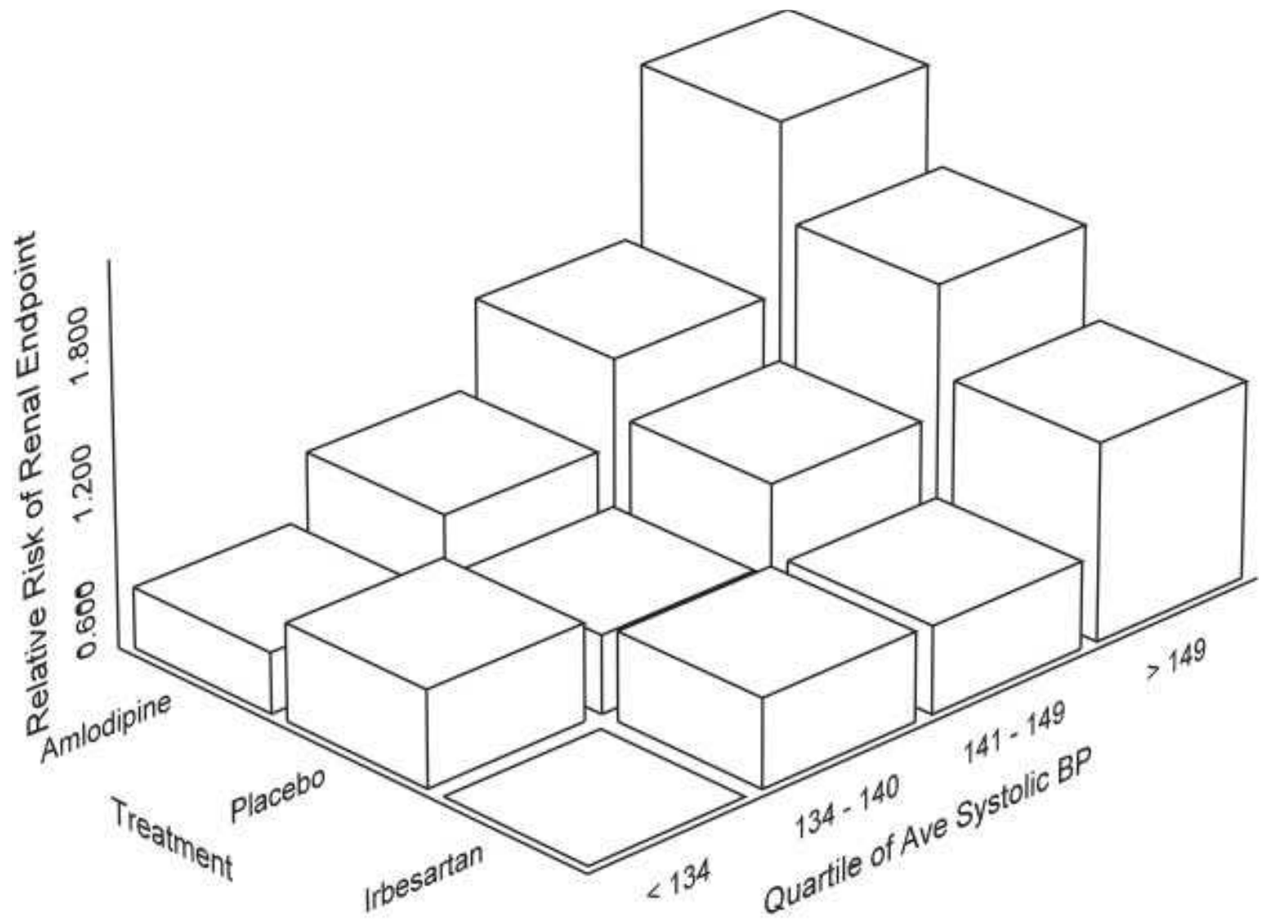


FIGURE 58.8 There is benefit to the use of irbesartan beyond its ability to control blood pressure on the relative risk of reaching a renal endpoint. In this case, the renal endpoint was defined as a doubling of serum creatinine (SCr) or end-stage renal disease (considered present when SCr ≥ 6.0 mg per dL or renal replacement therapy commenced). (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.)

Additionally, supratherapeutic doses (i.e., higher than the maximum approved dose) of ARB have shown improvement in proteinuria in small clinical studies, as opposed to the above-noted large clinical trials.[146–148] Irbesartan 900 mg daily reduced proteinuria more than 300 mg daily when administered over 2 months.[146] Similar studies have been conducted with telmisartan and valsartan as well. However, use of this approach to therapy has not yet been tested in large clinical trials with ESRD as an outcome.

Use of More Than One Inhibitor of the Renin Angiotensin System

A variety of clinical studies have examined the efficacy of combining inhibitors of the RAS but have often been limited by small sample size, submaximal doses of drugs, or surrogate renal outcomes, such as decreased proteinuria. These studies have employed dual therapy of ACE inhibitor plus ARB, the mineralocorticoid antagonists spironolactone and eplerenone, or the direct renin inhibitor (DRI) aliskiren, in combination with ACE inhibitor or ARB. In general, these small studies have shown a benefit to combination therapy.[149–161] The Aliskiren in the eValuation Of proteinuria In Diabetes (AVOID) trial[162] studied the effect on proteinuria of adding aliskiren versus placebo to losartan in type 2 diabetic nephropathy. Five hundred and ninety-nine subjects with type 2 diabetes, HTN, albuminuria 300 to 3,500 mg per g creatinine (200 to 3,500 mg per g if on RAS blocking agents), and eGFR >30 mL/min/1.73 m^2 were studied. Aliskiren reduced albuminuria at 24 weeks, but subjects treated with this combination therapy developed hyperkalemia more often (4.7% vs. 1.7%). The trial, although large and appropriately powered for a surrogate outcome of the change in UAE, could not assess the effect of aliskiren on the clinically significant outcome of ESRD.

