

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

Marc A. Pohl,* Samuel Blumenthal,[†] Daniel J. Cordonnier,[‡] Fernando De Alvaro,[§] Giacomo DeFerrari,^{||} Gilbert Eisner,[¶] Enric Esmatjes,[#] Richard E. Gilbert,** Lawrence G. Hunsicker,^{††} Jose B. Lopes de Faria,^{‡‡} Ruggero Mangili,^{§§} Jack Moore, Jr.,^{|||} Efrain Reisin,^{¶¶} Eberhard Ritz,^{###} Guntram Schernthaner,^{***} Samuel Spitalowitz,^{†††} Hilary Tindall,^{‡‡‡} Roger A. Rodby,^{§§§} and Edmund J. Lewis,^{§§§} for the Collaborative Study Group^{§§§a}

*Department of Nephrology and Hypertension, Cleveland Clinic Foundation, Cleveland, Ohio; [†]Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin; [‡]Department of Medicine, University of Grenoble, Grenoble, France; [§]Department of Medicine, Hospital la Paz, Madrid, Spain; ^{||}Department of Internal Medicine, University of Genova, Genova, Italy; [¶]Department of Internal Medicine, Washington Hospital Center, Washington, DC; [#]Hospital Clinicoy Provincial, Barcelona, Spain; ^{**}Department of Medicine, University of Melbourne, Fitzroy, Victoria, Australia; ^{††}Department of Medicine, University of Iowa, Iowa City, Iowa; ^{‡‡}Department of Medicine, University of Campinas, Campinas, Brazil; ^{§§}Department of Medicine, Hospital Bolognini, Seriate, Italy; ^{|||}Department of Medicine, Washington Hospital Center, Washington, DC; ^{¶¶}Department of Medicine, Louisiana State University Medical Center, New Orleans, Louisiana; ^{###}Department of Internal Medicine, University of Heidelberg, Heidelberg, Germany; ^{***}Department of Internal Medicine, Rudolphstiftung Hospital, Vienna, Austria; ^{†††}Department of Internal Medicine, Brookdale Hospital Medical Center, Brooklyn, New York; ^{‡‡‡}Department of Diabetes, North Middlesex Hospital, London, United Kingdom; and ^{§§§}Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois

Elevated arterial pressure is a major risk factor for progression to ESRD in diabetic nephropathy. However, the component of arterial pressure and level of BP control for optimal renal outcomes are disputed. Data from 1590 hypertensive patients with type 2 diabetes in the Irbesartan Diabetic Nephropathy Trial (IDNT), a randomized, double-blind, placebo-controlled trial performed in 209 clinics worldwide, were examined, and the effects of baseline and mean follow-up systolic BP (SBP) and diastolic BP and the interaction of assigned study medications (irbesartan, amlodipine, and placebo) on progressive renal failure and all-cause mortality were assessed. Other antihypertensive agents were added to achieve predetermined BP goals. Entry criteria included elevated baseline serum creatinine concentration up to 266 $\mu\text{mol/L}$ (3.0 mg/dl) and urine protein excretion >900 mg/d. Baseline BP averaged $159/87 \pm 20/11$ mmHg. Median patient follow-up was 2.6 yr. Follow-up achieved SBP most strongly predicted renal outcomes. SBP >149 mmHg was associated with a 2.2-fold increase in the risk for doubling serum creatinine or ESRD compared with SBP <134 mmHg. Progressive lowering of SBP to 120 mmHg was associated with improved renal and patient survival, an effect independent of baseline renal function. Below this threshold, all-cause mortality increased. An additional renoprotective effect of irbesartan, independent of achieved SBP, was observed down to 120 mmHg. There was no correlation between diastolic BP and renal outcomes. We recommend a SBP target between 120 and 130 mmHg, in conjunction with blockade of the renin-angiotensin system, in patients with type 2 diabetic nephropathy.

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Patients with type 2 diabetes and hypertension have a two- to four-fold greater risk for developing cardiovascular sequelae such as myocardial infarction, stroke, or

death and have a seven-fold greater likelihood for developing renal failure compared with age-matched control subjects (1,2). Patients with type 2 diabetes now constitute the single largest group of patients who enter ESRD programs in the United States (3). This report, presenting an analysis of the impact of BP control on clinical outcomes in a large cohort of hypertensive adults with overt type 2 diabetic nephropathy, was undertaken with the purpose of determining (1) the optimal targets for the component(s) of arterial pressure most closely associated with renal deterioration as well as all-cause mortality and

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*See Appendix 2 for a list of study group members.

Address correspondence to: Dr. Marc A. Pohl, Cleveland Clinic Foundation, 9500 Euclid Avenue, Desk A51, Cleveland, OH 44195. Phone: 216-444-6776; Fax: 216-444-9378; E-mail: pohlm@ccf.org

(2) to examine the interaction between the renoprotective action of the antihypertensive agents tested, the level of BP achieved, and renal outcomes.

Materials and Methods

Study Patients

This study is based on analysis of data from the Irbesartan in Diabetic Nephropathy Trial (IDNT) (4) (Appendix 1); some of the information in this article has been referred to in previous publications (4,5). Methods and baseline characteristics of the 1715 participants and the primary outcome of the IDNT have been published (4–6). Entry criteria included age between 30 and 70 yr; documented type 2 diabetes; and hypertension defined as any of the following: seated office systolic BP (SBP) >135 mmHg, seated office diastolic BP (DBP) >85 mmHg, or documented treatment with antihypertensive agents. All participants had established diabetic nephropathy with overt proteinuria (>900 mg/24 h) and mild to moderate renal insufficiency (serum creatinine between 88 and 266 $\mu\text{mol/L}$ [1.0 and 3.0 mg/dl] in women and between 106 and 266 $\mu\text{mol/L}$ [1.2 and 3.0 mg/dl] in men). The institutional review board or appropriate ethics committee at each center approved the study protocol.

Study Design

Consenting eligible patients were randomized 1:1:1 into one of three treatment arms: irbesartan 300 mg/d, amlodipine 10 mg/d, or placebo. The target for SBP control was (1) <135 mmHg when baseline SBP was 145 mmHg or less; (2) 10 mmHg below the baseline SBP when baseline SBP was between 146 and 170 mmHg; (3) 160 mmHg, the maximum allowable SBP, for all patients with baseline SBP >170 mmHg. The seated DBP target for all participants was ≤ 85 mmHg. To achieve these goals, patients were prescribed additional antihypertensive therapy. The use of other angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, or calcium channel blockers was excluded. The primary outcome for the IDNT was the time to a composite end point of doubling of the baseline serum creatinine, ESRD (defined as a serum creatinine ≥ 530 $\mu\text{mol/L}$ [6 mg/dl] or renal replacement therapy), or all-cause mortality. For the purposes of this study, the term *renal end point* refers to patients who reached a doubling of serum creatinine (SCr) or end-stage renal failure. Analysis for each end point was on an intention-to-treat basis. Patients who reached an end point stopped coded medication but continued to be followed until the closing date of the trial.