The largest trial performed to date which utilized a combination of RAS agents is The ONgoing Telmisartan Alone and in combination with Ramipril Global EndpoinT (ONTARGET) trial.[163] ONTARGET studied 25,260 patients with CV risk (coronary, peripheral, or cerebrovascular vascular disease or diabetes with end-organ damage) with ramipril, telmisartan, or both, for the effect on the composite primary CV outcome, namely death from a CV cause, myocardial infarction, stroke, or hospitalization for heart failure. There was no difference in the primary outcome among the three arms. Although not designed primarily as a renal trial, ONTARGET enrolled 9,612 subjects with diabetes and 2,781 subjects with MA. The renal post-hoc analyses[164] showed less worsening of proteinuria with combination therapy, but GFR decreased more in the combination arm as compared to the single-agent arms (by about 2 mL/min/1.73 m^2). Additionally, there was a significant increase in the renal endpoint (dialysis, doubling of serum creatinine, or death) in the combination arm as compared to single-agent arms. This suggested the possibility that combination therapy might actually be harmful to renal function in some patient populations. The biggest contributor to this endpoint was the need for acute dialysis. It is important to note that this trial was not designed to test the renal outcomes, and its interpretation must be treated with caution; a trial designed specifically to answer this question is ongoing (see later text).

Lipid-Lowering Therapy

Many small studies have tested the use of lipid-lowering medications for their ability to delay the progression of DN, along with a meta-analysis which included these DN trials, suggested that treatment of dyslipidemia may help preserve GFR.[165] The largest trial performed on the role of aggressive lipid reduction in diabetes is the ACCORD Lipid trial,[166] which was embedded within the main ACCORD trial. As described previously, all subjects of the ACCORD trial were randomized to either intensive or standard glycemic control,

but half (5,518 subjects) were also randomized (in a 2 × 2 factorial design) to intensive lipid lowering with simvastatin and fenofibrate versus simvastatin and placebo. The addition of fenofibrate did not affect the primary CV outcome of the trial, nor was there a difference in the incidence of ESRD or dialysis. There was, however, a reduction in both MA and overt proteinuria in the intensive group. Thus, intensive lipid lowering with simvastatin and fenofibrate may reduce proteinuria but may not prevent death or dialysis in type 2 diabetes. This trial was not designed to detect these renal endpoints, but the results are hypothesis-generating nonetheless. With the well-described CV risk conferred by the presence of diabetes, and specifically DN, treatment of dyslipidemia is indicated to reduce CV risk, irrespective of its specific impact on renal outcomes.

Multi-Intervention Treatments

The value of multiple-intervention risk reduction in patients with type 2 diabetes has been well studied, but most trials excluded subjects with DN. These are the very subjects who are at the highest risk for CV complications and death. The Steno-2 study[167] tested the hypothesis that a multifactorial intervention (consisting of lifestyle modification, smoking cessation, tight glucose control, and the use of RAS agents, aspirin, and lipid-lowering therapies) would affect the risk of death (from any cause and CV death) in patients with DN. One hundred sixty subjects with type 2 diabetes and persistent MA were studied for a mean of 7.8 years, and those who received intensive therapy had a significant reduction in CV death, peripheral vascular disease, urinary albumin excretion, retinopathy, and neuropathy. Although this study was not designed to detect which of the interventions was responsible for what proportion of effect, it is clear that a multitargeted approach was beneficial for the endpoints studied. There are no large trials which test the value of cessation of smoking, a specific component on the multiple-intervention study above, on the progression of DN. Epidemiologic studies associate smoking with a faster rate of loss of renal function. A small study suggests that smokers are more likely to progress to overt proteinuria and lose kidney function at a faster rate than nonsmokers or those who quit.[168] We recommend smoking cessation for all our patients, including those with DN.

ONGOING AND RECENTLY COMPLETED TRIALS

Several ongoing and recently completed trials should address current uncertainties in the landscape of the progression of DN, particularly with respect to combination therapies. The Department of Veterans' Affairs NEPHROpathy iN Diabetes (VA NEPHRON-D) Study[169] is testing whether the combination of lisinopril and losartan is superior to losartan alone to delay the progression of DN in type 2 diabetes. Approximately 1,900 subjects will be recruited until 2013. The ALiskiren Trial In Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) study[170] tested whether dual RAS blockade with aliskiren and an ACE inhibitor or ARB reduces CV and renal morbidity and mortality. It was recently terminated early after there was an increase in adverse events and no apparent benefit to dual RAS blockade.[171] These trials were designed to assess if use of more than one agent that blocks that RAS affects clinically meaningful outcomes such as CV death or ESRD.

FUTURE DIRECTIONS

The future of DN perhaps centers around the prevention of it, and of diabetes, entirely. Once DN has begun, the few currently available therapies are limited in that they slow but do not prevent progression completely. Agents that are aimed at modulating physiologic inflammatory networks, or inhibiting cell proliferation, transforming growth factor beta (TGF-beta), matrix metalloproteinases, the accumulation of advanced glycosylation end-products, or interstitial fibrosis are currently under study for their ability to prevent or delay the progression of DN. Reversal of the lesions of DN[172] with a cure for diabetes (e.g., in the case of pancreas or islet-cell transplantation in type 1 diabetes) is unlikely to be successful for patients with type 2 diabetes. Large, well-powered, and properly designed clinical trials will be necessary to test the effect of these novel interventions and their combinations on clinically relevant and intermediate endpoints.

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