Medical Management

Patients were seen in routine hypertension clinic settings at specified study visit intervals: Screening, enrollment, randomization, week 1, week 2, week 4, week 8, month 3, and every 3 mo thereafter until reaching ESRD, death, or administrative censoring of the study (December 31, 2000). SBP and DBP were determined at baseline and throughout the trial per study protocol. Proper technique for BP measurement was detailed in the Manual of Operations and reviewed with study coordinators at the investigators' meetings before study initiation. Briefly, the BP cuff bladder was centered over the brachial artery and inflated to 30 mmHg above the pressure at which the radial pulse could no longer be palpated. Air in the blood cuff was released so that pressure fell at a rate of 2 mmHg/s. SBP was taken when two consecutive beats were audible, read to the nearest 2 mmHg. DBP was taken as the phase V Korotkoff sounds. Office BP measurements were performed 1 min apart in triplicate after the patient remained quiet in a seated position for 10 min, followed by triplicate measurements after remaining in a standing position for 2 min. More frequent visits were required when, at any regularly scheduled visit, the recorded BP was not at treatment goal. These return visits to bring BP

under control were generally at 2-wk intervals until goal BP was reached. A Clinical Management Committee (CMC) reviewed achieved BP and therapeutic regimens on any participant who did not meet his or her respective BP goal on a quarterly basis after the eighth study week. The CMC provided recommendations for improved BP management in accord with Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI) (7). More frequent study visits were scheduled as deemed necessary by the investigator, either for BP management or for other aspects of medical care. Direct telephone contact and written correspondence occurred regularly between the CMC and individual investigators or centers that seemed to have difficulty meeting goal BP in their patients. Serum for determination of creatinine and 24-h urine collections for creatinine and albumin were obtained twice at baseline from all patients and analyzed in central laboratories.

Statistical Analyses

Baseline BP were taken as the average of seated BP during two prerandomization visits. Patients in each treatment group achieved stable BP by the 6-mo scheduled visit, and average BP in each group varied little over the subsequent mean study follow-up of 2.6 yr (4). Therefore, mean follow-up BP in each patient were calculated as the average of the recorded seated BP at scheduled visits from 6 mo to the end of the study. Of the 1715 patients in the original study cohort, 123 patients had no scheduled visit BP recorded after the 3-mo visit (60 reached either a primary or a secondary study end point, and 63 stopped regular study follow-up for other reasons). These patients and two additional patients in whom time to doubling of SCr (a renal end point) could not be ascertained were excluded from further analysis. The remaining 1590 patients are the subjects of this report. In these patients, seated BP were recorded at an average of 9 ± 4 scheduled visits. Ninety-one percent of these patients had BP recorded at four or more follow-up visits at and after 6 mo. Fewer than 10 patients were lost to follow-up. GFR at baseline was estimated from the mean of the two baseline serum creatinine values, using the four-variable Modification of Diet in Renal Disease formula (8). Proteinuria was expressed as the ratio of albumin to creatinine concentration in the two baseline 24-h urine collections and was log-transformed to obtain an approximately normal distribution for use in statistical analyses.

We used SAS for Windows Version 8 (Cary, NC) for data management and S-Plus for Windows Version 6.1 (Insightful, Seattle, WA) for most data analysis and generation of graphics. Kaplan-Meier methods were used to plot survival over time in strata corresponding to approximate quartiles of baseline and mean follow-up seated SBP and DBP. For other analyses, we grouped patients into strata by 10-mmHg bands of seated BP. Relative risks were estimated in univariate and multivariate models using Cox proportional hazards methods. Validity of the proportionality of hazards assumption was confirmed for all models using the *cox.zph* function in S-Plus (9).

Results

Baseline BP (mean \pm SD) for the 1590 patients was 159/87 \pm 20/11 mmHg and was similar among treatment groups. BP was controlled during the course of the trial in the irbesartan group to a mean of 141/78 \pm 14/8 mmHg ($n = 537$), in the amlodipine group to 142/77 \pm 13/8 mmHg ($n = 523$), and in the placebo (usual care) group to 144/80 \pm 13/8 mmHg ($n = 530$). Thirty percent of participants achieved an SBP ≤ 135 mmHg; 82% of patients achieved their DBP goal of 85 mmHg. The use of nonstudy drugs to achieve target BP was similar in the three cohorts: The placebo group received an average of 3.3 nonstudy

drugs; the other two groups received an average of 3.0 non-study drugs (4,10). There was a significantly greater use of sympathetic depressant agents in the placebo group. There was no statistically significant difference in the use of thiazide or loop diuretics among the three study cohorts (10).

Baseline SBP correlated significantly with the renal outcomes (doubling of SCr or ESRD) in univariate analysis (Figure 1A). The risk for reaching a renal end point increased progressively with higher baseline SBP ($P < 0.0001$), with 36% of patients in the

highest quartile (baseline SBP >170 mmHg) reaching a renal end point compared with 18% of patients in the lowest SBP quartile (SBP <145 mmHg) over the 4 yr of the study. Baseline DBP was weakly correlated with the renal outcome ($P = 0.065$). There was no correlation of DBP with renal outcome among the 152 patients with baseline DBP >100 mmHg. When baseline SBP and DBP were included in the same model (Table 1), only SBP was independently correlated with outcome.

The impact of achieved follow-up SBP on renal outcomes is

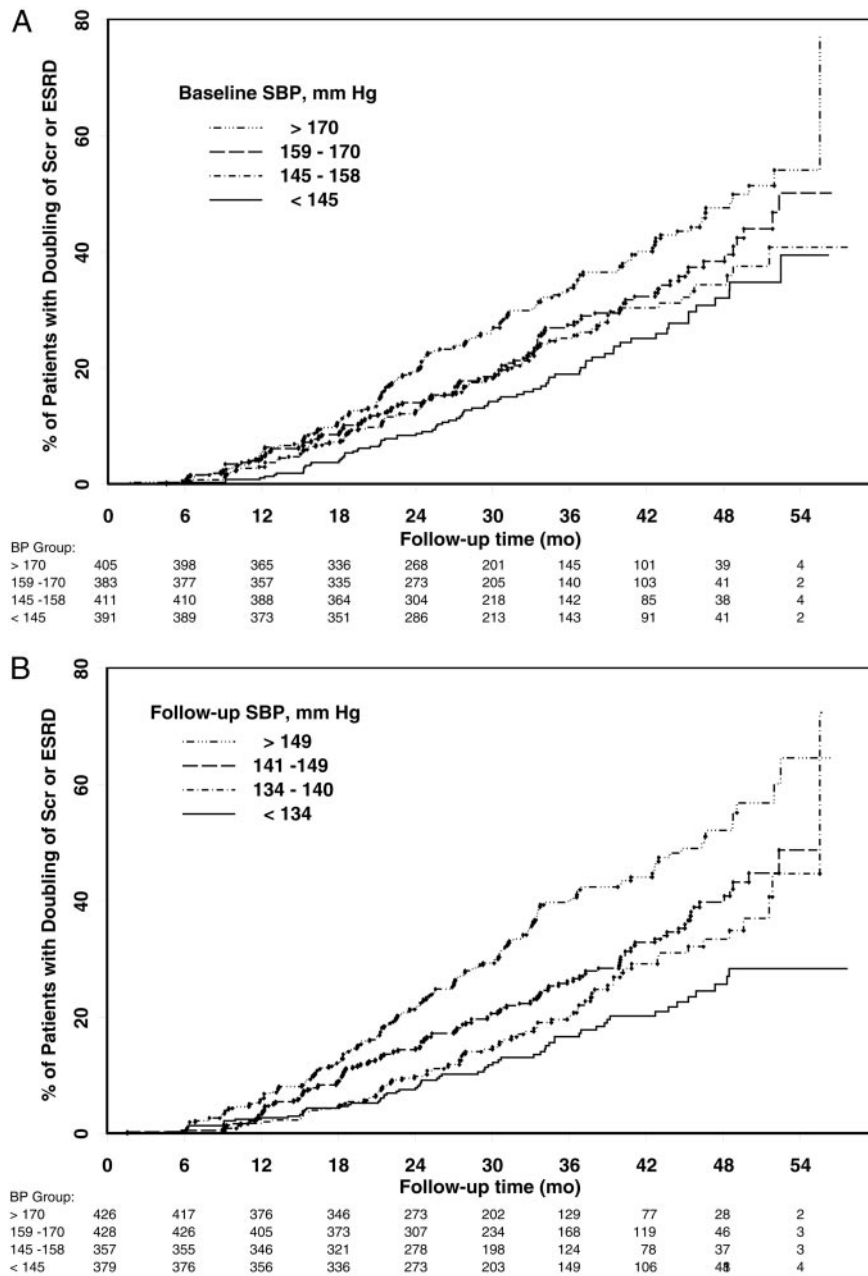


Figure 1. (A) Cumulative proportions of patients who reached a renal end point (doubling of baseline serum creatinine [SCr] or ESRD, defined as SCr ≥ 6.0 mg/dl or renal replacement therapy) by quartile of baseline systolic BP (SBP). The number of patients who were at risk for reaching a renal end point is tabulated for each period during follow-up. (B) Cumulative proportions of patients who reached a renal end point (doubling of baseline SCr or ESRD, defined as SCr ≥ 6.0 mg/dl or renal replacement therapy) by quartile of achieved SBP. The number of patients who were at risk for reaching a renal end point is tabulated for each period during follow-up.

Table 1. Simultaneous impact of SBP and DBP on risk for subsequent renal end point (doubling of SCr or ESRD)^a

	RR	95% CI	P
Baseline			
decrease of 20 mmHg in SBP	0.79	0.71 to 0.88	<0.0001
decrease of 20 mmHg in DBP	1.02	0.85 to 1.22	0.86
Achieved			
decrease of 20 mmHg in SBP	0.52	0.45 to 0.60	<0.0001
decrease of 20 mmHg in DBP	1.06	0.84 to 1.35	0.61
Baseline and achieved			
decrease of 20 mmHg in baseline SBP	0.96	0.87 to 1.07	0.50
decrease of 20 mmHg in achieved SBP	0.53	0.46 to 0.64	<0.0001

^aSBP, systolic BP; DBP, diastolic BP; SCr, serum creatinine; RR, relative risk; CI, confidence interval.

illustrated in Figure 1B. The best renal outcome was observed in patients who achieved SBP <134 mmHg, among whom only 17% (63 of 379) reached a renal end point during the course of follow-up. In contrast, the risk for a renal end point was 2.2-fold higher among patients with follow-up SBP >149 mmHg, 38% (164 of 426) of whom reached a doubling of their SCr or ESRD. After accounting for this impact of achieved SBP, the achieved DBP did not correlate significantly with renal outcome (Table 1).

We determined whether baseline or achieved SBP was more closely associated with renal outcome by examining the simultaneous impact of these variables on the risk for renal end points in a multivariate model. The results (Table 1) demonstrated that achieved follow-up SBP is an independent predictor of the risk for an adverse renal outcome irrespective of the baseline SBP. A decrease of 20 mmHg in achieved SBP was associated with a 47% decrease in the risk for developing a renal end point. Although baseline SBP was an independent predictor of renal outcome, this relationship was lost when achieved SBP was taken into account.

These results indicate that the renal outcomes in the IDNT were better at lower quartiles of follow-up SBP but do not exclude the possibility of an adverse effect on renal outcomes or all-cause mortality at the lowest follow-up SBP (10). We therefore examined renal outcomes and mortality of patients with mean follow-up seated SBP grouped in 10-mmHg increments. Renal outcomes (Figure 2A) in patients with a follow-up SBP <120 mmHg were not substantially better than in patients with follow-up SBP between 120 and 130 mmHg. The association of achieved SBP with all-cause mortality among patients in these same SBP categories is shown in Figure 2B; average follow-up SBP and risk for all-cause mortality are essentially linear from SBP of 120 mmHg to SBP >180 mmHg. However, patients with the lowest follow-up SBP (<120 mmHg) had sharply higher mortality, and a test of the shape of the entire relationship depicted in Figure 2B demonstrated significant nonlinearity ($P < 0.001$).

The relationship of follow-up BP to renal outcomes that might be attributable to differences in baseline renal function was investigated. Baseline estimated GFR (eGFR) and albumin/creatinine ratio (ACR) both were linearly and significantly correlated with both mean follow-up BP and with the risk for a renal end point (11,12). The assessed risk for a renal outcome

associated with lower follow-up SBP after adjustment for baseline eGFR and ACR continued to reveal a relationship between SBP and the likelihood of a renal event. Uncorrected, each

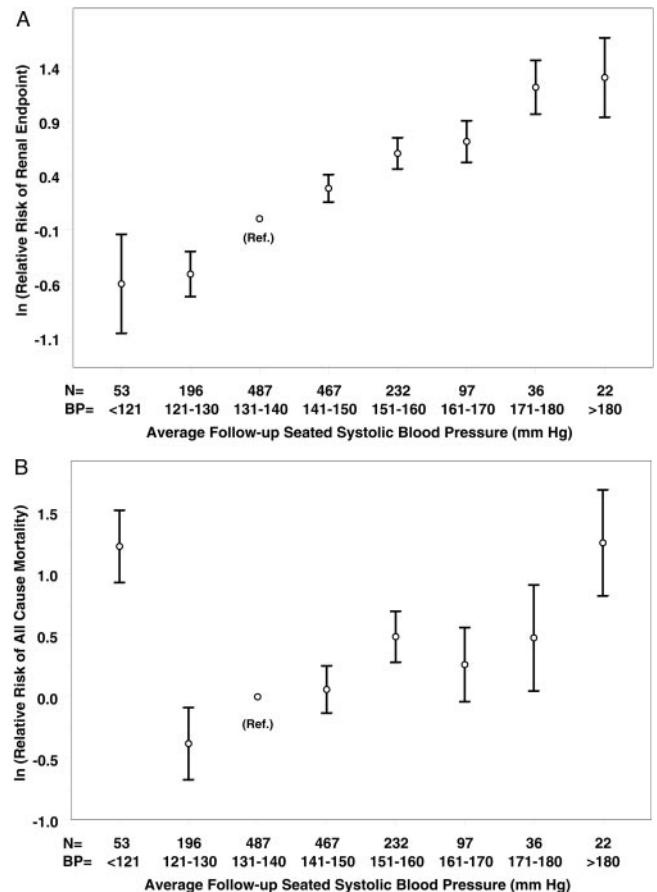


Figure 2. (A) Natural log of the relative risk for reaching a renal end point by level of achieved follow-up SBP. The number of patients who were at risk for reaching a renal end point is tabulated for each level of achieved follow-up SBP. (B) Natural log of the relative risk for all-cause mortality by level of achieved follow-up SBP. The number of patients who were at risk for death by any cause is tabulated for each level of achieved follow-up SBP.

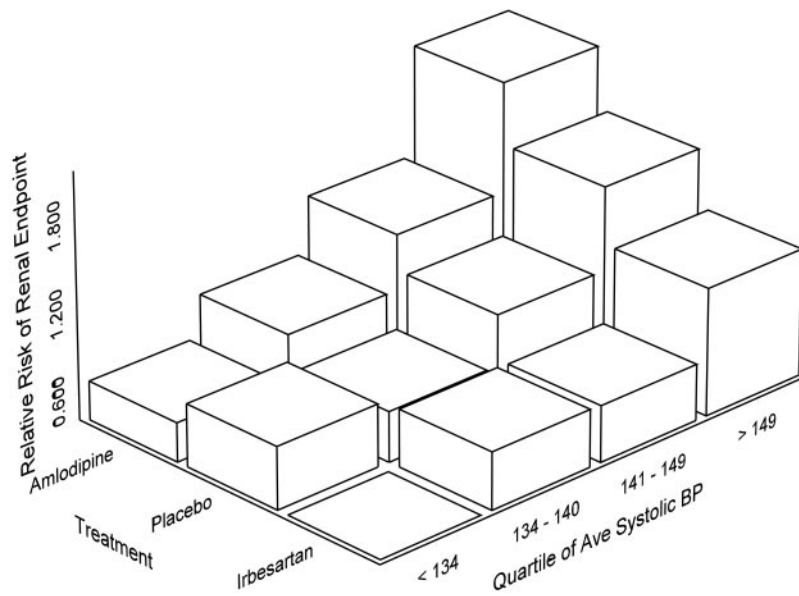


Figure 3. Simultaneous impact of quartile of achieved SBP and treatment modality on the relative risk for reaching a renal end point (doubling of baseline SCr or ESRD, defined as SCr \geq 6.0 mg/dl or renal replacement therapy).

20-mmHg decrease in SBP was associated with a 47% decrease in the risk for a renal outcome ($P < 0.0001$). After correction for eGFR and ACR, each 20-mmHg decrease in SBP was still associated with a 30% reduction in the risk for a renal event ($P < 0.0001$), independent of these two baseline renal covariates.

Figure 3 presents the renal outcomes among the follow-up SBP quartiles, further divided by treatment assignment (irbesartan, amlodipine, or placebo). In each treatment group, renal outcomes improved progressively at lower follow-up SBP levels. Furthermore, in all SBP strata, patients who were assigned to irbesartan had better renal outcomes than patients who were assigned to the other treatments. Renal outcomes in patients who were assigned to amlodipine and to placebo did not differ significantly. Table 2 presents the crude event rate and relative renal risk reduction for quartiles of achieved SBP and for irbesartan versus the two other treatment groups combined. Overall, assignment to irbesartan resulted in a 33% reduction in risk ($P < 0.001$) for reaching a renal end point beyond that achieved by lowering the SBP. Even in patients who achieved a SBP < 134 mmHg, adverse renal outcomes were significantly reduced with irbesartan (12%) compared with amlodipine plus placebo

(20%; relative risk = 0.55, $P = 0.034$). These two effects, lower SBP and treatment with irbesartan, were completely independent ($P = 0.61$ for interaction) and therefore additive.

Discussion

We conclude that there is a direct relationship between control of SBP and adverse renal outcomes in patients with type 2 diabetic nephropathy, independent of baseline renal function. We also conclude that angiotensin receptor blockade is renoprotective across a wide range of SBP. Both of these results are consistent with the well-documented beneficial effects of BP control upon the course of diabetic nephropathy (13,14) and current theories regarding pathophysiology of diabetic glomerulosclerosis (15,16).

The glomerulus in the diabetic kidney seems to be particularly vulnerable to the barotrauma caused by systemic arterial hypertension. The explanation for this sensitivity of the glomerular capillary bed to elevated systemic BP has been explored in experimental models of diabetes and may reside in the fact that the glomerular capillary bed is part of an arteriolar portal system. Thus, in diabetes, the hemodynamic determinants of altered hy-

Table 2. Renal risk reduction (doubling of SCr or ESRD) by level of achieved seated SBP and assigned treatment

	SBP (mmHg)				Row Totals
	<134	134 to 140	141 to 149	>149	
No. of patients	379	357	428	426	1590
No. of events (%)	63 (17)	81 (22.7)	125 (29.2)	164 (38.5)	433 (27)
RR					
irbesartan versus amlodipine + placebo	18/151 versus 45/228	27/128 versus 54/229	28/122 versus 97/306	42/136 versus 122/290	115/537 versus 318/1053
irbesartan (%) versus amlodipine + placebo (%)	12 versus 20	21 versus 24	23 versus 32	31 versus 42	21 versus 30
irbesartan versus amlodipine + placebo	0.55 ($P = 0.034$)	0.92 ($P = 0.71$)	0.66 ($P = 0.05$)	0.70 ($P = 0.05$)	0.67 ($P = 0.0002$)

draulic pressure in the glomerulus may be associated with both relative arteriolar dilation and efferent arteriolar constriction (16,17).

It is known that a loss of autoregulatory function occurs in various experimental nephropathies and is manifest as afferent arteriolar dilation (18). Morphologic correlates of this functional abnormality of the afferent arteriole have also been described in the aging human kidney (19). Inability to autoregulate afferent arteriolar tone in response to changes in renal perfusion pressure has been shown in diabetic rats (20). Decreased afferent arteriolar resistance increases glomerular blood flow while simultaneously exposing glomerular capillaries to the elevated systemic pressures of the hypertensive state (16). This pathophysiologic abnormality may explain the vulnerability of the diabetic glomerulus to elevated SBP. The action of agents that can inhibit the renin-angiotensin system and dilate the efferent arteriole provides a second, independent mechanism for relieving the potential traumatic effects of elevated glomerular capillary hydraulic pressure (17).

The data presented herein indicate that it is SBP achieved during follow-up that is most strongly associated with renal outcomes in patients with progressive nephropathy as a result of type 2 diabetes. Although the level of SBP at baseline predicts renal outcome in these patients, the ability to alter significantly renal prognosis according to the SBP that is achieved emphasizes the importance of antihypertensive therapy in caring for this patient population. Conversely, failure to achieve lower SBP levels was an important predictor of an adverse renal outcome. In contrast to the findings of other investigators (21–23), DBP (even DBP >100 mmHg), whether baseline or follow-up, were not significant predictors of renal outcomes. Mean arterial pressure and pulse pressure also were not independent predictors of adverse renal outcomes; any relationship between these two BP calculations and renal outcomes in this study were merely reflections of their dependent relationship upon SBP (24).

Our data indicate continuous renal protection with reduction of SBP to levels down to 120 mmHg. Limited data from patients whose SBP was reduced below 120 mmHg preclude definitive statements about the course of renal function below this level. However, our data do suggest that the risk for mortality increases when SBP is reduced below this threshold (25). This observation, referred to as a J-curve phenomenon, was evident in all three treatment groups and in patients with and without a history of cardiovascular disease at entry into the trial. Boutitie *et al.* (26), in a recent meta-analysis, also noted the presence of higher cardiovascular and all-cause mortality in elderly individuals with hypertension and with SBP <120 mmHg. Similarly, Hasebe *et al.* (27) noted increased cardiovascular events in patients with angina pectoris and SBP <124 mmHg. In our study, the reasons for increased mortality at follow-up SBP levels <120 mmHg are not clear and may reflect severe preexisting intrinsic cardiac disease, adverse effects of multiple antihypertensive agents, a tendency to orthostatic hypotension, or some combination of these clinical factors.

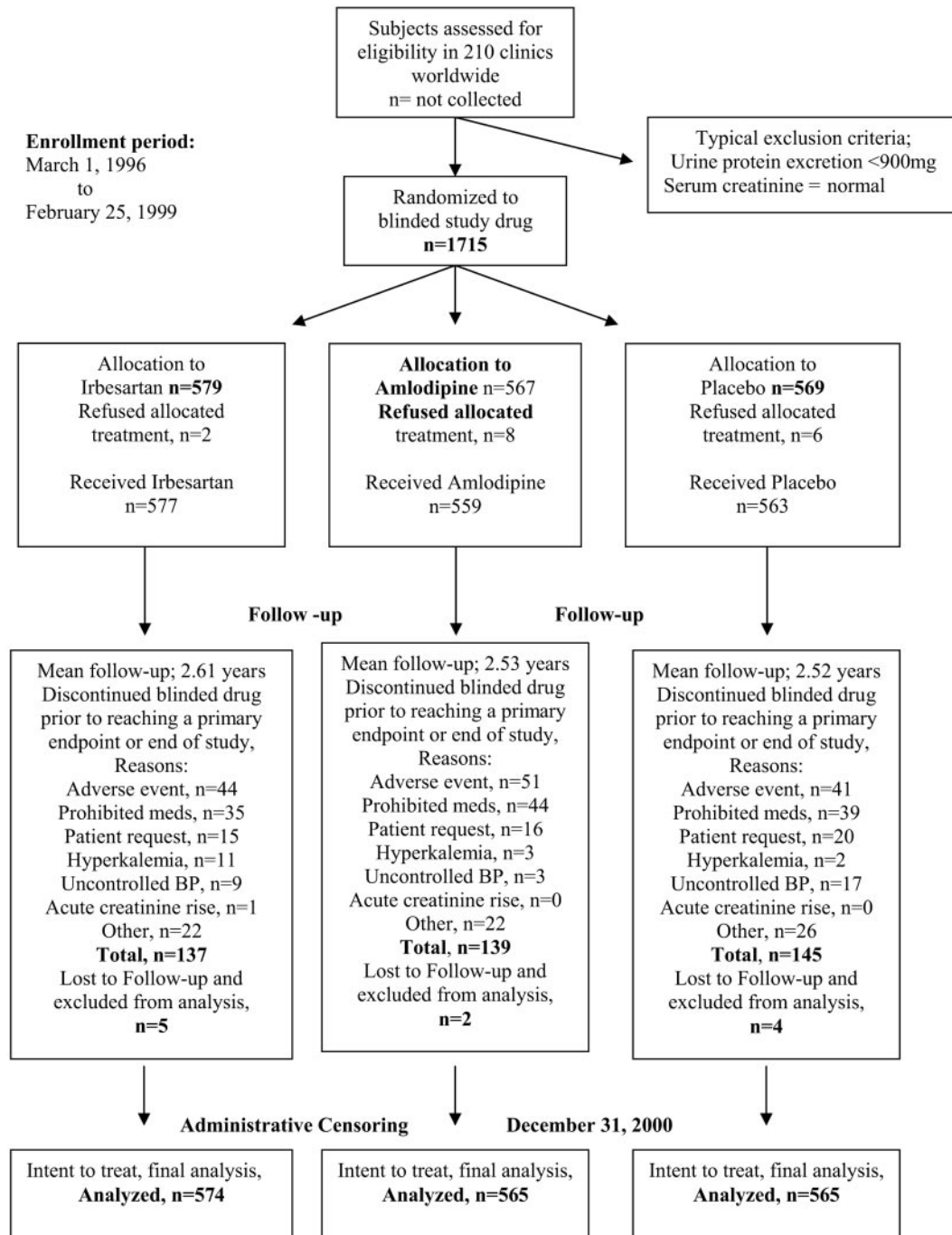
These analyses of the relationship of BP with renal outcomes, with data collected prospectively but analyzed retrospectively, are observational in nature and not based on a randomized assignment to BP goal. As such, they show only a correlation of

follow-up SBP to outcomes. There is a possibility of confounding by some unmeasured baseline factor that might fully account for the effect of follow-up BP. The only way to examine the impact of lower achieved BP on renal outcomes with complete confidence would be with a controlled clinical trial in which patients are randomized to different BP goals. Unfortunately, there are no such trials in patients with advanced diabetic kidney disease. Furthermore, the correlation of risk for progression with higher achieved SBP that we have observed is independent of baseline renal function and is consistent with current understanding of the underlying pathophysiology of progressive renal injury. We believe, therefore, that this study has important implications for antihypertensive therapy guidelines for the practicing physician.

Our observation that achieved SBP during follow-up has a stronger correlation with renal and mortality outcomes than does SBP at entrance into the study indicates that the course of renal disease in this vulnerable patient population can be altered to the benefit of the patient. The SBP targets are consistent with data from other clinical trials and retrospective observations (23,28–30). Furthermore, these data emphasize the importance of additional renoprotection by blockade of the renin-angiotensin system (4,30–32). Irbesartan therapy reduced the risk for reaching a renal end point at all BP levels, and its renoprotective effect was independent of level of BP control. Thus, the concomitant treatment goals of reducing SBP and use of angiotensin receptor blockade with irbesartan are both critical in slowing the progression of renal disease in individuals with type 2 diabetes. These observations are also consistent with previous observations in type 1 diabetic nephropathy with use of the angiotensin-converting enzyme inhibitors captopril or ramipril (30,33).

Although the benefits of decreasing SBP in proteinuric renal disease are supported in other reports, there are sparse data about an appropriate lower limit for SBP (28,34,35). We found evidence for renoprotection down to an SBP level of 120 mmHg, but all-cause mortality rose below this threshold. Jafar *et al.* (13), in a recent meta-analysis in nondiabetic renal disease, noted an increased incidence of renal failure when SBP fell below 110 mmHg. The recently published JNC VII recommends that BP in patients with chronic kidney disease be reduced to at least 130/80 and suggests an even lower limit as appropriate for individuals with diabetes (36). JNC VII also notes that a SBP >115 mmHg is associated with increased cardiovascular risk. Because our data describe an increase in mortality below 120 mmHg, we believe that treating individuals with diabetes and nephropathy to the suggested lower limits of the JNC be undertaken only with the utmost care. We recommend a SBP target between 120 and 130 mmHg, in conjunction with blockade of the renin-angiotensin system, to provide optimal protection from progressive renal insufficiency in patients with type 2 diabetic nephropathy. Caution should be exercised in reducing SBP below 120 mmHg, even with the use of renin-angiotensin system blockade, as this treatment approach may not offer additional renoprotection and may be associated with increased mortality in this patient population.

Appendix 1



Appendix 2

The Collaborative Study Group

Clinical Coordinating Center. Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL; Principal Investigator and Director: Edmund J. Lewis, MD; Co-Principal Investigator and Associate Director: Tomas Berl, MD, University of Colorado Health Science Center, Denver, CO; Project Coordinator and Director of Central Laboratory: Richard D.

Rohde, BS, Chicago, IL; Associate Project Coordinator: Elizabeth Muskwe, Chicago, IL.

European Clinical Coordinating Center. University of Heidelberg, Heidelberg, Germany; Director: Professor Eberhard Ritz, MD; Associate Director: Luis Ruilope, MD, Hospital 12 de Octubre, Madrid, Spain; Medical Consultant: Pieter Klooker, MD, Heidelberg, Germany; Project Coordinator: Beatrix Spiller, Pharm.D, Heidelberg, Germany.

Pacific Clinical Coordinating Center. Monash Medical Center, Clayton, Victoria, Australia; Director: Professor Robert Atkins, MD; Associate Director: George Jerums, MD, Austin & Repatriation Medical Center, Heidelberg, Victoria, Australia; Project Coordinator: Raphael Bartholomeusz, PhD, Clayton, Victoria, Australia.

European Country Coordinators. UK—Rudolf W. Bilous, MD; Sweden, Denmark and Finland—Lennart Hulthen, MD, Staffan Björck, MD; France—Daniel J. Cordonnier, MD; Italy—Giacomo DeFerrari, MD; Spain—Luis Ruilope, MD; Hungary—Gyula Tamas, MD, PhD; Belgium and Netherlands—Luc F. Van Gaal, MD.

Biostatistical Coordinating Center. The University of Iowa Hospitals and Clinics, Iowa City, IA; Principal Investigator: Lawrence G. Hunsicker, MD; Co-Principal Investigator: William R. Clarke, PhD, Iowa City, IA.

Executive Committee. Edmund J. Lewis, MD, Robert Atkins, MD, Eberhard Ritz, MD, Tomas Berl, MD, George Jerums, MD, Luis Ruilope, MD, Rudolf Bilous, MD, Samuel Blumenthal, MD, William Clarke, PhD, Daniel J. Cordonnier, MD, Donald Hricik, MD, Lawrence G. Hunsicker, MD, Pieter Klooker, MD, Julia Lewis, MD, Otegbola Ojo, MD, Marc Pfeffer, MD, Marc A. Pohl, MD, Jerome G. Porush, MD, Itamar Raz, MD, Roger A. Rodby, MD, Thomas B. Wiegmann, MD.

Clinical Management Committee. Marc A. Pohl, MD (Chair), Daniel J. Cordonnier, MD (Co-chair), Staffan Björck, MD, Samuel Blumenthal, MD, William Clarke, PhD, Fernando De Alvaro, MD, Giacomo Deferrari, MD, Richard Gilbert, MD, Lawrence G. Hunsicker, MD, Pieter Klooker, MD, José B. Lopes de Faria, MD, Ruggero Mangili, MD, Efrain Reisin, MD, Roger A. Rodby, MD, Guntram Scherthaner, MD, Samuel Spitalewitz, MD, Hilary Tindall, MD.

Outcomes Confirmation and Classification Committee. Tomas Berl, MD (Chair), Paul Drury, MD, Enric Esmatjes, MD, Donald Hricik, MD, Julia Lewis, MD, Francesco Locatelli, MD, Jerome G. Porush, MD, Itamar Raz, MD, Luis Ruilope, MD, Krzysztof Strojek, MD, Robert Toto, MD, Philippe Vanhille, MD, Thomas B. Wiegmann, MD, Bernard M. Wolfe, MD.

Mortality Committee. Tomas Berl, MD, Samuel Z. Goldhaber, MD, Andrew Levey, MD, Julia Lewis, MD, Marc Pfeffer, MD, Jerome G. Porush, MD, Jean-Lucien Rouleau, MD.

Collaborating Clinics/Investigators

North America

USA. Veterans Affairs Medical Center and Creighton University, Omaha, NE: R.J. Anderson, MD; Oregon Health Sciences University, Portland, OR: S. Anderson, MD; Research Institute of Dallas, Dallas, TX: S. Aronoff, MD; Cedars Sinai Medical Center, Los Angeles, CA: P. Barnett, MD; University of Colorado Health Science Center, Denver, CO: T. Berl, MD; Radiant Research of Phoenix, Phoenix, AZ: M. Block, MD, L. Nelson, MD; Medical College of Wisconsin, Milwaukee, WI: S. Blumenthal, MD, B. Bresnahan, MD; Renal Research Baystate Medical Center, Springfield, MA: G.L. Braden, MD, E.M. Benjamin, MD, M.H. O'Shea, MD; Vanderbilt University Medical Center, Nashville, TN: J. Lewis, MD, G. Schulman, MD; Thomas Jefferson University, Philadelphia, PA: J.F. Burke, Jr., MD, K. Sharma, MD; Charlotte Clinical Research, Charlotte, NC: G. Collins, MD; Louisville Metabolic & Atherosclerosis Research Center, Louisville, KY: J. Cyrus, MD; Maricopa Medical Center, Phoenix, AZ: W. Dachman, MD; Diabetes Center of Western New York, Buffalo, NY: P. Dandona, MD; Marshfield Clinic, Marshfield, WI: R.A. Dart, MD; Veterans Administration Medical Center, Northport, NY: T. Dixon, MD; Beaumont Nutritional Clinic, Birmingham, MI: M. Doyle, MD; Theodore Duncan & Associates, Philadelphia, PA: T. Duncan, MD; Rhode Island Hospital, Providence, RI: L. Dworkin, MD; Diabetes, Endocrinology & Metabolic Disorders, San Diego, CA: D. Einhorn, MD; Washington Hospital Center, Washington,

DC: G. Eisner, MD, J. Moore Jr, MD; University Hospital Clinic Ohio State University, Columbus, OH: M. Falkenhain, MD; Cardiovascular Research Center of South Florida, Miami, FL: J. Fialkow, MD; Hill Top Research, Portland, OR: P. Fisher, MD; Veterans Administration Medical Center, Spokane, WA: E. Fishman, MD; New York Medical College and Nephrology Associates of Westchester, Hawthorne, NY: R. Garrick, MD; Veterans Administration Hospital, Tucson, AZ: S. Goldman, MD; Florida West Coast Clinical Research Group, Tampa, FL: R. Goldstein, MD, J. Navarro, MD; University of Iowa Hospitals & Clinics, Iowa City, IA: R. Hegeman, MD; Rochester General Hospital, Rochester, NY: R.E. Heinig, MD; University Hospitals of Cleveland, Cleveland, OH: D. Hricik, MD; East Bay Clinical Trial Center, Concord, CA: R. Kaplan, MD; Boston Veterans Administration Medical Center, Boston, MA: J. Kaufman, MD; Indiana University Medical Center, Indianapolis, IN: S. Kirkman, MD; Lehigh Valley Hospital, Allentown, PA: N. Kopyt, DO; Mecklenberg Medical Group, Charlotte, NC: N. Kramer, MD; Veterans Administration Medical Center, Los Angeles, CA: B. Levine, MD; Encompass Clinical Research, Spring Valley, CA: R. Lipetz, MD; Diabetes Care Research Center, Birmingham, AL: P. Lodewick, MD; Veterans Administration Medical Center, Buffalo, NY: J. Lohr, MD; Oklahoma Medical Research Foundation, Oklahoma City, OK: C. Manion, MD; Greater Baltimore Medical Center, Baltimore, MD: J.H. Mersey, MD, J.B. Tyzack, MD, J.A. Dicke, MD; Nephron Associates, Southfield, MI: R. Michaels, MD; University of Texas Southwestern Medical Center, Dallas, TX: J. Middleton, MD, R. Toto, MD; Danville Urologic Clinic, Danville, VA: M. Moore, MD; Internal Medicine Memorial Clinic, Lacey, WA: C. Ott, MD; Cleveland Clinic Foundation, Cleveland, OH: M. Pohl, MD; Brookdale Hospital Medical Center, Brooklyn, NY: J. Porush, MD, S. Spitalewitz, MD; Endocrinology & Metabolism, Santa Rosa, CA: D. Price, MD; University of Texas Health Science Center, Houston, TX: S.N. Rahman, MD; Louisiana State University Medical School, New Orleans, LA: E. Reisin, MD; Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL: R.A. Rodby, MD, J. Rydel, MD; Radiant Research, Greer, SC: F.D. Rogoff, MD, V.A. Klimas, MD, W.T. Ellison, MD, W.J. Henry, III, MD, J.M. Milas, MD; WJB Dorn Veterans Hospital, Columbia, SC: S.J. Rosansky, MD; Veterans Administration Medical Center, Bronx, NY: C. Rosendorff, MD; University of Medicine & Dentistry of New Jersey-Robert Wood Johnson Medical School, New Brunswick, NJ: M. Ruddy, MD; Graduate Hospital, Philadelphia, PA: M. Rudnick, MD; Health Care Discoveries, San Antonio, TX: D. Ruff, MD; Allegheny University Hospital-Hahnemann, Philadelphia, PA: A. Schwartz, MD; Diabetes & Glandular Disease Clinic, San Antonio, TX: S. Schwartz, MD; Washington Nephrology Association, Washington, DC: K. Sethi, MD; Rockland Renal Associates, West Nyack, NY: K. Shapiro, MD; Northern Michigan Hospital-Nisus Research, Petoskey, MI: G. Shaw, MD; VA Puget Sound Health Care System, Seattle, WA: D. Sherrard, MD, C. Stehman-Breen, MD; Medical College of Virginia, Richmond, VA: D. Sica, MD; Physicians Research Center, Toms River, NJ: H.J. Simon, MD, R.T. Simon, MD; Wake Forest University Baptist Medical Center, Winston-Salem, NC: R. Smith, MD; Health Care Plan, West Seneca, NY: B. Snyder, MD; Nephrology & Hypertension Specialists, Liverpool, NY: N. Tolchin, DO; The Heart Institute of Spokane, Spokane, WA: K. Tuttle, MD; George Washington University, Washington, DC: M. Velasquez, MD; King Drew Medical Center, Los Angeles, CA: H. Ward, MD; Internal Medicine Group, P.C., Cheyenne, WY: E. Wedell, MD; University of Maryland Hospital, Baltimore, MD: M. Weir, MD; Veterans Administration Medical Center, Kansas City, MO: T. Wiegmann, MD; Georgetown University Medical Center, Washington, DC: C. Wilcox, MD; Medical Plaza I, Kansas City, MO: B. Wood, MD; Northern California Research Corp., Fair Oaks, CA: D. Young, MD; University of California San Diego Medical Center, San

Diego, CA: M. Ziegler, MD; Hunter Holmes McGuire Veterans Administration Medical Center, Richmond, VA: F.J. Zieve, MD.

Canada. The Bailey Clinic, Red Deer: G.R. Bailey, MD; University Health Network-Toronto General Hospital, Toronto: D. Cattran, MD; Hotel-Dieu de Montreal, Montreal: P. Hamet, MD; Atlantic Health Science Centre, Saint John: S.P. Handa, MD; Canadian Institute of Stress Medicine & Cardiovascular Performance Evaluation, Oshawa, ON: O. Ojo, MD, P. Tam, MD, R. Ting, MD; Saskatoon District Health Board, SK: G. Pylypchuk, MD; Calgary Metabolic Education & Research Centre, Calgary, AL: S.A. Ross, MD; Endocrine Research Society, Vancouver, BC: H. Tildesley, MD, W. Vlahos, MD, R. Bebb, MD, G. Bondy, MD; London Health Science Centre University, London, ON: B.M. Wolfe, MD.

Latin America

Argentina. Instituto Investigaciones Cardiológicas, Buenos Aires: L.F. Ferder, MD; Hospital Argerich, Buenos Aires: F. Margulis, MD; Instituto De Investigaciones Medicas, Buenos Aires: A. Zucchini, MD.

Brazil. Faculdade de Ciências Medicas de Sorocaba, Sorocaba: F.A. de Almeida, MD; Universidade Estadual de Campinas, Campinas: J.B. Lopes de Faria, MD, V. Pavan, MD; Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais: R. Milagres, MD; UERJ Pedro Ernesto, Rio de Janeiro: W. Oigman, MD; Escola Paulista de Medicina, Sao Paulo: M.T. Zanella, MD; Faculdade de Medicina, Sao Paulo: R. Zatz, MD.

Mexico. Instituto Nacional de la Nutrición, Salvador Zubirán, Mexico City, DF: R. Correa-Rotter, MD, M. Sieiro-Muradas, MD.

Puerto Rico. San Juan Veterans Administration Medical Center, San Juan: J. Benabe, MD; San Juan Bautista School of Medicine, Caguas: J.L. Cangiano, MD.

Europe, United Kingdom, and Israel

Austria. General Hospital Linz, Linz: G. Biesenbach, MD; Krankenanstalt Rudolf-Stiftung, Wien: G. Scherthaner, MD; Universitätsklinik AKII, Wien: W. Waldhäusl, MD.

Belgium. Akademisch Ziekenhuis VUB, Brussels: B. Keymeulen, MD; Universitaire Instelling Antwerpen, Egedem: L. Van Gaal, MD; Centre Hospitalier Regionale de la Citadelle, Liege: X. Warling, MD.

Denmark. Bispebjerg Hospital, Copenhagen: H. Perrild, MD.

Finland. Helsinki University Central Hospital, Helsinki: C. Grönhagen-Riska, MD.

The Netherlands. Academic Hospital, Groningen: K. Hoogenberg, MD; TweeSteden Ziekenhuis, Tilburg: P.F.M.J. Spooren, MD; Ziekenhuis Centrum Apeldoorn, Apeldoorn: R.P. Verhoeven, MD.

France. Hospital du Dr Duchenne, Boulogne S/Mer: P. Bataille, MD; Maison Blanche Hospital, Reims: J. Chanard, MD; Hospital de Corbeil, Corbeil Essonnes: G. Charpentier, MD; Saint-Quentin Hospital Center, Saint Quentin: B. Coevoet, MD; Centre Hospitalier Universitaire, Grenoble: D.J. Cordonnier, MD, C. Maynard, MD, P. Zaoui, MD; C.H.U. de Nancy Hospital Jeanne d'Arc, Toul: P. Drouin, MD; C.H.U. Amiens Hospital, Amiens: A. Fournier, MD, El Esper, MD; C.H.R.U. Hospices Civils, Strasbourg: T. Hannedouche, MD, F. Chantrel, MD; C.H.U. Nancy Hospital Brabois, Vandoeuvre: M. Kessler, MD; Centre Hospitalier Beauvais, Beauvais: G. Lambrey, MD; C.H.U. de Caen, Caen: J. Mahoudeau, MD; BICHAT Hospital, Paris: F. Mignon-Henrion, MD; Hospital Center, Valenciennes: P. Vanhille, MD.

Germany. Buergerhospital, Stuttgart: W. Beischer, MD; Diabetes-Zentrum Bad Mergentheim, Bad Mergentheim: K. Bergis, MD, C. Hammermeister, MD; Internal Medicine, Aschaffenburg: G.P. Dragoun, MD; Bielefeld: H.H. Echthoff, MD; Gemeinschaftspraxis Karlstrasse, Düsseldorf: W. Kleophas, MD; Ernst-Moritz-Arndt-Universität, Greifswald: G. Kraatz, MD; Universitätsklinik Göttingen, Göttingen: G.A. Müller, MD; Institute of Diabetes Research, City Hospital Schwabing, Munich: E. Standl, MD; Klinik für Innere Medizin IV, Jena: G. Stein,

MD; Medizinische Universitätsklinik, Würzburg: C. Wanner, MD; Metabolic Research Munich, Munich: P. Weisweiler, MD.

Hungary. Bajcsy-Zsilinszky Hospital, Budapest: G. Jermendy, MD, K. Farkas, MD; University Medical School of Debrecen, Debrecen: G. Kakuk, MD; St. István Hospital, Budapest: L. Kammerer, MD; University Medical School of Pecs, Pecs: J. Nagy, MD; Semmelweis University, Budapest: G. Tamas, MD, G. Bibok, MD.

Israel. Hadassah University Hospital, Jerusalem: I. Raz, MD.

Italy. Nuovo Policlinico, Naples: V.E. Andreucci, MD; Università degli Studi La Sapienza, Rome: G.A. Cinotti, MD; Policlinico Universitario, Padova: G. Crepaldi, MD; Università degli Studi di Pavia, Pavia: A. Dal Canton, MD, C. Esposito, MD, N. Bellotti, MD; Università degli Studi di Genova, Genova: G. DeFerrari, MD; Ospedale S. Maria della Croci, Ravenna: E. Degli Esposti, MD; Ospedale di Lecco, Lecco: F. Locatelli, MD; Ospedale E. Agnelli, Pinerolo: U. Malcangi, MD; Ospedale Civile Maggiore, Verona: G. Maschio, MD; Ospedale di Cisanello, Pisa: R. Navalesi, MD, S. Bandinelli, MD, G. Penno, MD; Ospedale Luigi Sacco, Milan: G. Norbiato, MD; Ospedale S. Giovanni Battista LeMolinette, Torino: G. Piccoli, MD; Istituto Scientifico S. Raffaele, Milan: G. Pozza, MD, R. Mangili, MD; Ospedale Giovanni Bosco, Torino: F. Quarello, MD; Ospedale Mauriziano Umberto Primo, Torino: A. Ramello, MD; Ospedaliero Mutizonale, Bari: F. Paolo Schena, MD; Vimercate Hospital, Vimercate: A. Sessa, MD; Policlinico Universitario S. Orsola, Bologna: S. Stefoni, M.D; Clinia CNR, Reggio Calabria: C. Zoccali, MD.

Poland. Kliniika Endokrinology Akademii Mediczne, Szczecin: S. Czekalski, MD, H. Fuchs, MD, K. Pynka, MD; Medical University of Lodz, Lodz: J. Drezwoski, MD; Department of Internal Diseases & Diabetology, Zabrze: W. Grzeszczak, MD, K. Strojek, MD, M. Snit, MD; Medical Academy, Bialystok: I. Kinalska, MD; Klinika Chorob Metabolicznych, Krakow: J. Sieradzki, MD.

Portugal. Hospital Distrital de Faro, Faro: P.L. Neves, MD; Hospital Espirito Santo, Evora: C. Pires, MD.

Spain. Hospital La Paz, Madrid: F. De Alvaro, MD; Hospital Clinico y Provincial, Barcelona: E. Esmatjes, MD; Hospital Couadonga, Oviedo: R. Marin Iranzo, MD; Dr. J. Trueta Hospital, Girona: J.M. Mauri, MD; Hospital Universitari Germans Trias I Pujol, Badalona, Barcelona: R. Romero, MD, J. Bonet, MD; Hospital 12 de Octubre, Madrid: L. Ruilope, MD; Hospital de Cruces, Cruces: J.A. Vazquez, MD.

Sweden. Universiterssjukhuset, Linköping: H. Arnqvist, MD; Sahlgrenska sjukhuset, Gotenburg: S. Björck, MD; Malmö University Hospital, Malmö: L. Hulthen, MD.

United Kingdom. South Cleveland Hospital, Middlesbrough: R. Bilous, MD; Hope Hospital, Manchester: T.L. Dornan, MD, J. New, MD; Leeds General Infirmary, Leeds: P. Grant, MD; Central Middlesex Hospital, London: D. Hopkins, MD, A. Grenfell, MD; Maelor Hospital, Wrexham: J.N. Harvey, MD; Northern General Hospital, Sheffield: S.R. Heller, MD; St. Georges Hospital, London: A. Panahloo, MD, N.W. Oakley, MD; New Cross Hospital, Wolverhampton: P.B. Rylance, MD; Royal Berkshire Hospital, Reading: H. Simpson, MD; North Middlesex Hospital, London: H. Tindall, MD; Royal Sussex County Hospital, East Sussex: N.J.A. Vaughn, MD; Royal Liverpool Hospital, Liverpool: J.P. Vora, MD.

Australia, New Zealand, and South East Asia

Australia. Monash Medical Center, Clayton: R. Atkins, MD, P. Kerr, MD; Royal Melbourne Hospital, Parkville: P.J. Champion de Crespigny, MD; Royal Brisbane Hospital, Brisbane, Queensland: M.C. D'Emden, MD, D. Saltissi, MD; Northern Hospital, Epping, Victoria: B. Jackson, MD; Austin & Repatriation Medical Centre, Victoria: G. Jerums, MD, R. Gilbert, MD; Westmead Hospital, Westmead, NSW: P. O'Connell, MD; The Queen Elizabeth Hospital, Woodville South, SA: P.

Phillips, MD; Gosford Hospital, Gosford, NSW: S. Roger, MD; The St. George Hospital, Kogarah, NSW: J. Kelly, MD, J. Whitworth, MD; Royal Prince Alfred Hospital, Camperdown, NSW: D. Yue, MD.

New Zealand. Auckland Diabetes Centre, Auckland: P. Drury, MD, G. Braatvedt, MD, W. Bagg, MD; Dunedin Hospital, Dunedin: P. Manning, FRACP; Middlemore Hospital, Auckland: J. Baker, MD, D. Simons, MD.

Hong Kong. Prince of Wales Hospital, Hong Kong: J. Chan, MD; Queen Mary Hospital, Hong Kong: T.M.D. Chan, MD.

Malaysia. National University of Malaysia Hospital, Kuala Lumpur: N. Kong, MD

Singapore. National University Hospital, Singapore: A.C. Thai, MD.

Taiwan. Veterans General Hospital, Taipei: W.C. Yang, MD.

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